

U.S. Food and Drug Administration

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

CHARLES M. SINGLETON, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

RECOMMENDED DECISION

This is a clinical investigator disqualification proceeding conducted in accordance with 21 C.F.R. Part 16 and 21 C.F.R. § 312.70. The Center for Drug Evaluation and Research ("CDER") asserts that Charles M. Singleton, M.D., repeatedly and deliberately violated certain requirements of 21 C.F.R. Part 312 associated with his conduct of a human clinical study.

Specifically, CDER charges that Dr. Singleton:

1. Failed to prepare and maintain adequate and accurate written case histories, in violation of 21 C.F.R. § 312.62 (b);
2. Failed to prepare and maintain adequate and accurate drug accountability records, in violation of 21 C.F.R. § 312.62 (a); and
3. Failed to identify on Form FDA—1572 a study site at which five subjects were enrolled, in violation of 21 C.F.R. § 312.53 (c)(1)(iii).

PROCEDURAL HISTORY

After FDA's inspection of Dr. Singleton's study in February and March 1996, FDA sent Dr. Singleton a Warning Letter dated July 2, 1996, regarding certain violations the investigators observed. The Warning Letter was sent by certified mail to Dr. Singleton at ()

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() CDER states in its April 6, 2000 Motion for Summary Decision (“MSD”) that this was Dr. Singleton's last known address.¹

Although someone at the () address accepted the Warning Letter for delivery, Dr. Singleton was no longer at that business address, as FDA investigators had previously noted in their March 1991 inspection report.² FDA received no response to the Warning Letter.

On April 2, 1997, a Notice of Opportunity for a Hearing (“NOOH”) was sent to Dr. Singleton, also at the incorrect () address. This time someone there refused to accept delivery, and the NOOH was returned to FDA. On April 24, 1997, an FDA investigator hand-delivered the NOOH to Dr. Singleton at () ,

³ On April 30, 1997, Dr. Singleton responded to the NOOH by letter, stating that he had discarded the records of Protocol () because he thought that the records pertained to the study of the non-sustained release form of () , which had been approved on () 1991, and not the sustained release form of ()⁴ Because more than two years had passed since the NDA had been approved for the nonsustained release form of the drug, Dr. Singleton believed that FDA regulations no longer required that he retain the records. On December 5, 1997, the FDA sent a letter to Dr. Singleton, telling him that he had failed to specifically address the issues raised in the NOOH, and had failed to indicate whether he was requesting a hearing.⁵ On December 18, 1997, Ms. Dawna R. Carr, Esq., an attorney representing Dr. Singleton, sent a

¹ CDER MSD at 2.

² CDER MSD Ex. 11 at 3.

³ CDER MSD at 2, citing Ex. 4.

⁴ CDER MSD at 2, citing Ex. 5.

⁵ CDER MSD at 2, citing Ex. 6.

letter to FDA requesting a hearing.⁶ On January 6, 1998, Ms. Carr sent a second letter containing Dr. Singleton's response to the charges in the NOOH.⁷

On April 6, 2000, CDER filed its Motion for Summary Decision. Dr. Singleton did not file a response to CDER's summary decision motion, despite several notices from FDA that a response was due. By memorandum dated January 30, 2004, the Office of the Ombudsman referred this matter to this officer for a decision pursuant to the authority granted in 21 C.F.R. § 16.42(a).

Although Dr. Singleton declined to participate further in this proceeding following the MSD, CDER nevertheless bears the burden of establishing the necessary facts to support a finding that the violations occurred as alleged.

In accordance with 21 C.F.R. Part 16 and § 312.70, CDER's Motion for Summary Decision, and the supporting exhibits submitted by CDER have been reviewed. Based upon said review, it appears that there are no factual disputes of a genuine nature with respect to the material facts associated with the alleged violations. However, since the undisputed facts do not support the charges made, CDER's motion must be denied. Because Dr. Singleton did not repeatedly or deliberately violate the requirements of 21 C.F.R. § 312.62 (a), (b), or § 312.53 (c)(1)(iii), it is recommended that the Commissioner not disqualify Dr. Singleton from being eligible to receive investigational new drugs.

As provided in 21 C.F.R. § 16.60 (e), this recommended decision includes a recommendation on the summary decision as well as CDER's motion for disposition of this proceeding. This recommended decision will be referred to the Commissioner of Food and

⁶ CDER MSD at 3, citing Ex. 7.

⁷ CDER MSD at 3, citing Ex. 8.

Drugs who will render a final decision on this matter in accordance with 21 C.F.R. §§ 16.95 and 312.70.

REGULATORY BASIS FOR DISQUALIFICATION

In its motion, CDER alleges that Dr. Singleton repeatedly or deliberately violated several specific requirements of the regulations set forth in 21 C.F.R. Part 312. Based on these violations, CDER moves for disqualification pursuant to 21 C.F.R. § 312.70 (b). Section 312.70 (b) provides:

After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has *repeatedly or deliberately failed to comply with the requirements of [Part 312] . . . , 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. [Emphasis added].

The term "deliberately" includes conduct that is "willful," as well as conduct demonstrating reckless disregard.⁸ Accordingly, when a clinical investigator knowingly fails to comply with FDA's regulations, the clinical investigator may be found to have deliberately violated the regulations. Likewise, an investigator who shows a reckless disregard for whether his or her conduct may result in a regulatory violation may be found to have deliberately violated the regulations. A violation occurs "repeatedly" if it happens more than once, or "again and again."⁹

Under 21 C.F.R. § 16.26 (b), a hearing commences upon receipt by FDA of a request for a hearing submitted under said section. Pursuant to 21 C.F.R. § 16.26, the Presiding Officer of a

⁸ Black's Law Dictionary (6th ed. 1990); In *The Matter Of James A. Halikas, Jr., M.D.*, Commissioner's Decision, (January 17, 2001) ; In *The Matter Of Huibert M. Vriesendorp, M.D.*, Commissioner's Decision, (December, 31, 2001) ; In *The Matter Of Layne O. Gentry, M.D.*, Presiding Officer's Decision, (September 12, 2001).

⁹ Webster's New World College Dictionary (4th ed. 2000); In *The Matter Of James A. Halikas, Jr., M.D.*, Commissioner's Decision, (January 17, 2001); In *The Matter Of Huibert M. Vriesendorp, M. D.*, Commissioner's Decision, (December, 31, 2001).

Part 16 hearing is authorized to issue a summary decision on any issue if the Presiding Officer determines from material submitted in connection with the hearing or from matters officially noticed that there is no genuine and substantial issue of fact respecting that issue.

The standard for administrative summary decision contained in 21 C.F.R. § 16.26 (b) mirrors that contained in Rule 56 (c) of the Federal Rules of Civil Procedure.¹⁰ Therefore, the body of law developed under Rule 56 serves as a guide in determining whether summary decision is warranted.¹¹

In ruling on a summary decision motion, the Presiding Officer as decision-maker must determine whether there are disputed issues of material fact that need to be decided at a hearing.¹² The party requesting summary judgment bears the burden of establishing the absence of a genuine issue of material fact with respect to the essential elements of the alleged offense.¹³ A party opposing a properly supported motion for summary decision has the burden of showing that a rational trier of fact could find in his or her favor and that there is a "genuine issue for trial."¹⁴

Any doubts are to be resolved in favor of the non-moving party, and the non-moving party is entitled to all justifiable inferences.¹⁵ To fulfill this burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial."¹⁶ The mere existence of a scintilla of evidence in support of the non-moving party's position will be insufficient to

¹⁰ Rule 56(c) states that summary judgment "shall be rendered ... if ... there is no genuine issue as to any material fact and ... the moving party is entitled to a judgment as a matter of law."

¹¹ See *Puerto Rico Aqueduct & Sewer Authority v. EPA*, 35 F.3d 600, 607 (1st Cir. 1994) (finding that "[f]rom its inception, the concept of administrative summary judgment has been linked inextricably to Fed. R. Civ. P. 56," and that, "[m]any agencies habitually look to Rule 56 case law for guidance in respect to administrative summary judgments."); See also 53 Fed. Reg. 4613 (Feb. 17, 1988) (stating that the standard for summary decision set forth in 21 C.F.R. "§ 16.26 for denying a hearing conforms to well-settled law.").

¹² See *Celotex Corp. v. Catrett*, 477 U.S. 317 (1986).

¹³ *Adickes v. S. H. Kress*, 398 U.S. 144, 157 (1970).

¹⁴ *Matsushita Electrical Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986).

¹⁵ *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

¹⁶ Fed. R. Civ. P. 56(e); *Matsushita Electrical*, 475 U.S. at 586; *First Nat'l Bank v. Cities Service Co.*, 391 U.S. 253, 289 (1968).

overcome a motion for summary judgment.¹⁷ Further, the opposition to a properly supported motion for summary judgment “must do more than simply show that there is some metaphysical doubt as to the material facts”¹⁸ and cannot rest on mere allegations.¹⁹

FACTUAL BACKGROUND

Between May 1989, and March 1991, Dr. Singleton conducted a study of a sustained-release formulation of two strengths of the drug () for the sponsor, ().²⁰ Dr. Singleton’s study, conducted under Protocol ()²¹ was entitled “Double-Blind Comparison of () Sustained-Release (SR) 400 and 600 mg Tablets Administered Once Daily Versus () 300 mg Capsules Administered Twice Daily Followed by a 52-Week Open-Label Safety Study of () SR 400 and 600 mg Tablets in patients with Osteoarthritis ()”.²² On (), 1991, before Dr. Singleton’s study was completed, FDA approved () NDA for () 300 mg Capsules.²³

In April 1994, after Dr. Singleton completed the () study, he closed his private practice and moved all of the study records to a storage facility. Dr. Singleton states that, during 1995, he discarded records of studies that he believed were no longer required to be kept under the regulations.²⁴ The discarded documents included Dr. Singleton’s records from his () study.

On March 31, 1995, () submitted data collected from Dr. Singleton’s study to CDER in support of its NDA for () extended release tablets.²⁵ In February and March

¹⁷ *Anderson*, 477 U.S. at 252.

¹⁸ *Matsushita Electrical*, 475 U.S. at 586.

¹⁹ *First Nat’l Bank*, 391 U. S. at 289.

²⁰ CDER MSD at 5.

²¹ CDER MSD Ex. 8 at 1.

²² CDER MSD Ex. 9 at 1.

²³ CDER MSD at 10-11.

²⁴ CDER MSD Ex. 8 at 1.

²⁵ CDER MSD at 5-6.

1996, FDA visited Dr. Singleton to audit his study records for Protocol (_____) .²⁶ On October 25, 1996, FDA approved (_____) NDA for (_____) extended release tablets (400 and 600 mg).²⁷

CHARGES

CHARGE I. Failure to maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation.

CDER alleges that Dr. Singleton violated 21 C.F.R. § 312.62 (b) by destroying and, thus, failing to maintain copies of his study records. As the factual basis for this charge, CDER asserts that, sometime in the year following April 1994, Dr. Singleton discarded the study-related records for most of the subjects enrolled in Protocol (_____) .²⁸ CDER argues that Dr. Singleton's admission that he mistakenly destroyed his records proves that he failed to "maintain adequate and accurate case histories" of the study subjects and, thus, violated the requirements of 21 C. F. R. § 312.62 (b).²⁹

CDER, however, has misapplied § 312.62 (b) and, therefore, has charged Dr. Singleton with a violation that he did not commit. Section 312.62 (b) requires a clinical investigator 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. [Emphasis added].

In addition, § 312.62 (c) requires a clinical investigator to:

retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the

²⁶ CDER MSD at 7.

²⁷ CDER MSD at 10.

²⁸ CDER MSD at 7-8.

²⁹ CDER MSD at 8-10 and Ex. 5.

application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. [Emphasis added].

CDER charged Dr. Singleton with violating § 312.62 (b) when it should have charged him with violating § 312.62 (c). Read alone, § 312.62 (b) may be construed to mean that a clinical investigator must "maintain" his study records beyond the end of a study. However, when read in concert with § 312.62 (c), it is clear that § 312.62 (c), not § 312.62 (b), required Dr. Singleton to "retain" his records beyond the date that he destroyed them. CDER's argument that Dr. Singleton failed to *maintain* study records does not properly distinguish the requirements of the two different regulations. Neither the regulations themselves, nor their preamble, define the terms "maintain" and "retain."³⁰ When read together, however, the intended distinction is clear. Section 312.62 (c), not § 312.62 (b), clearly establishes the requirement that a clinical investigator not destroy study records for a certain period of time after a study is complete. The language in § 312.62 (c) requiring an investigator "to retain records required to be maintained" would be a redundancy if the terms "maintain" and "retain" were not intended to have different meanings.

Dr. Singleton did comply with the requirements of 21 C. F. R. § 312.62 (b). The evidence in this matter, as presented by CDER in its motion, clearly shows that Dr. Singleton did prepare and maintain case history records during his study. Original records for 5 of the 21 study subjects were found in Dr. Singleton's files, and the originals of the remaining records were obtained by FDA from the study sponsor.

Accordingly, there is no genuine and substantial issue of fact regarding whether Dr. Singleton prepared and maintained case history records during his conduct of the () study. The evidence in this matter simply does not support the charge that Dr. Singleton's destruction of

³⁰52 Fed. Reg. 8798, 8827 (March 19, 1987).

the () study records in 1994 violated the requirements of 21 C. F. R. § 312.62 (b).

CDER's Motion For Summary Decision as to Charge I is, therefore, denied.

CHARGE II. Failure to maintain adequate drug accountability records.

In its second charge, CDER alleges that Dr. Singleton committed two violations of 21 C.F.R. § 312.62 (a), which requires clinical investigators "to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects." Each alleged violation is discussed separately below.

A. Dr. Singleton did not have documentation showing the receipt of the Patient Package from () that contained the study medication administered to subject #31 (randomization #91).

In its motion, CDER alleges that the drug accountability records made available to FDA during FDA's 1996 inspection of Dr. Singleton's () study contained no documentation that Dr. Singleton received a patient package for subject number 31, who was assigned randomization number 91.³¹ CDER alleges that because subject number 31 was assigned a randomization number, it is apparent that Dr. Singleton must have received a patient package for this subject. Dr. Singleton asserts that subject number 31 was dropped from the study for protocol violations, which is why he lacked such documentation for the subject.³²

Review of the study documents discloses that the shipping records show that four separate shipments sent by () to Dr. Singleton included patient packages numbered 67 through 78, 97 through 102, 139, and 141.³³ There is no record of shipment of a patient package numbered 91 to Dr. Singleton.

³¹ CDER MSD at 13.

³² CDER MSD at 13, citing Ex. 8.

³³ CDER MSD Ex. 16 at 1.

Dr. Singleton's record of randomization for subject number 31, whose initials are () do show that subject 31 was assigned randomization number 91.³⁴ However, Dr. Singleton's Clinical Stock Record shows that study subject () was assigned randomization number 99.³⁵ According to the Clinical Stock Record, subject () was seen only during "Week 0," which, apparently, was during the pre-study washout period. The study protocol states that only acetaminophen, and not the study drug, () was permitted to be given during the washout period. It is noted that the entry in the Clinical Stock Record for subject () is crossed out with a line drawn through the entire entry. This appears to be consistent with Dr. Singleton's statement that patient number 31 was dropped from the study.³⁶

Although based on the record in this matter it appears rather clearly that Dr. Singleton made a typographical error in recording that patient () was allocated randomization number 91, there is no need to decide whether there is a genuine dispute regarding a material fact in this allegation. Even if Dr. Singleton committed this single violation, CDER does not allege that the violation was intentional. Given the denial of summary decision on the remaining charges in this matter, a single unintentional violation does not warrant disqualification under 21 C.F.R. § 312.70, and is therefore, immaterial to the outcome of this matter. Accordingly, CDER's motion for summary decision as to this violation in Charge II is denied.

B. Dr. Singleton did not have documentation showing receipt from () () of the () 300 mg capsules, which were required by Protocol () to be administered to the study subjects.

CDER also alleges that Dr. Singleton committed a second violation of 21 C.F.R. § 312.62 (a) because he was unable to produce records during the FDA inspection to show the receipt

³⁴ CDER MSD Ex. 17.

³⁵ CDER MSD Ex. 8 at 5.

³⁶ CDER MSD Ex. 8 at 2.

of the () 300 mg capsules from ().³⁷ CDER argues that because of the absence of receipts for the bottles of 300 mg capsules, CDER could not verify that all of the study medication was given to the subjects enrolled in the study.

Dr. Singleton did not specifically respond to this allegation in his two letters to FDA. Putting aside the question of whether 21 C.F.R. § 312.62 (a) requires a clinical investigator to maintain records of the receipt of the study drug from the sponsor, the facts are undisputed and they do not support the alleged violation.

According to the protocol for Dr. Singleton's () study, the first part of the study was a double-blind segment.³⁸ Initially, the subjects went through a washout period, during which acetaminophen, and not the study drug (), was to be used for pain relief. Subjects were then randomly assigned to one of three active treatment groups and given sealed patient packages that contained an allotment of two dosages per day of the test articles, consistent with one of the three blinded regimens: (a) () SR 400 mg in the morning and a placebo in the afternoon; (b) () SR 600 mg in the morning and a placebo in the afternoon; or (c) () 300 mg in the morning and a second () 300 mg in the afternoon.³⁹

Sufficient medication for each study subject was individually packaged and code-labeled by ().⁴⁰ Each package contained some additional dosages to allow for damage, loss, and minor variations in the date of a patient's visit.⁴¹

At the completion of the double-blind segment, subjects were permitted to enter an open-label extension of the study. In the open-label extension, the subjects received () SR

³⁷ CDER MSD at 13-14.

³⁸ CDER MSD Ex. 9 at 17.

³⁹ CDER MSD Ex. 9 at 17 and 51.

⁴⁰ CDER MSD Ex. 9 at 21.

⁴¹ *Id.*

400 mg once daily. After two weeks, the dose given to the subjects could, at the discretion of the investigator, be increased to the () SR 600 mg dose once daily.⁴²

In support of the charge that Dr. Singleton did not have documentation, CDER offers as evidence copies of shipment records from () to Dr. Singleton. The shipment records show that Dr. Singleton was sent bottles of () SR 400 mg and 600 mg, bottles of acetaminophen, sealed patient packages containing sufficient amounts of one of the study medications or placebos for Study (), and boxes of hemocults. There is no record of the shipment of bottles of () 300 mg to Dr. Singleton.⁴³ As to these facts, there is no genuine and substantial dispute.

() 300 mg capsules were to be given to the study subjects *only* during the double-blinded phase of the study. () shipped sufficient quantities of all test articles and placebos for this phase in the sealed individual patient packages sent to Dr. Singleton, which he then randomly gave to the study subjects. Further, in the open-label phase of the study, Dr. Singleton was permitted to give the subjects only doses of either () 400 mg or 600 mg. () 300 mg was not part of the open label study.

In sum, it is clear from the record in this matter that () did not ship any bottles of () 300 mg to Dr. Singleton for his study, except in the sealed individual patient packages. The record clearly shows that Dr. Singleton kept records of his receipt of these packages. There is nothing in the study protocol or elsewhere in the record of this matter requiring Dr. Singleton to have received any bottles of () 300 mg capsules.

Based upon the above, there are no genuine and substantial issues of fact regarding this part of Charge II and the facts do not support a conclusion that Dr. Singleton violated 21 C.F.R.

⁴² CDER MSD Ex. 9 at 6 and 17.

⁴³ CDER MSD Ex. 16.

§ 312.62 (a). Since the facts do not support either of the violations under Charge II, CDER's motion for summary decision as to Charge II is denied.

CHARGE III. Failure to identify one of the study sites on FDA Form 1572.

CDER alleges that Dr. Singleton violated 21 C.F.R. 312.53 (c)(1)(iii) by failing to identify on Form FDA 1572 the _____
_____, as a study site location. CDER states that Dr. Singleton identified only the _____, as a facility where the clinical investigation would be conducted, despite the fact that five subjects were also enrolled from the _____⁴⁴

Dr. Singleton contended that he did write the address for the _____ on Form FDA 1572, in response to the question on the form asking for the name and address of the investigator.⁴⁵ CDER responds that, while Dr. Singleton did list the address of the _____
_____ as the address of the investigator in response to item #1 on Form FDA 1572, he should have also given this address in response to item #3 ("Name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted").

CDER charges that, in putting the address of the additional study site in the wrong place on the form, Dr. Singleton violated 21 C.F.R. § 312.53 (c), which provides:

Before permitting an investigator to begin participation in an investigation, the *sponsor* shall obtain the following:
(1) A signed investigator statement (Form FDA-1572) containing: ...
(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted.
[Emphasis added].

⁴⁴ CDER MSD at 15, citing Ex. 15.

⁴⁵ CDER MSD Ex. 15.

Neither CDER nor Dr. Singleton disputes that the information was on the form, albeit not in its proper place. There is no need, however, to reach the issue of whether this constitutes a violation of § 312.53 because that section clearly requires a sponsor to submit this information, not the clinical investigator. Investigators are mentioned only as persons from whom the sponsor must obtain the required information. Accordingly, Charge III is not supported by the facts, and therefore, CDER's motion with respect to Charge III is denied.

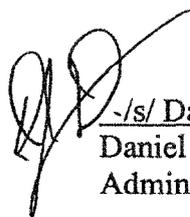
CONCLUSION

After reviewing the charges and evidence presented by both parties, it appears that there is no genuine dispute as to any material fact in this matter. The undisputed facts do not support a finding that Dr. Singleton violated any of the regulations as charged by CDER in its NOOH and as contained in its Motion for Summary Decision. Accordingly, CDER's motion is denied as to all charges.

RECOMMENDATION

The retention of clinical study records by a clinical investigator for the required amount of time is an important regulatory requirement. FDA depends upon the ability to inspect such records at a study site as part of its new drug approval process. Although Dr. Singleton's destruction of his () study records for Protocol () was premature and in clear violation of FDA regulation, whether done mistakenly or not, it was incumbent upon CDER to cite the proper violation(s) in this matter. The incorrect charges in this case preclude a finding of the essential elements of the alleged violations. Accordingly, it is recommended that Dr. Singleton not be disqualified.

DATED this 13th day of February, 2004.


-/s/ Daniel J. Davidson
Daniel J. Davidson
Administrative Law Judge