DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Food and Drug Administration
Rockville MD 20857

September 18, 2001

CERTFIED MAIL
RETURN RECEIPT REQUESTED

Lynn Whipkey, Esq.
Office of Chief Counsel, GCF-1
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

HAND DELIVERY

Re: Layne O. Gentry, M.D.
Clinical Investigator Disqualification Hearing

Counsel:

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

In accordance with 21 C.F.R. § 16.26(c), you may request that the Commissioner review this summary decision. A request for Commissioner's review must be in writing, and delivered to me, at the address provided above, by 4:30 p.m., EST, on November 2, 2001. If you do not submit a request for Commissioner's review by this time, you will be deemed to have waived such review.

Note: You must also deliver a copy of your request for Commissioner's reivew to the opposing party, by the opposing party's close of business on November 2, 2001.

The Commissioner will issue the final determination in this matter after November 2, 2001. If you have any questions about the process, please call me at 301-827-3390.

Sincerely,

Suzanne M. O'Shea

Suzanne M. O'Shea
Hearing Coordinator

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

LAYNE O. GENTRY, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

SUMMARY DECISION OF THE PRESIDING OFFICER

I. INTRODUCTION

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

- the Initial Request for Summary Decision and supporting exhibits submitted by the Center for Drug Evaluation and Research ("CDER" or the "Center") ("CDER MSD" (motion for summary decision)),
- the Request for Summary Decision and supporting exhibits submitted by Layne O. Gentry, M.D. ("Gentry MSD" (motion for summary decision)),
- the Reply Memorandum in Support of Center's Motion for Summary Decision and in Opposition to Dr. Gentry's Motion for Summary Decision and supporting exhibits ("CDER Opposition"), and
- the Opposition to CDER's Initial Request for Summary Decision and supporting exhibits ("Gentry Opposition"),
- the Center's Written Response to Request for Clarification and in Support of Center's Motion for Summary Decision, and
- Dr. Gentry's Reply to CDER's Response to Clarification and in Support of Center's Motion for Summary Decision

These documents were submitted following Dr. Gentry's request for a hearing to consider CDER's proposal to disqualify him from being eligible to receive investigational drugs as provided in 21 U.S.C. 355(i) and 21 C.F.R.§ 312.70.

As provided in 21 C.F.R. § 16.26(b), this summary decision constitutes my rulings on the Center's and Dr. Gentry's requests for summary decision. In accordance with 21 C.F.R. §§ 16.95 and 312.70, this decision will be referred to the Commissioner of Food and Drugs, who will make a final determination whether to disqualify Dr. Gentry.

II. BACKGROUND

Layne O. Gentry, M.D., was the principal investigator for three multi-center phase 3 clinical studies on the drug levofloxacin:

[ ] - evaluating the safety and effectiveness of levofloxacin vs. cefaclor in the treatment of lower respiratory infections in adults, initiated in August 1992 and completed in March 1993;

[ ] - evaluating the safety and effectiveness of levofloxacin vs. ticarcillin in the treatment of moderate to severe skin and skin structure infections in hospitalized adults, initiated in August 1992 and completed in July 1994; and

[ ] - evaluating the safety and effectiveness of levofloxacin vs. ciprofloxacin in the treatment of mild to moderate skin and skin structure infections in adults, initiated in September 1993 and completed in July 1994.

The sponsor, RW Johnson Pharmaceutical Research Institute (Johnson & Johnson) submitted New Drug Applications (NDAs) 20-634 (tablet) and 20-635 (injectable) in December 1995; CDER approved the NDAs in December 1996.

One of the study sites was St. Luke's Episcopal Hospital in Houston, Texas, where Dr. Gentry was located. However, nearly all of the 223 study subjects were in multiple sites in Costa Rica. These sites included four institutions that are part of the Costa Rican Social Security Hospital System ("CRSSHS") (Hospital Calderon Guardia, Hospital Mexico, Hospital San Juan de Dios and Centro Nacional de Rehabilitacion (CENARE)) and a private facility, [ ] [ ] M.D., who was located in Costa Rica, was the supervisory subinvestigator for the Costa Rica sites. Both Dr. Gentry and Dr. [ ] have had extensive experience in conducting clinical trials related to infectious diseases including, since the mid-1980s, research involving antimicrobials in the quinolone class.[1] However, as of May 1999 Dr. Gentry had not been involved in any clinical investigations after completion of the levofloxacin studies that are subject of this proceeding.[2]

Forms FDA 1572 submitted by Dr. Gentry identified the St. Luke's Episcopal Hospital Institutional Review Board as the Institutional Review Board (IRB) for the Houston site, and [ ] IRB (located in [ ] for the Costa Rica sites.[3]

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[1] Additional details on the qualifications and experience of these two investigators are found in Dr. Gentry's Request for Hearing, CDER MSD Exhibit 2, pp. 17-18. Dr. Gentry describes himself as "an internationally known leader in the field of infectious disease research, scholarship and clinical practice." Id., p. 17.

[2] Id., p. 19.

[3] The investigator submits Form FDA 1572 ("Statement of Investigator") at the initiation of a study. The form asks the investigator to list, among other things, the institutions in which the study will be conducted, the names of subinvestigators and the name(s) of the IRB(s). The form also lists various commitments, which the investigator agrees to undertake when he or she signs the form. Forms signed by Dr. Gentry for the studies at issue are at CDER MSD Exhibit 9.

III. PROCEDURAL HISTORY

FDA investigators conducted an inspection at the Houston site from June 20-24, 1996, issuing a Form FDA 483 (Notice of Inspectional Observations) at the conclusion of the inspection.[4] Dr. Gentry submitted a response to the Form FDA 483 on July 10, 1996.[5] FDA investigators then conducted an inspection at the Costa Rica sites from May 19-23, 1997, issuing a Form FDA 483 at the conclusion of the inspection.[6] A response to the Costa Rica Form FDA 483, signed by Dr.[ ]was submitted July 8, 1997.[7]

CDER issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) dated March 23, 1998.[8] Dr. Gentry submitted a written response to the NIDPOE,[9] and responded further to the NIDPOE allegations in an informal conference with FDA June 17, 1998.[10]

FDA's Associate Commissioner for Regulatory Affairs on April 15, 1999 issued a Notice of Opportunity for Hearing (NOOH) under 21 C.F.R. Part 16 to determine whether Dr. Gentry should be disqualified from receiving investigational drugs.[11] Briefly, the charges and relevant regulations were as follows:

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[4] The Form FDA 483 (Inspectional Observations) and the Establishment Inspection Report (EIR) Summary of Findings for the Houston inspection are at CDER MSD Exhibit 10.
[5] CDER MSD Exhibit 4.
[6] Id., Exhibit 11.
[7] Id., Exhibit 4.
[8] Id., Exhibit 3.
[9] Dr. Gentry's initial response to the NIDPOE, submitted March 31, 1998, consisted of the earlier responses to the Forms FDA 483. CDER MSD Exhibit 4. Following a telephone conference in which CDER explained that the responses to the Forms FDA 483 did not change CDER's position (memo of Telecon is Exhibit 5 to the CDER MSD), Dr. Gentry submitted a further response to the NIDPOE June 17, 1998. Dr. Gentry's Opposition includes the second NIDPOE Response (as attachment 10 to Exhibit 2), as well as the attachments to the NIDPOE Response. For convenience, the document will be referred to as "NIDPOE Response" with reference where appropriate to attachments thereto. The second NIDPOE response, without attachments, also appears at CDER MSD Exhibit 6.
[10] The transcript of the conference is Exhibit 7 to the CDER MSD.
[11] CDER MSD Exhibit 1. CDER had previously informed Dr. Gentry that it accepted his explanation for three allegations in the NIDPOE letter. CDER MSD, Exhibit 8.

Charge 1 – failure to maintain records of all observations and other pertinent data (21 CFR §§ 312.62(b) and (c)), specifically:

Charge 1A1 – failure to maintain x-ray films for all 60 subjects in Study[ ]for the required two years.

Charge 1A2 – failure to ensure that radiology reports for Study[ ]were signed and dated.

Charge 1B – failure to maintain accurate records (record discrepancies were allegedly found in study[ ]

Charge 1C – failure to maintain a subject enrollment screening log for study[ ]

Charge 2 – failure to obtain IRB approval before enrolling 25 subjects in studies[ ] and[ ](at Hospital Calderon Guardia) (21 C.F.R. §§ 50.27, 56.103(a), 312.53(c)(1)(vii), 312.60, and 312.66)).

Charge 3 – failure to document drug shipments in all three studies (21 C.F.R. §§ 312.62(a) and (c)).

Charge 4 – collection of a baseline blood sample after administration of the test article in study[ ](21 C.F.R. §§ 312.60 and 312.53(c)(1)(vi)(a)).

Charge 5 – failure to list three subinvestigators in FDA Forms 1572 for all three studies (21 C.F.R. §§ 312.53(c)(1)(viii) and 312.60)).

Charge 6A – failure to personally conduct or supervise any of the three studies (21 C.F.R. §§ 312.53(c)(1)(vi)(c) and 312.60)).

Charge 6B – submission of false information (21 C.F.R. § 312.70).

Charge 7 – reclassification of the clinical outcome for one subject in study[ ]in violation of the protocol (21 C.F.R. §§ 312.53(c)(1), 312.60 and 312.62(b)).

The first six charges concerned alleged violations at the Costa Rica locations; charge 7 concerned an alleged violation at the Houston site.

Dr. Gentry responded to the NOOH and requested a hearing on May 19, 1999.[12]

The parties submitted their requests for summary decision on July 7, 2000 and their oppositions on September 8, 2000. As explained further below (see Section VI.B.), at the request of the FDA Office of the Ombudsman the Center subsequently submitted a memorandum on the definitions of "repeated" and "deliberate." The Office of the Ombudsman accepted Dr. Gentry's memorandum responding to CDER's memorandum, over objection of counsel to CDER.[13] The Office of the Ombudsman also denied Dr. Gentry's request for a stay in the summary decision proceedings based on a December 21, 2000 press report that Dr. [ ] clinical trials had passed FDA inspection.[14]

IV. STANDARD FOR SUMMARY DECISION

Under 21 C.F.R. § 16.26(b), the Presiding Officer is authorized to issue a summary decision on any issue in the hearing if the Presiding Officer determines from material submitted in connection with the hearing, or from matters officially noticed, that there is no genuine and substantial issue of fact respecting that issue. A summary decision may be issued any time after FDA receives a request for a hearing in response to an NOOH.[15] The standard for administrative summary decision contained in

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[12] CDER MSD Exhibit 2.

[13] See letters dated February 28, 2001 from Sonal Vaid, Office of Chief Counsel to Suzanne O'Shea, Office of the Ombudsman, and March 6, 2001 from Suzanne O'Shea to Sonal Vaid.

[14] See letters dated January 25, 2001 from [ ] to Suzanne O'Shea, and February 7, 2001 from Suzanne O'Shea to [ ]

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

21 C.F.R. § 16.26(b) mirrors that contained in Rule 56 of the Federal Rules of Civil Procedure ("Fed.R.Civ.P."), which provides that summary judgment "shall be rendered ... if ... there is no genuine issue as to any material fact and ... the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c). Therefore, the Presiding Officer may be guided by the body of law developed under Rule 56 in determining whether summary decision is warranted.[16]

The party moving for summary judgment bears the burden of establishing the absence of a genuine issue of material fact. *Adickes v. S.H. Kress*, 398 U.S. 144, 157 (1970). A party opposing a properly supported motion for summary decision has the burden of showing that a rational trier of fact could find for the nonmoving party and thus that there is a "genuine issue for trial." *Matsushita Electrical Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). Any doubts are to be resolved in favor of the non-moving party and the non-moving party is entitled to all justifiable inferences. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). To fulfill this burden, the non-moving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e); *Matsushita Electrical*, 475 U.S. at 586; *First Nat'l Bank v. Cities Service Co.*, 391 U.S. 253, 289 (1968).

The mere existence of a scintilla of evidence in support of the non-moving party's position will be insufficient to overcome a motion for summary judgment. *Anderson*, 477 U.S. at 252. Further, the opposition to a properly supported motion for summary

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

judgment "must do more than simply show that there is some metaphysical doubt as to the material facts," *Matsushita Electrical*, 475 U.S. at 586, and cannot rest on mere allegations. *First Nat'l Bank*, 391 U.S. at 289.

V. REGULATORY FRAMEWORK

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

> After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has deliberately or repeatedly submitted false information 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). CDER has alleged both that Dr. Gentry repeatedly and deliberately failed to comply with the requirements of 21 C.F.R. Parts 50, 56, or 312, and that he repeatedly and deliberately submitted false information.

56," and that "[m]any agencies habitually look to Rule 56 case law for guidance in respect to administrative summary judgments.").

VI. DISCUSSION

A. Introduction

The Center and Dr. Gentry have both requested summary decision on all the charges that were included in the NOOH.[17] CDER has moved for summary decision on each of the charges individually. Dr. Gentry has moved for summary decision on all the charges based on his proposed definitions of "repeated" and "deliberate;" he contends that there is no evidence that his violations of the regulations (if any) were repeated or deliberate.[18] In addition to opposing CDER's request for summary decision on each of the charges individually, Dr. Gentry has requested summary decision on five of the individual charges: 1A2 (radiology reports); 1C (subject enrollment screening log); 5 (listing of subinvestigators); 6A (supervision) and 6B (submission of false information).

I will consider first Dr. Gentry's challenge to the charges based on differences between the parties' positions as to the definitions of the words "repeated" and "deliberate." I will then discuss the individual charges one by one.

B. Definitions of "Repeated" and "Deliberate"

Referring to the reports of previous clinical investigator disqualifications, CDER asserts that "repeated" means "more than one violation in a single study," and that "submission of more than one piece of false information in a single study constitutes 'repeated' submission of false information."[19] The Center also argues that it is "well

[17] See CDER MSD and Gentry MSD.
[18] Gentry MSD pp. 16-20.
[19] CDER MSD p. 5.

settled" by prior disqualification decisions that "deliberate" means "intentional" or having a "'reckless' disregard for the regulations' requirements."[20]

Dr. Gentry, on the other hand, argues that "deliberate" means "willfully and with careful consideration and forethought,"[21] requiring evidence that the investigator "knew of, planned or intended that any of the actions undertaken by him or his subordinates would violate FDA regulatory requirements."[22] He also states that "repeated" means "more than once."[23] However, Dr. Gentry asserts that FDA has stated that it will limit disqualifications, whether based on "deliberate" or "repeated" violations (or both), to situations in which a Center can "establish a reckless (although not necessarily an intentional) disregard of regulatory obligations, such as a broad pattern of systematic failure to comply with Agency regulations ...."[24]

Dr. Gentry further argues that by citing previous disqualification decisions, CDER improperly relies on "secret law" because the reports of those decisions had not been made available to the public in the manner required by the Freedom of Information Act (FOIA), and that Dr. Gentry did not have fair notice of what behavior constituted a legal infraction in accordance with due process.[25] Dr. Gentry adds that "no written guidelines exist at a Center level for bioresearch monitoring staff on what 'repeated or deliberate' violations mean."[26]

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[20] Id., pp. 5-6, citing a number of earlier FDA clinical investigator disqualification decisions.
[21] Gentry MSD, p. 16, citing *Black's Law Dictionary* 427 (6th Ed. 1990).
[22] Id., p. 17.
[23] Gentry MSD, p. 18, citing lay dictionaries.
[24] Id., pp. 18-19, citing language from an FDA preamble to proposed clinical investigator regulations.
[25] Gentry Opposition, pp. 2-3.
[26] Id., p. 3, citing a June 2000 report of the Department of Health and Human Services' Inspector General.

After the parties filed their summary decision briefs, and in response to a request from the FDA Office of the Ombudsman,[27] CDER submitted a written response on the "secret law" issue.[28] In its response, CDER argues that FOIA does not prohibit the Center from relying on previous clinical investigator disqualification decisions; that Dr. Gentry did have fair notice of the prohibited conduct in accordance with due process because clinical investigator disqualification decisions are in fact made public; that case law provides that agency interpretations can be advanced for the first time in agency adjudications and these interpretations are entitled to deference; and that the plain language of the regulation provides more than fair notice as to what behavior constitutes a legal infraction.[29]

Dr. Gentry's reply[30] disputes CDER's assertions that it has fulfilled FOIA's requirements by preparing and making available an index of decisions,[31] and that it provided Dr. Gentry with actual and timely notice of the decisions on which the Center relies.[32] Dr. Gentry also claims that CDER misrepresents his "reliance" on the older decisions.[33] Finally, Dr. Gentry asserts that CDER is not entitled to deference on its interpretation of the regulation because the concept of deference to an agency's interpretation does not become legally relevant until there is judicial review.[34]

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[27] Letter, Suzanne M. O'Shea, Hearing Coordinator, to Lynn Whipkey, Office of Chief Counsel, November 29, 2000.
[28] Center's Written Response to Request for Clarification and in Support of Center's Motion for Summary Decision, December 22, 2000.
[29] Id., pp. 1-2.
[30] Dr. Gentry's Reply to CDER's Response to Request for Clarification and in Support of Center's Motion for Summary Decision, January 25, 2001.
[31] Id., pp. 2-5.
[32] Id., pp. 5-8.
[33] Id., pp. 8-9.
[34] Id., pp. 9-12.

Dr. Gentry essentially raises three issues: (1) whether CDER may rely on previous clinical investigator decisions for the definitions of "repeated" and "deliberate" (the "secret law" issue); (2) if not, how the terms should be defined; and (3) under what circumstances an investigator should be disqualified if the Center proves that the investigator repeatedly or deliberately violated the regulations.

Dr. Gentry's "secret law" argument appears to have merit but I find it unnecessary to resolve the issue. I believe that the terms "repeated" and "deliberate" can be defined without reference to the previous clinical investigator decisions, but instead by examining the plain meaning of the words as defined by dictionaries and legal authorities. Thus, I turn to the second issue.

Even without the precedent from the clinical investigator decisions, it is reasonable to interpret "repeatedly" as meaning more than once. The plain meaning of "repeatedly" is "again and again," see Webster's Ninth New College Dictionary, 1991, Merriam-Webster Inc. Dr. Gentry agrees with this definition, although as noted above (and as discussed further below) he places an additional burden on the Center to justify disqualification. The regulation does not specify that violations in more than one study are prerequisite to a finding that an investigator "repeatedly" violated the regulations. I conclude that an investigator can commit violations "repeatedly" in one study, i.e. disqualification does not require transgressions in more than one study.

"Deliberate" includes "willful;"[35] willful conduct could be viewed as conduct demonstrating reckless disregard.[36] When a clinical investigator engages in conduct that

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[35] See Black's Law Dictionary 426 (6th ed. 1990); McLaughlin v. Richland Shoe Co., 486 U.S. 128, 133 (1988).
[36] McLaughlin, supra, 486 U.S. at 133.

he or she either knew or showed reckless disregard for whether his or her conduct failed to comply 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. Gentry's proposed definition – which would require evidence that the investigator "knew of, planned or intended" regulatory violations – is too restrictive. 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.

Dr. Gentry has "fair notice" of the FDA's interpretation of the definitions of "repeated" and "deliberate" because FDA's interpretation is consistent with the plain meaning of the words in the applicable regulations. I believe that the foregoing interpretations meet that standard. Because the definitions that I have adopted are consistent with those advanced by CDER, I find it unnecessary to resolve the "deference" issue raised by the parties.

The third issue can be readily resolved. Dr. Gentry advances the theory that FDA will disqualify an investigator who has been found to have repeatedly or deliberately violated the regulations only where there is a reckless disregard, such that the violations are of a widespread or fundamental nature. The Federal Register notice which Dr. Gentry cites to support this proposition is the preamble to a proposed rule that was withdrawn in 1991.[37] But Dr. Gentry also cites a valid preamble statement, one which accompanied the final clinical investigator regulations that are applicable in this case, and which states

[37] 56 Fed. Reg. 67440, 67446 (December 30, 1991).

that FDA will "not disqualify an investigator if the violations are insignificant or if lesser sanctions would be adequate."[38]

Also relevant is the agency's statement (in the context of a discussion of submission of false information in the preamble to the medical device Clinical Investigator Disqualification Final Rule) that it "does not intend isolated or inadvertent failures to be the basis for disqualification .... the agency's threshold for taking action against a clinical investigator requires the submission of false information to be deliberate or frequent enough to call into question the individual's eligibility to continue the investigation."[39] The agency, however, has not limited itself in the manner that Dr. Gentry suggests.

It is essential to note, in any case, that a decision not to disqualify an investigator who has repeatedly or deliberately violated the regulations is committed to the Commissioner's discretion.

C. Rulings on Individual Charges

1. Introduction

I have concluded that there are no genuine issues of material fact for a hearing, and that CDER is entitled to judgment as a matter of law on the following charges, discussed in detail in subsection C.2., below. That is, I have concluded that CDER met its burden of proving that Dr. Gentry violated the specified regulations, and did so repeatedly or deliberately, with regard to the following charges:

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[38] 52 Fed. Reg. 8798, 8826 (March 19, 1987).
[39] 62 Fed. Reg. 12087, 12089 (March 15, 1997).

Charge 1A1 – Failure to maintain x-ray films for the required period of time

Charge 1A2 – Failure to ensure that radiology reports were *signed*[40]

Charge 1B – Failure to maintain accurate records (record discrepancies)

Charge 2 – Failure to obtain IRB approval

Charge 5 – Failure to list subinvestigators on Forms FDA 1572

Charge 6A – Failure to personally conduct or supervise studies

Accordingly, I will deny Dr. Gentry's requests for summary decision on the foregoing charges based on his contention that he did not repeatedly or deliberately violate any regulations, and also deny his requests for summary decision on charges 1A2 (signatures on radiology reports), 5 (listing of subinvestigators), and 6A (supervision) based on his contentions that he did not violate the specific regulations as charged.

I will deny CDER's requests for summary decisions on all the remaining charges except Charge 6B (false information), which I have determined not to decide; these charges are discussed in subsection C.3, below. However, I will also deny Dr. Gentry's requests for summary decision on the remaining charges, including charges 1A2 (dates on radiology reports), and 1C (screening logs), for the reasons explained in subsection C.3 below. The charges discussed in subsection C.3 are as follows:

Charge 1A2 – failure to *date* radiology reports

Charge 1C – failure to maintain subject enrollment screening log or source documents

Charge 3 – Failure to document drug shipments

Charge 4 – Baseline blood sample violation

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[40] As explained below, I have not concluded that CDER is entitled to summary decision as to whether the radiology reports were *dated*.

Charge 6B – Submission of false information

Charge 7 – Reclassification of clinical outcome

2. Summary Decision Granted to CDER

Charge 1 – Failure to Maintain Adequate and Accurate Records

The Center charged Dr. Gentry with several violations of 21 C.F.R. § 312.62.[41] That regulation requires investigators to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (21 C.F.R. § 312.62(b)). The regulation also requires investigators to keep the records for two years after a marketing application is approved or, if no application is to be filed, two years after the investigation is discontinued and FDA is notified (21 C.F.R. § 312.62(c)).

Charge 1A1 – X-ray Films

The Center charged that Dr. Gentry violated 21 C.F.R. § 312.62(c) in that x-ray films for all 60 subjects in study [ ] were not maintained for the required two years after NDA approval.[42] In accordance with their routine practice, the films were discarded

[41] CDER MSD pp. 7-8.

[42] Id. p. 8. Because NDAs were submitted, and approved in December 1996, the records should have been kept until December 1998.

by the CRSSHS institutions six months after the x-rays were taken.[43] The Center contends that Dr. Gentry admitted the violation.[44]

The Center further contends that the violations were repeated and deliberate.[45] CDER bases its charge of deliberateness on, among other things, Dr. Gentry's extensive experience as a clinical investigator,[46] and Dr. Gentry's statement that he was well aware of his obligation with respect to the keeping of records.[47] CDER points out that although Dr. Gentry claims to have corrected the problem by employing a private radiologist to comply with the record retention requirement,[48] this did not happen until April 1996, almost two years after the study was completed and long after the films were destroyed.[49]

Dr. Gentry offers several arguments to support his assertion that he did not violate the regulation repeatedly or deliberately.[50] He argues that the failure to maintain the records was not his fault but happened because of the actions of others (i.e., CRSSHS) who, without his knowledge, changed routine practices and destroyed the records. He claims that it is undisputed that once Drs. Gentry and [ ] learned of CRSSHS'

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[43] Study [ ] was initiated in August 1992 and completed in March 1993. The x-ray films were not available at the time of the FDA inspection in May 1997. CDER MSD Exhibit 11, Form FDA 483, p. 1.
[44] CDER MSD Exhibit 2, pp. 21-2; Exhibit 6, p. 10-11; Exhibit 7, pp. 24-25.
[45] CDER MSD pp. 8-9.
[46] Dr. Gentry had participated in at least 15 studies involving investigational new drugs, and signed numerous Forms FDA 1572 including those for the studies at issue. CDER MSD Exhibit 9.
[47] CDER MSD Exhibit 7, p. 25.
[48] NIDPOE Response, p. 11.
[49] Dr. [ ] retained a private radiologist who began to perform radiological studies and x-ray interpretations "... to guarantee the integrity and preservation of source documents (x-rays and other radiological studies)." CDER MSD Exhibit 13, June 19, 1997 letter from [ ] M.D., Radiologist, to Dr. [ ] Costa Rica Institute for Clinical Investigations.
[50] Gentry Opposition, pp. 8-10.

change, they took prompt and effective steps to prevent recurrence, and did so before the FDA inspection.[51]

Dr. Gentry also asserts that CDER has not met its burden of proving that Dr. Gentry knew of CRSSHS' policy change, that he delayed acting once he learned of the change, or that the action was ineffective in preventing recurrence. He also maintains that in arguing that the violation was "repeated and deliberate," CDER creates a standard beyond strict liability (i.e., liability for actions of third parties) because in clinical studies investigators routinely rely on others to use standard care and follow historic procedures.

It is undisputed that the x-ray films were not kept as required by the regulation. I conclude that the record establishes that Dr. Gentry violated 21 C.F.R. § 312.62(c) repeatedly and deliberately by failing to keep the x-ray films for the required time period. Dr. Gentry has not raised genuine factual issues for hearing.

Dr. Gentry had a responsibility to ensure that the records would be kept for the required period; that responsibility could not be shifted to the CRSSHS. The regulation states that "[a]n *investigator shall retain records* required to be maintained under this part ..." for the specified time period. 21 C.F.R. § 312.62(c)(emphasis added). Certainly the investigator does not have to have physical custody of the records, but just as surely he must take reasonable steps to ensure that the person to whom he entrusts the records will maintain them in accordance with the regulations. The argument that Dr. Gentry pursues most vigorously is that CRSSHS changed its x-ray film retention period to six months and did not inform Dr. Gentry, and that he took prompt corrective action once he

[51] NIDPOE Response p. 11 and Attachments 7 and 8. Attachment 7 is a June 19, 1997 letter from the Clinic Head, Radiological Service, Calderon Guardia Hospital, which confirms the hospital's practice of discarding radiological studies after six months. Attachment 8 is the letter from Dr. [ ] referred to in footnote 49.

discovered the change. There are several reasons why Dr. Gentry's argument does not raise credible factual issues.

It is axiomatic that, to comply with the regulation, Dr. Gentry needed to verify, some time before the initiation of the study, that the x-ray films would be kept for the required time period. Had he done so, Dr. Gentry would have discovered that *the hospital's policy of keeping the x-ray films for only six months was adopted in 1990,*[52] two years before the study was initiated. Moreover, Dr. Gentry provided no evidence concerning the pre-1990 policy, i.e. he offered no evidence to establish that prior to the 1990 change in policy the CRSSHS in fact maintained x-ray films for the time periods required by the FDA regulation, and that he had been aware of such policy.

The implication that Dr. Gentry personally took remedial action on a timely basis, even if relevant, is disingenuous for two reasons. First, the retention of a private radiologist was done by Dr.[ ] and not Dr. Gentry.[53] This is understandable because Dr. Gentry did not participate in clinical research after 1994;[54] obviously, he was not in collaboration with Dr.[ ] in clinical research in 1996 when Dr.[ ] retained the private radiologist. Second, the "remedial action" clearly was not timely because it was taken in 1996, six years after CRSSHS changed its practice, four years after the study started, and two years after it ended.[55]

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[52] See the letter from Calderon Guardia Hospital, NIDPOE Response Attachment 7.
[53] The letter from Dr.[ ] referenced above, was addressed to Dr.[ ] as president of the Costa Rica Institute of Clinical Investigation, and stated that he had been performing interpretations of x-ray films for the institute since April 1996.
[54] Dr. Gentry's involvement in <u>any</u> clinical investigation ended in 1994 when the studies at issue terminated. CDER MSD Exhibit 2, p. 19.
[55] Dr. Gentry provides no details of his "discovery" of the change in the hospital's record retention policy, i.e., when and how the "discovery" occurred.

CDER met its burden by establishing that x-ray films were not available at the time of the FDA inspection, as required by the regulation.[56] Because Dr. Gentry did not offer credible rebuttal evidence, CDER did not have the additional burdens that Dr. Gentry would place on it.

The violations were repeated because the x-ray films of sixty subjects were not kept. The violations were deliberate because of Dr. Gentry's reckless disregard for the necessity to take steps to verify and ensure that the records would be kept as required by the regulation.

Therefore, I find that Dr. Gentry repeatedly and deliberately violated the cited regulation, 21 C.F.R. § 312.62(c) as charged by the Center. There are no genuine issues of fact for hearing on this charge.

Charge 1A2 - Radiology Reports

a. Introduction

The Center charged that radiology reports for the study were unsigned and/or undated in violation of 21 C.F.R. § 312.62(b), which requires medical records to be signed and dated.[57] The Center included in its request for summary decision two radiology reports which it presented as examples of reports that were undated and/or unsigned.[58] The Center contends that Dr. Gentry admitted the violation,[59] and alleges that the violations were repeated and deliberate.[60]

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[56] Because NDA's were pending at the time of the inspection, the point at which the records could be destroyed had not yet been reached.
[57] CDER MSD p. 8.
[58] Id., Exhibit 12.

Dr. Gentry counters that the two radiology reports submitted by CDER were in fact dated and signed in that the forms contained typed dates, and the name of the radiologist was typed above the signature lines.[61] Dr. Gentry uses this contention as the basis for his request for summary decision on this issue.[62]

In response to CDER's MSD, Dr. Gentry argues that CDER has not met its burdens of demonstrating that a handwritten signature was a regulatory requirement, that a typewritten date and signature undermined the validity of the information, and that the typed information could not be verified as easily as a handwritten entry. He offers similar arguments in support of his request for summary decision.[63] Dr. Gentry also asserts that CDER's request for summary decision is based entirely on admissions made by Dr. Gentry before he had access to the documents in CDER's possession,[64] suggesting that the admissions are no longer viable in light of the fact that the two exhibits contained typed dates and names.

The Center responds[65] by pointing out that the regulation (21 C.F.R. § 312.62(b)) requires case histories to be signed and dated,[66] and by asserting that a "signature" is handwritten, by dictionary definition. The Center argues that "[t]he dated signature is

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[59] CDER MSD Exhibit 2, pp. 21-2; Exhibit 6, p. 10-11; Exhibit 7, pp. 24-25. During the informal conference with FDA, Dr. Gentry's counsel stated that "you identified two reports [in the NIDPOE] that were either undated or unsigned, and Dr. Gentry does not contest that observation." Exhibit 7, p. 26

[60] CDER's evidence for deliberateness is the same for this charge as for Charge 1A1, "X-ray films."

[61] Gentry Opposition pp. 10-11.

[62] Gentry MSD p. 6.

[63] Gentry MSD pp. 6-7.

[64] Language in the Opposition suggests that the admission was premature because when he made the admission Dr. Gentry had not seen the two radiology reports which CDER submitted with its request for summary decision, and because after he saw the reports he concluded that the typewritten dates and name were legally sufficient. Gentry Opposition, p. 10, n. 8.

[65] CDER Opposition, pp. 2-3.

[66] "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 the nurses' notes." 21 CFR § 312.62(b). [emphasis added].

essential information to evidence whether the radiology reports were reviewed, which is especially important given that Dr. Gentry admits to discarding the actual x-ray films."[67]

CDER appears to argue that both the signature and date must be handwritten. Because my conclusion with regard to the need for a handwritten signature differs from that with regard to the requirement for a handwritten date, I will discuss the requirements of the two items separately.

b. Signatures

I look first at the evidence with respect to *signatures*. The record contains undisputed evidence that at least some of the radiological reports did not contain the radiologist's handwritten signature. The two examples CDER submitted[68] did not have handwritten signatures. In addition, the hospital's routine practice did not provide for handwritten signatures in all cases. Dr. Gentry described this practice in his NIDPOE Response:

> "At the hospital, the radiologist would dictate his or her findings when reviewing the x-ray film. The departmental secretary would transcribe the report and have it signed and dated if the radiologist was present, otherwise, the report was simply archived in the patient's medical chart."[69]

I agree with CDER that 21 C.F.R. § 312.62(b) requires handwritten signatures in this instance. The regulation requires "... signed and dated consent forms and medical records...." Thus, the regulation literally requires that all medical records be signed. Obviously, common sense exceptions may apply where there is no rationale for requiring signatures. But such an exception would not apply in this case, where there is no way (absent the signature) to verify the accuracy of the reports' contents. Thus, I conclude

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[67] CDER Opposition, p. 3.
[68] CDER MSD Exhibit 12.
[69] NIDPOE Response, p. 11.

that, as a matter of law, the radiologists' signature is required on the reports. The plain language of the regulation, and the rationale for signatures on radiology reports, meet CDER's burden in this instance.

Therefore I conclude that Dr. Gentry violated the regulation because he did not ensure that the records bore the required signatures.

I also conclude that the violation was repeated and deliberate. It was repeated because the records of at least two (and most likely more) subjects did not bear handwritten signatures. The violations were deliberate because of Dr. Gentry's reckless disregard of the need to take reasonable steps to verify and ensure that the records would be kept as required by the regulation, i.e., to ensure that the radiology reports would be signed.

Dr. Gentry's post hoc legal theory – that a typed name is sufficient – therefore does not shelter him from the charge of deliberateness. As explained above, Dr. Gentry admitted that the radiology reports were not signed but, after seeing the CDER exhibits, raised the defense that typed names were legally sufficient. The contention that his admission was premature is irrelevant because Dr. Gentry was charged with the responsibility of knowing how the records were prepared. In any event, because he had that responsibility, I do not need to rely on his admission to establish that he repeatedly and deliberately violated the regulation.

There are no genuine issues of material fact for hearing with respect to the absence of handwritten signatures on the radiology reports.

c. Dates

I turn now to the question as to whether as a legal matter the *dates* on the radiology reports need to be handwritten by the radiologist.[70] Both CDER and Dr. Gentry have moved for summary decision on this issue. The Center did not explain the basis for its apparent position that the dates need to be handwritten. Although I have agreed with the Center that the dictionary definition of "signed" leads to the conclusion that a handwritten signature is required, no such conclusion can be supported – from CDER's filings or from matters on which I can take official notice – with respect to the word "dated" in the regulation. Thus I will deny CDER's motion for summary decision.[71]

There may, however, be a viable legal theory, supported by important policy considerations, that would validate the Center's apparent position.[72] Dr. Gentry has not persuaded me with appropriate analysis that a typewritten date is adequate as a matter of law. He simply makes the conclusory statement that "(a) typewritten date ... does not in any way undermine the validity of the information and can be verified as easily as a handwritten entry."[73] Therefore I will deny summary judgment to Dr. Gentry on this aspect of Charge 1A2. I simply conclude that on the record before me neither party has met its burden with respect to the dates on the radiology reports.

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[70] CDER MSD p. 8, Gentry MSD pp. 6-7.

[71] Dr. Gentry's "admissions" do not lead to a contrary conclusion where I have found that CDER cannot prevail as a matter of law. Further, CDER's charge was phrased in the alternative (i.e. the reports were unsigned and/or undated) and Dr. Gentry's "admission" with respect to CDER's two examples was that the reports were "either undated or unsigned." CDER MSD Exhibit 7, p. 26. I am required to resolve doubts in favor of the nonmoving party, in this case Dr. Gentry.

[72] For example, it may be important to be able to verify the date that the report was signed, or to assure that the date shown on the report is the same as the date the report was actually signed.

Charge 1B – Study [ ] Record Discrepancies

The Center alleges that there were seven record discrepancies, involving five subjects. Based on these allegations, the Center charged that Dr. Gentry failed to prepare and maintain adequate and accurate case histories, in violation of 21 C.F.R. § 312.62(b), and that Dr. Gentry failed to retain such records for a period of two years as required by 21 C.F.R. § 312.62(c).[74]

The alleged violations fall into the following categories:

1. "Fabricated" records (2 subjects) – Duplicative medication dosing records

- Subject 1903

The individuals who actually administered the study medications completed one medication record, recording their initials on that form. A second medication dosing record was prepared -- based on information supplied by a nurse -- by a physician who placed the nurse's initials on the form. CDER does not attempt to explain the possible implications of having two forms. It does appear that the two forms show different drug administration patterns.[75]

- Subject 1403

Duplicative forms were prepared, as for subject 1903. The forms showed different drug administration patterns.[76]

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[73] Gentry MSD p. 7
[74] CDER MSD pp. 9-11.
[75] Id., Exhibit 14.

[76] Id., Exhibit 15. One form shows administration of Timentin from 9/24 to 9/29/92 and Augmentin from 9/29 to 9/31/92. (Note that September has only 30 days). The other form does not reflect administration of either drug between 9/24 and 10/1/92.

2. Subject numbers were wrong on the medication labels on the Case Report Forms (CRFs) for two subjects (1403 and 1916).[77]

3. Records show administration of study medications past the post-therapy date:[78]

- Subject 1403: the CRF shows a post-therapy date of 9/28/92, but the CRF also documents administration of study medications until 10/5/92.[79]
- Subject 2117: the CRF shows a post-therapy date of 5/10/93, but the hospital medication chart and physician's notes show administration of study medication until 5/13/93.[80]

4. Concomitant therapy (furosemide and cimetidine in addition to the test drug) is shown on the hospital medication chart, but not on the CRF (1 subject, 1920)[81]

CDER contends that Dr. Gentry admitted that the discrepancies occurred.[82] The Center also asserts that the violations were repeated and deliberate; the charge of "deliberateness" is based on Dr. Gentry's experience, and his duty to prepare and maintain adequate case histories.

Dr. Gentry does not dispute the inaccuracies.[83] However, he argues that CDER has not provided evidence that the discrepancies were *material* – a standard which he

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[77] Id., Exhibits 16 and 17.
[78] "Post-therapy date" is the date the subject completed the prescribed course of therapy.
[79] CDER MSD Exhibit 18.
[80] Id., Exhibit 19.
[81] Id., Exhibit 20.
[82] CDER MSD Exhibit 2, p 22; Exhibit 6, pp. 12-13.
[83] Gentry Opposition pp. 11-13. Dr. Gentry does assert that the errors were not the result of intentional wrongdoing. Gentry Opposition Exhibit 2, p. 23.

claims FDA adopted in prior public FDA interpretations, specifically in the preamble to the proposed clinical investigator regulation.[84]

Dr. Gentry points out that the discrepancies occurred in trials involving 220 subjects, arguing that the handful of errors identified by FDA is inconsequential, and shows no pervasive disregard for the need for accurate and complete record-keeping. He relies on an FDA statement that the agency is "well aware of the exigencies of clinical investigations and does not intend to invoke severe sanctions for ... minor human error."[85]

Finally, Dr. Gentry asserts that many of the record-keeping errors originally cited by CDER in the Form FDA 483 and the NIDPOE were corrected by study staff before the FDA inspection.[86]

CDER addresses the question of materiality in its Opposition, pointing out that the final clinical investigator regulation adopted in 1987 did not include certain criteria relating to significance that had been in the proposed rule, and that therefore the language in the preamble to the proposed rule cited by Dr. Gentry is irrelevant.[87] The preamble to the final rule did state, however, that the Commissioner retained discretion not to disqualify an investigator for insignificant violations.[88]

There is no factual dispute that the discrepancies occurred as alleged. I agree with CDER that the discrepancies are not required to be material to constitute a violation of

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[84] Gentry Opposition p. 7, referencing Gentry MSD pp. 10-11, which cites language in the preamble to proposed clinical investigator regulation, 43 Fed. Reg. 35210, 35217 (August 8, 1978).
[85] 42 Fed. Reg. at 35295.
[86] Dr Gentry cites CDER MSD p. 10, fn. 3, which states that the Center accepted Dr. Gentry's NIDPOE explanation with respect to one alleged discrepancy, incorrect patient number on the CRF for patient #1916, because a clinical correction form had been issued to the sponsor.
[87] CDER Opposition p. 11.
[88] Id.

the regulation.[89] Further, most of the discrepancies CDER identified are significant or potentially significant. For example, some of the entries in the "fabricated" records do not make sense, calling the validity of those records into question.

I disagree with Dr. Gentry's contention that the *number* of violations is insignificant when one considers that the study involved 220 subjects. FDA inspected records of just 19 patients.[90] The Establishment Inspection Report (EIR) did not state how many individual records were examined in the course of inspecting the 19 patients' records. However, errors were found in the records of five patients, or more than 25% of those whose records were examined. I consider this frequency to be significant.

Finally, I will address Dr. Gentry's claim that many of the record-keeping errors originally cited by CDER in the Form FDA 483 and NIDPOE were corrected before the FDA inspections.[91] Dr. Gentry does not document this contention, or explain how an error reported in the inspection could have been corrected prior to the inspection. In any event, he cites only one example,[92] and that error is not subject of CDER's motion for summary decision. That is, Dr. Gentry corrected an erroneous patient number on the *case report form* for one subject (#1916) in 1993; however, a different erroneous patient number on the *medication label* for that patient was not corrected, and Dr. Gentry admits that it went undetected throughout the study.[93] The latter error was one found in the inspection, cited in the CDER motion for summary decision, and described above.

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[89] In addition to CDER's explanation it should be noted that the proposed rule the preamble of which Dr. Gentry cited was ultimately withdrawn. 56 Fed. Reg. 67440, 674456 (December 31, 1991).
[90] CDER MSD Exhibit 11, pp. 6-7 (EIR Summary of Findings).
[91] Gentry Opposition p. 12.
[92] Id. See discussion above.
[93] NIDPOE Response p. 12.

I conclude that Dr. Gentry violated 21 C.F.R. § 312.62(b) as charged by the Center and that there is no genuine and substantial issue of material fact requiring a hearing. It is not clear how 21 C.F.R. § 312.62(c) (requiring records to be retained for two years) could be applied in this circumstance as charged by CDER, except through a novel argument. However, it is unnecessary to decide that regulation's applicability in view of my decision with respect to violation of 21 C.F.R. § 312.62(b), which requires the maintenance of adequate and accurate case histories.

I also conclude that the violation of 21 C.F.R. § 312.62(b) was repeated and deliberate. It was repeated because there was more than one violation of the regulation in a single study. It was deliberate because there is no evidence that Dr. Gentry maintained *any* direct oversight of the record-keeping process to ensure accuracy, and thus acted with reckless disregard for whether the record-keeping process ensured accuracy. His list of direct supervision activities that he carried out[94] does not include review of records.[95] It is evident that Dr. Gentry took so little care with regard to record keeping that regulatory violations were nearly certain to (and did) result.

Charge 2 - IRB Approval of Studies at Hospital Calderon Guardia

CDER alleges that Dr. Gentry did not obtain IRB approval to conduct studies [ ] and [ ] at Hospital Calderon Guardia before enrolling 25 subjects into the

[94] Gentry Opposition, p. 20, n. 16.
[95] See further discussion in Charge 6A.

studies at that hospital.[96] CDER charges that the omission resulted in violation of several regulations.[97]

CDER contends that [ ] IRB (located in [ ] is the IRB of record for the studies at the Costa Rica sites.[98] The [ ] IRB approved protocols for the studies, and approved conduct of the studies at several sites. However, it did not approve conduct of the studies at Hospital Calderon Guardia until November 25, 1992.[99] FDA's inspection revealed that 25 subjects were enrolled in the studies at that hospital between September 9, 1992 and November 25, 1992.[100]

CDER also states that Dr. Gentry admitted enrolling the subjects at Hospital Calderon Guardia prior to the [ ] IRB approval.[101] Responding to claims made in Dr. Gentry's early submissions that he had obtained approval from local IRB committees for conducting the studies at Hospital Calderon Guardia,[102] CDER asserts that he presented no evidence that the local IRBs complied with FDA requirements or that the local IRBs were even aware of the studies.[103] CDER claims that the Ministry of Health's Institutional Scientific Committee (ISC) approved studies to be conducted by

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[96] CDER MSD pp. 13-15.

[97] CDER charges violation of 21 C.F.R. § 312.66, which requires that an investigator "assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study;" 21 C.F.R. § 56.103(a), which requires that an investigator "ensure that the investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of Part 56;" 21 C.F.R. § 312.53(c)(1)(vii), which provides "that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review of the approval of the clinical investigation ..." (this is a commitment on the investigator statement, Form FDA 1572); and 21 C.F.R. §§ 50.27 and 312.60.

[98] CDER MSD Exhibit 9 (Forms FDA 1572 signed by Dr. Gentry).

[99] Id., Exhibit 23.

[100] Id., Exhibit 11, Summary of Inspectional Findings, p. 21.

[101] CDER MSD Exhibit 2, p. 25; Exhibit 6, pp. 19-23; Exhibit 7, pp. 38-40.

[102] Id.

[103] CDER MSD, p. 14.

Dr.[ ]only in Hospital Mexico,[104] and that there is no evidence that the committee in each of the study sites (including Hospital Calderon Guardia) was a legally authorized IRB during the time of the studies.[105]

CDER contends that the violations were repeated[106] and deliberate,[107] the latter based on CDER's contentions that the[ ]IRB was the IRB of record; that Dr. Gentry's responsibility was clearly set forth in the cited regulations; and the fact that Dr. Gentry is an experienced clinical investigator who has signed numerous Forms FDA 1572.

In his Opposition,[108] Dr. Gentry contends that the phrase "IRB of record" is not in the regulations, and that obtaining local IRB approvals satisfied the record requirement. He states that he obtained local IRB review and approval from the Ministry of Health's ISC and committees at the individual hospitals including Hospital Calderon Guardia.[109] He claims to have submitted documents showing that FDA had previously permitted the sponsor of these studies and other sponsors to utilize these same IRBs.[110] He argues that CDER must prove that the local IRBs failed to satisfy FDA regulations. He also states

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[104] CDER MSD Exhibit 24, 7/30/91 letter from the Vice-Minister of the Costa Rica Ministry Health to Dr. [ ] Chief of Intensive Care, Hospital Mexico. The letter approves protocols for Studies [ ].

[105] In addition to the letter from the Ministry of Health, the record contains letters from Hospital Calderon Guardia's Investigating Committee to Dr.[ ] Chief of the Hospital's Infectious Disease Unit, 2/10 and 11/92, stating that the Committee had authorized studies[ ]based on the Ministry of Health approval.

[106] CDER MSD p. 14.

[107] Id., pp. 14-15.

[108] Gentry Opposition pp. 14-16.

[109] Id., Exhibit 2, p. 25; NIDPOE Response pp. 20-23 and attachments 17-22.

[110] NIDPOE Response p. 20; attachment 20 to the NIDPOE Response includes Forms FDA 1572 from 1988 and 1990, listing committees in individual hospitals but not including Hospital Calderon Guardia, and not including the Ministry of Health ISC.

that after obtaining the local approvals, he obtained a national IRB approval[ ] at the sponsor's urging for added assurance.[111]

I conclude that Dr. Gentry was required to obtain the approval of the[ ]IRB before he initiated studies at Hospital Calderon Guardia. Because he did not do so, he violated the regulations as alleged by the Center.

Dr. Gentry listed the[ ]IRB as the only IRB for the Costa Rica studies, when he submitted the Forms FDA 1572 to the FDA for studies[ ]and[ ]in March 1992.[112] He did not list the local committees in these or subsequent Forms FDA 1572 even though the local committees had "approved" the studies before Dr. Gentry submitted any of the forms.[113]

Dr. Gentry was aware of the need for the[ ]IRB to approve the research sites. In addition to earlier actions,[114] he submitted a request to the[ ]IRB in October 1992 to add Hospital Calderon Guardia as a site for studies[ ]and[ ][115] He also submitted Forms FDA 1572 to FDA in October 1992 to add Hospital Calderon Guardia as a site; again, he listed[ ]as the only IRB for the Costa Rica studies.[116]

There are several problems with Dr. Gentry's explanations with regard to the local IRBs. First, the explanations are incomplete. The record contains no evidence that

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[111] NIDPOE Response pp. 20-23. Dr. Gentry provides two different explanations for "adding" the[ ] IRB: to provide an additional level of assurance with respect to the protection of human subjects, NIDPOE response at 20, and "to facilitate the coordination of IRB approval at multiple sites, and to facilitate records retention at one local facility." CDER Exhibit 7 p. 40.

[112] CDER MSD Exhibit 9.

[113] Dr. Gentry listed sites in the March 1992 Forms FDA 1572 but did not include Hospital Calderon Guardia.

[114] See 3/11/92[ ]IRB approval of Study[ ]and 3/24/92 approval of Study[ ]and correspondence in which Dr. Gentry obtained[ ]IRB approval for the protocols and the initiation of the studies, including approvals of research sites, NIDPOE Attachments 21 and 22.

[115] 10/13/92 letter from Dr. Gentry to[ ]IRB, NIDPOE Response Attachment 22.

[116] 10/15/92 submissions, see CDER MSD Exhibit 9.

the local committees acted as IRBs under the FDA regulations, for example, by approving the consent forms for the studies, or by providing continuing supervision of the studies. Dr. Gentry provided no documentation that he submitted annual or final reports to the Costa Rica committees, that he sought the approval of the committees on any matter, or that the committees took any action while the studies were underway.[117]

The fact that Dr. Gentry offered several inconsistent explanations for the designation of the [ ] IRB as IRB for the studies further undermines his position.[118] Moreover, the possibility that local committees served as IRBs in earlier studies is irrelevant; but even assuming relevance, the committees identified by Dr. Gentry were only those for individual hospitals and *not including the committee for Hospital Calderon Guardia.*[119] Finally, his position is illogical, i.e., it makes little sense to have three IRBs for studies at one site [ ] Ministry of Health ISC and Hospital Calderon Guardia IC) considering the possibilities for conflict and duplication among the IRBs.

In sum, Dr. Gentry's explanations appear to be post hoc rationalizations.[120]

I conclude that Dr. Gentry failed to ensure that the part of the investigation conducted at Hospital Calderon Guardia was subject to approval and continuing review by the IRB designated on the Forms FDA 1572, in violation of regulations listed above. Approval of the research site is an inherent part of the IRB function. This is evidenced

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[117] The fact that the 2/10 and 2/11/92 letters from the Hospital Calderon Guardia committee were addressed to the head of the Infectious Disease Unit (and not Drs. Gentry or [ ] suggests that the "approval" was an internal clearance for the study to be conducted within the hospital. NIDPOE Response Attachments 18 and 19.

[118] See footnote 113 above.

[119] NIDPOE Response Attachment 20.

[120] CDER's contentions that the ISC approval was limited to Hospital Mexico, and that the local committees were unaware of the existence of the studies, are disputed by the record. The Hospital Calderon Guardia IC concluded that the ISC approval covered research in Calderon Guardia, and the committees were obviously aware of the existence of the studies because they approved them.

by the actions of the [ ] IRB with respect to approval of Dr. Gentry's studies, and is supported by the regulations: "*IRB approval* means the determination that the clinical investigation has been reviewed and *may be conducted at an institution* ... ." 21 C.F.R. § 56.102(m).[121] (emphasis added)

I conclude that the violations were repeated, i.e. Dr. Gentry failed to obtain IRB site approval for two studies. They were also deliberate. Dr. Gentry ignored the regulation's requirement for ensuring continuing IRB review of the studies. Dr. Gentry received a copy of an August 19, 1992 letter from the sponsor to the [ ] IRB stating that the Hospital Calderon Guardia would not participate in studies [ ] and [ ][122] Thus, before the first patient was enrolled at Hospital Calderon Guardia (September 9, 1992) Dr. Gentry was aware of the sponsor's position that the [ ] IRB was the IRB for the study. Nevertheless Dr. Gentry did nothing to obtain [ ] IRB approval of the site until October 1992. Dr. Gentry's failure to act exhibited a reckless disregard for whether or not FDA's regulatory requirements were met, indeed, his conduct assured that the regulation would be violated.

There are no factual issues for hearing. I conclude that Dr. Gentry repeatedly and deliberately violated the regulations as charged by the Center.

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[121] Dr. Gentry also violated 21 C.F.R. § 312.60 by initiating the study at Hospital Calderon Guardia without having submitted a Form FDA 1572 that listed the hospital. That regulation requires an investigator to conduct the study in accordance with the signed investigator statement. However, CDER did not make this charge and so I will not utilize it as a basis for my conclusion.

[122] NIDPOE Exhibits 21 and 22.

Charge 5 – Listing of Subinvestigators

The Center alleges that Dr. Gentry did not include the names of three physician subinvestigators (Drs. [ ] in the investigator statements (Forms FDA 1572) he signed.[123] CDER charges violations of 21 C.F.R. §§ 312.53(c)(1)(viii)[124] and 312.60.[125]

According to CDER, Dr. [ ] was listed as the only subinvestigator on the Forms FDA 1572 signed by Dr. Gentry,[126] but he did not have direct contact with the subjects.[127] Instead, he delegated responsibility to the three physicians to perform all activities related to each protocol, including the administration and dispensing of study medications.[128]

CDER points out that Dr. Gentry admitted that it would have been appropriate to identify the three physicians on the form.[129]

CDER contends that the violations were repeated and deliberate. Dr. Gentry signed the Forms FDA 1572, which required listing of all subinvestigators. He "has not indicated that he was even aware that these three subinvestigators administered and dispensed study medications ...."[130]

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[123] CDER MSD pp. 18-20.
[124] This subsection requires that the names of the subinvestigators who will be assisting the investigator in the conduct of the investigations be listed in the Form FDA 1572.
[125] This section states that the investigator is responsible for ensuring that the investigation is carried out according to the signed investigator statement, the investigational plan and applicable regulations.
[126] CDER MSD Exhibit 9.
[127] CDER MSD Exhibit 2, p. 28; Exhibit 6, p. 19; Exhibit 7, pp. 37-38).
[128] "The Clinical Coordinators [Drs. [ ] were responsible for performing the routine duties required by each protocol that included: recruiting and screening candidates for enrollment, discussing and explaining the consent forms, explaining the patient about [sic] study objective and compliance with medication therapy, obtaining and coordinating delivery of blood samples, physical examinations, providing follow-up to subjects' clinical response, filling [sic] the Case Report Forms (CRFs), delivering study medication to the patient and sending unused medication to the drug custodian." CDER MSD Exhibit 11, p. 4.
[129] NIDPOE Response p. 19.
[130] CDER MSD Exhibit 2, p. 28.

Dr. Gentry moves for summary decision on the ground that "[a]s a matter of law, Dr. Gentry lacks notice of whom FDA would consider a 'subinvestigator.'"[131] Dr. Gentry asserts that the term has not been defined clearly in the regulations, and that FDA admits this.[132]

Dr. Gentry also argues in his Opposition[133] that the three physicians were considered "clinical coordinators" by Dr. [ ] because they were responsible for certain study-related activities such as documenting informed consent from the patients and completing case report forms.[134] Dr. Gentry claims that CDER does not controvert that assertion, but rather disputes Dr. Gentry's interpretation of the term "subinvestigator." This, according to Dr. Gentry, raises genuine issues of fact.

Dr. Gentry argues, moreover, that in view of the uncertainty of the definition of "subinvestigator," CDER cannot establish that the omission was deliberate. Even if Dr. Gentry violated the regulation, CDER cannot show that the violation was widespread or pervasive, or resulted from deliberate indifference or a refusal to be informed.

CDER responds[135] that 21 C.F.R. § 312.3(b) defines "subinvestigator" to include any other individual member of a team (in addition to the investigator) if the investigation is carried out by a team.[136] Further, the preamble to the final rule adopting

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[131] Gentry MSD p. 8.
[132] Gentry MSD pp. 8-9, Gentry Opposition Exhibit 2 pp. 28-9; Gentry Opposition Exhibit 7 (press article dated June 12, 2000 quoting FDA's Dr. Robert Temple as stating that the definitions of "investigator" and "subinvestigator" are "variable and imprecise.").
[133] Gentry Opposition pp. 18-19.
[134] Id., Exhibit 2, p. 28.
[135] CDER Opposition pp. 5-6.
[136] "*Investigator* means an individual who actually conducts a clinical investigation (i.e. under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." 21 C.F.R. § 312.3(b).

21 C.F.R. § 312.23 states that "subinvestigator" includes "all other professionals who assist the principal investigator in the design and conduct of the investigation."[137]

I conclude that Dr. Gentry violated the regulations as alleged because he did not list the names of the three physicians in the Forms FDA 1572. In reaching my conclusion, I have carefully examined all the references cited by both parties. I am compelled, of course, to give most weight to the definition contained in the regulations. The pertinent section, 21 C.F.R. § 312.3(b), defines "subinvestigator" to include "any other individual member [in addition to the principal investigator] of that team [that conducts the investigation]." Without question, the three physicians were members of the team that conducted the studies. Although the investigator need not list persons who are involved in the study but who assume no responsibility for the study's conduct,[138] it is clear that the three physicians did assume responsibilities for the conduct of the studies, e.g., for recruiting and screening candidates for enrollment, explaining the consent forms, conducting physical examinations, providing follow-up to subjects' clinical response and delivering study medications to the subjects.[139]

Dr. Gentry is responsible for knowledge of pertinent regulations, e.g., the definition of "subinvestigator" contained in 21 C.F.R. § 312.3(b). In addition, Dr. Gentry had specific notice of the definition when he signed Forms FDA 1572 that "subinvestigator" includes those persons "...(e.g. research fellows, resident associates)

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[137] 21 C.F.R. § 312.23, which specifies content and format for the Investigational New Drug Application, requires that the protocol submitted by the sponsor include the name of each subinvestigator. 21 C.F.R. § 312.23(a)(6)(iii)(b). The preamble states that "'subinvestigator' includes all other professionals who assist the principal investigator in the design and conduct of the investigation ... [it] would not include those professionals and other assistance [sic] who assume no responsibility for the conduct of the study." 52 Fed. Reg. 8798, 8809-10 (March 19, 1987).
[138] Id.
[139] CDER MSD Exhibit 11, p. 4.

who will be assisting the investigator in the conduct of the investigation(s)." Further, as explained above the language in the preamble to 21 C.F.R. § 312.23 supports CDER's position.

References cited by Dr. Gentry[140] are of limited relevance or persuasiveness in part because most were published after Dr. Gentry's studies were completed; but to the extent that they are relevant several references actually support CDER's position. For example, Dr. Gentry cited the definitions of "clinical investigator" and "subinvestigator" that are included in financial disclosure regulations.[141] The regulation in fact defines a "subinvestigator" for the purpose of that regulation as one who is "directly involved in the treatment or evaluation of research." 21 C.F.R. § 54.2(d). In addition, the preamble to that regulation states that "most of the individuals participating in the conduct of a clinical trial could be described as subinvestigators."[142]

Dr. Gentry also relies on a statement, attributed to FDA's Dr. Robert Temple and contained in a third party press release, that the definition of subinvestigator is "variable and imprecise."[143] However, Dr. Gentry does not assert that the quote, even if accurate, represents an official statement by the agency. Two other documents cited by Dr. Gentry, FDA's "Frequently Asked Questions,"[144] published in 1995, and the International Conference on Harmonization Consolidated Guidelines on Good Clinical

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[140] Gentry MSD p. 8, fn. 3.
[141] 21 C.F.R. § 54.2(d), incorrectly cited by Dr. Gentry as 21 C.F.R. § 54.3(d).
[142] 63 Fed. Reg. 72171, 72173-4 (December 31, 1998).
[143] See footnote 132 above.
[144] Gentry Opposition Exhibit 8, "Frequently Asked Questions Concerning the Identification of Persons Involved in a Study and Their Responsibilities" (FDA Clinical Investigator Information Sheet), Response to Question 1 (March 1995).

Practices, published in 1997,[145] essentially restate the definition contained in 21 C.F.R. § 312.3(b)

Thus, I disagree with Dr. Gentry's argument, made in support of his request for summary decision, that as a matter of law Dr. Gentry lacks notice of whom FDA would consider a subinvestigator. I find that there is no genuine and substantial issue of material fact that warrants a hearing.

The violations were repeated because they involved three studies, and more than three Forms FDA 1572. They were also deliberate because even if I were to concede that the regulation was unclear, Dr. Gentry's failure to contact FDA and clarify the requirement as it applied to his study amounted to a reckless disregard for whether or not his actions complied with the requirements of the regulation. I conclude that Dr. Gentry repeatedly and deliberately violated the regulations as alleged, and that there are no factual issues for hearing.

Charge 6 -- Lack of Supervision and Submission of False Information

CDER alleges that Dr. Gentry did not personally conduct or supervise the clinical studies, which he committed to do when he signed the Forms FDA 1572. The Center charges that Dr. Gentry thereby violated 21 C.F.R. § 312.53(c)(1)(vi)(c), which requires the investigator to personally conduct or supervise the study, and 21 C.F.R. § 312.60, which requires compliance with the Form FDA 1572. CDER further alleges that

[145] 62 Fed Reg. 25692, 25694-5 (May 9, 1997).

Dr. Gentry's failure to supervise the studies properly caused the submission of false information in violation of 21 C.F.R. § 312.70(b).[146]

Charge 6A – Lack of Supervision

The Center alleges that Dr. Gentry failed to personally conduct or supervise clinical studies as evidenced by the following examples: Charge 1A (failure to maintain x-ray films for the required period of time, and failure to assure that radiology reports were signed and dated); Charge 1B (failure to maintain adequate records); Charge 1C (failure to maintain subject enrollment screening log or source documents); Charge 5 (failure to list subinvestigators in Forms FDA 1572); and Charge 7 (reclassification of clinical outcome).[147] CDER further alleges that these violations show that Dr. Gentry did not adequately review the study records to ensure that they were being prepared and maintained properly.

CDER did not allege either repeated or deliberate violations in this charge, although it did so in the underlying violations used as examples.

Dr. Gentry's request for summary decision is based primarily on his allegation that CDER has not cited any specific facts to support its allegation that Dr. Gentry failed to personally conduct or supervise the clinical investigation.[148] In his Opposition,[149] Dr. Gentry argues that CDER has not shown that he failed to personally conduct or supervise the studies. He contends that CDER does not cite regulatory standards defining

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[146] CDER MSD pp. 20-23.

[147] CDER MSD pp. 21-2.
[148] Gentry MSD p. 12.
[149] Gentry Opposition pp. 19-21.

supervisory requirements, or facts to demonstrate that Dr. Gentry failed to meet these standards.[150]

Dr. Gentry asserts that he has shown that he complied with the standards of conduct prescribed by FDA for principal investigators in multi-institutional studies conducted at separate geographic locations.[151] He claims that these standards require that the investigator have full access to study records, but that the investigator is not required to have direct contact with subjects at each separate facility.[152]

Dr. Gentry states that he accomplished the following to comply with the standards: he had a long-standing professional relationship with Dr.[ ]he served as sole interface with the sponsor; he had access to all relevant records and information; he conducted a visit to the Costa Rican sites during the critical time period before the studies were initiated; and he worked continuously with Dr.[ ]and his staff including having frequent telephone conferences and several off-site meetings.[153]

Thus, Dr. Gentry contends, there is a genuine issue of material fact precluding summary decision for CDER. Further, Dr. Gentry argues that unless CDER can prevail on summary decision on "the unrelated substantive charges" (those listed as examples of failure to supervise), CDER cannot obtain summary decision on the charge of failure to supervise the studies adequately.[154]

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[150] Dr. Gentry contrasts his case by citing an example of an FDA Warning Letter in which the investigator did not have record access, did not visit the site, and did not identify the primary subinvestigator at that site. Gentry Opposition, p. 20.

[151] Id., p. 20, n. 16. Dr. Gentry previously asserted that the allegation of failure to supervise "is not an appropriate basis for disqualification 'when the FDA reviewing division permitted the sponsor to proceed with the IND under circumstances where a principal investigator has responsibility for conduct of studies at separate geographic sites.'" CDER MSD p. 21; Exhibit 2, pp. 29-30; NIDPOE Response, pp. 23-5.

[152] Citing FDA's "Frequently Asked Questions," Gentry Opposition Exhibit 8.

[153] Gentry Opposition p. 20, no. 16.

[154] CDER's Opposition essentially repeats the arguments contained in its MSD. CDER Opposition pp. 6-7.

I conclude that Dr. Gentry failed to supervise the studies as evidenced by the other substantive violations that I have found Dr. Gentry to have committed.[155] These violations, as CDER suggests, indicate that Dr. Gentry did not adequately review study records and take appropriate corrective action with respect to the conduct of the investigation by the subinvestigators. Thus, I disagree with Dr. Gentry's contention that CDER failed to cite specific facts to supports its allegations.

CDER's allegation of failure to supervise is based primarily on *results* (i.e. failure to supervise *resulted* in specific acts or omissions that were serious enough to constitute separate violations of the regulations), and that these violations indicate that Dr. Gentry did not adequately review the records. These violations were enough to meet CDER's burden of proof in this charge.

It could be argued that relying on a group of violations to establish violation of a separate regulation is superfluous or amounts to "double counting." I believe that these considerations are directed to the Commissioner's discretion, and that CDER's position is defensible in that the group of violations can be used as evidence of failure to supervise. Alternatively, the underlying acts and omissions, rather than the conclusions with respect to substantive violations, can be used as evidence of a failure to supervise. The pervasiveness with which these acts and omissions permeate the studies establishes the lack of supervision as the central focus for this disqualification proceeding.

Dr. Gentry's defense is based primarily on a contention that he followed proper *process*, although he does seem to acknowledge that a summary decision for failure to

[155] Charges 1A and B, Charge 2 and Charge 5. CDER did not include Charge 2 in its examples, but it is obvious evidence of a failure to supervise.

supervise could be based on summary decisions on the substantive violations.[156] However, his proposed definition of proper process is extremely limited,[157] and his contention that he followed proper process is based on generalities.[158] As explained above, he is required to set forth specific facts to show there is a genuine issue for hearing. Dr. Gentry did not provide evidence that he took actions that would be expected of someone who is a supervisor, including review of records. Dr. Gentry not only had access to the study records in Costa Rica, but also the CRFs were sent to him in Houston "to enable Dr. Gentry to review and order any needed corrections or additions."[159] Nevertheless, he made no allegation, much less provided evidence, that he actually reviewed any of the records. Nor did he offer any evidence that he took any corrective action during the course of the study, whether as a result of records review or otherwise.

Dr. Gentry's failure to supervise the studies resulted in a number of regulatory violations; therefore, his failure to supervise the study resulted in multiple violations. His failure to review the study records maintained by his subinvestigators to ensure compliance with FDA regulation demonstrated a reckless disregard for whether FDA requirements were being met during the study. His failure to supervise the studies was therefore deliberate. There are no factual issues for hearing on this charge

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[156] "Unless CDER can prevail on summary decision on the related underlying charges – which it cannot – CDER cannot obtain summary judgment that the underlying charges prove a failure to supervise." Gentry Opposition p. 21.

[157] As noted earlier, Dr. Gentry states that the standards for multi-institutional studies require the investigator to have full access to study records, but that the investigator is not required to have direct contact with subjects at each separate facility.

[158] e.g. "had a long-standing professional relationship with Dr. [ ] "had access to records," and "conducted a site visit."

[159] CDER MSD Exhibit 2, p. 19.

3. Summary Judgment Requests Denied or Decision Deferred

Charge 1C – [ ] Screening Log

The Center alleges that Dr. Gentry did not maintain a subject enrollment screening log, or source documents in lieu of a log, to document that approximately 150 subjects were screened. The Center charges a violation of 21 C.F.R. § 312.62(b) for failure to maintain required records, and 21 C.F.R. § 312.62(c) because the records were not maintained for two years.[160]

As evidence, CDER points to Dr. Gentry's final report to the [ ] IRB, March 17, 1993, which stated that 150 subjects were screened.[161] Dr. [ ] admitted that screening logs were not available for review at the time of inspection.[162] Dr. [ ] submitted an incomplete screening log in response to the NIDPOE.[163]

CDER contends that the violations were repeated and deliberate, the latter because Dr. Gentry had a duty to know and understand requirements for conducting clinical studies.

In his Opposition[164] and in his request for summary decision on this issue,[165] Dr. Gentry argues that the regulation does not require an investigator to maintain a screening log; that after he initiated the study FDA issued non-binding guidance suggesting that screening logs be maintained;[166] and that the study protocol did not require a screening log.[167]

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[160] CDER MSD pp. 11-12.
[161] Id., Exhibit 21.
[162] Id., Exhibit 11, p. 3.
[163] Id., Exhibit 22. The log listed only 13 subjects and incorrectly identified Dr. [ ] as the Investigator.
[164] Gentry Opposition pp. 13-14.
[165] Gentry MSD p. 7.
[166] Id., Exhibit 2, p. 24; NIDPOE Response p. 14, attachment 14.
[167] Id., Exhibit 2, p. 24; NIDPOE Response p. 14.

Dr. Gentry argues that the function of a screening log is provide information on subjects that are not enrolled, to provide an ability to assess for potential bias in the screening process. Thus, the screening log has a different purpose than the case report forms for enrolled subjects.[168]

In its Opposition, the Center argues that although the regulation does not specifically require a screening log, it does require adequate and accurate case histories. The problem, according to CDER, is that Dr. Gentry did not maintain adequate source documents to explain how he determined that 150 subjects were screened.[169]

I must deny CDER's motion because the Center has not articulated a legal basis for its charge. The regulation CDER relies on, 21 C.F.R. § 312.62(b), requires the investigator to maintain records related to "each individual *administered the investigational drug or employed as a control* in the investigation." (emphasis added). Therefore, the regulation does not appear to impose any record-keeping requirements related to persons not enrolled in the study. Although fifty-nine of the 150 persons allegedly screened were accepted into the study,[170] CDER does not explain the function of screening as related to those accepted into the study vis-à-vis those who were not accepted. Significantly, CDER does not dispute Dr. Gentry's contention that the purpose of screening records is to account for those individuals who were not selected.

I will therefore deny CDER's Motion for Summary Decision on Charge 1C because I find that CDER did not establish that Dr. Gentry violated the regulation as charged. I will also deny Dr. Gentry's request for summary decision. I will not rule out the possibility that a legal basis could be found for requiring documentation (not

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[168] Gentry Opposition, p. 14.
[169] CDER Opposition p. 4.

necessarily limited to a screening log per se) supported by policy considerations, e.g., assessment of potential for bias in the selection process as articulated by Dr. Gentry. CDER did not establish an adequate basis for its position but, on the other hand, Dr. Gentry's argument did not rule it out.

Charge 3 -- Drug Shipment Records

CDER alleges that Dr. Gentry did not maintain adequate records to document shipment of study medications used in studies[ ] from the study site in Houston to Costa Rica.[171] The Center charges that Dr. Gentry violated 21 C.F.R. § 312.62(a), which requires the keeping of adequate records of drug disposition and, in addition, 21 C.F.R. § 312.62(c) because he did not maintain the adequate records for the required period of time.

CDER contends that the shipment records were inadequate for the following reasons:

(1) Air bills were not retained for all lots,[172] and the air bills that were retained state only that the shipment contained "medical supplies" without further explanation;

(2) Numerous drug inventory memos were undated or unsigned; and

(3) Dates of claimed shipment precedes dates when Dr. Gentry received the study drugs in Houston from the sponsor.[173]

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[170] CDER MSD Exhibit 21, p. 1.
[171] CDER MSD pp. 15-17.
[172] CDER claims that Dr. Gentry admitted this deficiency with the following statement: "[The] NIDPOE response contains a tabular summary ... and, for *some lots for which an airbill has been maintained*, the exact date of shipment to Costa Rica." CDER MSD Exhibit 2, p.26 (emphasis added). The tabular summary submitted with the NIDPOE Response shows sponsor shipping information, Gentry inventory memos, and shipment to Costa Rica. NIDPOE Response pp. 16-18.
[173] CDER cites one example and claims that there are additional examples. CDER MSD p. 16, n. 7.

In addition, CDER alleges that Dr. Gentry did not account for Lot #[ ](two boxes of Augmentin 500 mg tabs) in Protocol[ ]The drugs were received by Dr. Gentry from the sponsor and designated for subjects 1101-1120 in[ ][174] However, CDER asserts that Dr. Gentry did not enroll subjects with those numbers in study [ ]at his study sites,[175] and that Dr. Gentry has not provided records to document how he used and/or disposed of the medications.

CDER charges that the violations were repeated and deliberate, the latter because in addition to being an experienced clinical investigator, Dr. Gentry had previous warning that he had maintained inadequate records of disposition of drugs.[176]

In his Opposition,[177] Dr. Gentry maintains that he kept careful records of study drugs, based on procedures established over a number of years.[178] He argues that CDER does not attempt to prove that particular lots could not be traced, but takes issue with the form of the documentation; therefore CDER fails to establish the inadequacy of the records.

Dr. Gentry argues that his documentation shows the particular lots shipped to Costa Rica, the amount and dosage form shipped, and other pertinent information. Airbills were submitted as further proof of shipment.[179]

With regard to CDER's allegation that drug shipment dates preceded dates on which Dr. Gentry received the drug, Dr. Gentry maintains that drug inventory

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[174] CDER MSD Exhibit 26.
[175] Subjects in[ ]were assigned randomized numbers 1301 through 2120. CDER MSD Exhibit 11, p. 19.
[176] CDER MSD Exhibit 27, letter from Dr. Kelsey, FDA to Dr. Gentry 2/1/85.
[177] Gentry Opposition pp. 16-17.
[178] NIDPOE Response pp. 16-18, attachment 15. Dr. Gentry argues that the 1985 letter reminding Dr. Gentry of record keeping requirement doesn't show that Dr. Gentry violated the regulations repeatedly or deliberately. He argues that facts show that in the years since the letter issued, Dr. Gentry had established adequate practices to assure that drug lots could be traced.

memoranda (which showed drug shipment dates) were occasionally prepared while the drugs were enroute from the sponsor, to expedite processing; once received, the drugs were shipped to Costa Rica.[180]

Concerning the allegation that Dr. Gentry did not account for unused drug (lot # [ ] Dr. Gentry declares that as a routine practice, a representative of the study sponsor came on site (Houston and Costa Rica) and took responsibility for returning unused study drugs.[181]

I will deny summary decision to CDER because I find that CDER did not adequately articulate the criteria for determining whether the regulation was violated, and because genuine factual issues exist.

The applicable regulation, 21 C.F.R. § 312.62(a), requires the investigator to "maintain adequate records of the disposition of the drug including dates, quantity and use by subject."[182] The regulation does not specify what is "adequate." I understand that the regulation's purpose is to require records sufficient to establish accountability – in this case, that the drugs received by Dr. Gentry were actually shipped to Costa Rico or returned to the sponsor.

However, CDER did not reference any guidelines, provide affidavits by qualified persons, or otherwise define what would have been "adequate" in this case, i.e., what is necessary to establish accountability.[183] Nor did the Center explain the purposes for the various requirements it would impose. For example, CDER did not establish the need for

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[179] Gentry Opposition p. 16.
[180] Declaration of [ ] Gentry Opposition Exhibit 6.
[181] Id.; Gentry Opposition Exhibit 2, pp. 19, 27. The declaration does not document return of the specific lot at issue, but only explains the usual practice.
[182] The focus of the CDER's charge is not on disposition for use by the subjects, but at an earlier stage – receipt by Dr. Gentry and shipment to Costa Rica.

airbills to specify the particular medications that were being shipped, when one considers that the other shipment documentation provided by Dr. Gentry did show the details. Further, contrary to CDER's assertions, all of the drug inventory memos submitted by Dr. Gentry and included in the record were dated, and all but one were signed.

Finally, Dr. Gentry raised genuine factual issues as to whether the records showing that the date of claimed shipment preceded the date shown for drug receipt in fact represented discrepancies in drug shipments, and whether lot #[ ](unused drug) was properly accounted for.

Accordingly, I will deny CDER's request for summary decision on this charge.

Charge 4 -- Baseline Blood Sample

CDER alleges that the baseline blood sample for one subject (#1403) was collected after the first administration of the test drug, and that this constitutes failure to conduct study[ ]in accordance with the approved protocol.[184] This incident, according to CDER, violates 21 C.F.R. §§ 312.53(c)(1)(vi)(a)[185] and 312.60.[186]

CDER states that the protocol requires baseline blood samples to be collected prior to administration of the study drug.[187] CDER contends that the records show that study treatment for subject #1403 was initiated on September 24, 1992,[188] but that the

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[183] Dr. Gentry's point that CDER does not attempt to prove that particular lots could not be traced is well taken.
[184] CDER MSD pp. 17-18.
[185] This subsection provides that the investigator statement will contain a commitment to conduct the studies in accordance with the relevant, current protocol.
[186] This subsection requires the investigator to conduct a study in accordance with the signed investigator statement, the investigational plan and applicable regulations.
[187] CDER MSD Exhibit 28, Protocol for[ ]sections V.A.4. and 5.
[188] Id. Exhibit 29.

baseline blood sample for #1403 was collected the next day, September 25, 1992.[189] However, CDER does not allege that the violation was repeated or deliberate.

In his Opposition,[190] Dr. Gentry states that he and [ ] believe that the samples were in fact taken on September 24, the appropriate date, because of their standard procedure of not taking blood samples on Fridays (September 25, 1992 was a Friday). They believe that the clinical coordinator entered the wrong sample date.[191] Dr. Gentry also argues that even if CDER is correct, one protocol deviation is neither "repeated" nor "deliberate."

I conclude that Dr. Gentry's explanation raises a genuine issue of fact for hearing. Therefore, I find that CDER did not establish that the regulations were violated as charged, and I will deny summary decision to the Center.

Charge 6B – Submission of False Information

The Center alleges that Dr. Gentry submitted false information to the sponsor in required reports, because of his failure to supervise the studies properly.[192] The failure to supervise resulted in submission of false information because of violation of the following separate charges: Charge 1B (failure to maintain adequate records); Charge 1C (failure to maintain subject enrollment screening log or source documents); Charge 5 (failure to list subinvestigators in Forms FDA 1572), and Charge 7 (reclassification of clinical outcome). Presumably, CDER's position is that Dr. Gentry submitted false

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[189] Id. Exhibits 29 and 30.
[190] Gentry Opposition, pp. 17-18.
[191] Gentry Opposition Exhibit 2, p.27 and attachment 8; NIDPOE Response p. 7.
[192] CDER MSD pp. 20-23.

information when, for example, he submitted documents containing data discrepancies (Charge 1B) and omitted subinvestigator names on Forms FDA 1572.

The Center charges Dr. Gentry with a violation of 21 C.F.R. § 312.70(b), which provides for disqualification for repeatedly or deliberately submitting false information to FDA or the sponsor in any required report.

CDER contends that the violations were repeated and deliberate. The Center argues that Dr. Gentry was responsible for knowing the requirements for conducting clinical studies, and that the examples cited show his reckless disregard for the regulations' requirements.

Dr. Gentry argues that he should be granted a summary decision on this allegation because inclusion of this allegation violated his right to adequate notice;[193] because the allegedly false information was not material; and because the record does not support a finding that Dr. Gentry failed to supervise adequately.[194]

Dr. Gentry reiterates most of these arguments in his Opposition to CDER's Request for Summary Decision.[195] He argues that CDER has not established that Dr. Gentry failed to supervise the studies, so there is no basis for the charge of submitting false information. Further, he argues that substantial issues of *material* fact exist as to each of the statements that CDER contends are "false."[196] He states that CDER has not met its burden of establishing that the *data discrepancies* were material to the study outcome. He also states that a *screening log* was not a required report, and there is no

[193] The charge was not included in the NIDPOE but was added in the NOOH.
[194] Gentry MSD pp. 9-16.
[195] Gentry Opposition, pp. 22-3.
[196] See discussion of materiality under charge 1B.

evidence in the record to show that it was ever submitted to the sponsor.[197] Finally, he argues that the *reclassification* of clinical outcome (see charge 7, below) was done at the sponsor's urging, and was accompanied by a documented audit trail.[198] The reclassification was not material to the study outcome because the FDA reviewer understood the significance of the classification.[199]

In its Opposition,[200] CDER argues that "false information" is not required to be "material." The Center asserts that Dr. Gentry incorrectly cites the 1978 proposed rule, which stated that disqualification is appropriate when the quality and integrity of the studies "have probably been compromised." CDER notes that the final rule did not include this criterion, although FDA stated that it has the discretion not to disqualify an investigator if violations are insignificant. However, CDER contends that the false information submitted by Dr. Gentry was not only significant but also was material. Inaccurate information submitted in the CRFs corrupts the integrity of the investigation and has the potential to endanger the subjects and the public health, according to CDER.

I will not decide this charge. A decision on this charge is not needed to reach a decision on disqualification. CDER's theory is novel and complex; that is, the theory depends on violations at three levels – the Center argues that a group of violations of separate regulations (first level) establishes a different violation (failure to supervise) which in turn establishes still another violation (submission of false information). I have found that only two of the four first-level charges cited by CDER (Charges 1B and 5) are

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[197] Dr. Gentry apparently refers to the incomplete log he submitted to FDA, presumably contending that since it was not submitted to the sponsor it was not material. 21 C.F.R. § 312.70(b) applies to false information submitted "to FDA or to the sponsor."
[198] NIDPOE Response Attachment 4.
[199] See further discussion of this issue in Charge 7, below.
[200] CDER Opposition, pp. 10-13.

substantiated.[201] Further, although I agree with CDER that materiality is not the test for determining whether submitted information was false, the Center's evidence to support the false information charge is not clearly articulated but appears to be unconventional. I do not believe that CDER's addition of this charge at the NOOH stage denied Dr. Gentry due process, but the late addition does tend to support my decision not to decide this issue.

Similarly, I do not believe that Dr. Gentry's argument establishes that, as a matter of law, he did not submit false information. I do not wish to rule out the possibility that properly developed presentations based on these facts could lead to a decision for either party. Therefore I will not decide either motion.

Charge 7 – Reclassification of Clinical Outcome[202]

The Center alleges that Dr. Gentry reclassified the clinical outcome of one subject (#801), who had been given a non-study antimicrobial, from "unable to evaluate" to "improved." The protocol for the study, [ ] requires classification of "unable to evaluate" in such circumstances.[203] The Center charged violation of 21 C.F.R. §§ 312.62(b) and (c), which require the investigator to prepare and maintain adequate and accurate records of all observations, and 21 C.F.R. §§ 312.53(c)(1)(vi)(a) and 312.60, which require the investigator to conduct a clinical study in accordance with the approved protocol.

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[201] I have found, however, that the charge of failure to supervise (second level violation) is sustainable on a substantially different set of first level violations.
[202] The subject involved in this charge was at the Houston site.
[203] CDER MSD pp. 23-25.

The Center submitted evidence of the change in the evaluation[204] and the protocol provision it contended was violated.[205] CDER contends that Dr. Gentry admitted to the reclassification.[206] The Center asserts that the violation was deliberate, because the Forms FDA 1572, which Dr. Gentry signed,[207] required the investigator to follow the protocol, making changes only after notifying the sponsor; and Dr. Gentry did not follow the protocol in this case.

In his Opposition,[208] Dr. Gentry disputes that the reclassification violated study procedures. He states that the change was undertaken after the sponsor informed Dr. Gentry that such a change was consistent with more recent FDA expectations and policy, in particular a 1992 "Points to Consider" document.[209] Dr. Gentry asserts that the sponsor did not suggest that the *protocol* be amended, but instead sought to correct the out-of-date protocol on a case by case basis through a CRF review process. He argues

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[204] Id., Exhibit 33, Clinical Data Correction Form.
[205] Id., Exhibit 32, Protocol for section V.F.2.
[206] Id., Exhibit 2, pp. 32-33; NIDPOE Response, pp. 3-5.
[207] Id., Exhibit 9.
[208] Gentry Opposition pp. 23-4.
[209] NIDPOE Response pp. 3-5 and attachments 3-5. Dr. Gentry asserts that the FDA investigator did not understand that under post-protocol FDA guidelines, there was a difference between clinical response and evaluability. (1) A clinical response (cured, improved, etc.) can be determined for all patients except those lost to follow up. In the latter situation, the only appropriate clinical response is "unable to evaluate." This policy is reflected in a 1992 "Points to Consider" document, and acknowledged in the FDA medical officer's review. (Attachment 3 to the NIDPOE Response is an excerpt from the Medical Officer's review). The sponsor did not amend the protocol, which required "unable to evaluate" for subjects administered non-study antimcrobials, but (Dr. Gentry alleges) addressed the issue through the Case Report Form review process. Patient 801 was inadvertently administered vancomycin on the fourth day of the study. Although the patient was evaluated and did improve (as expected with a mixed infection), Dr. Gentry assessed the patient as "unable to evaluate." The sponsor asked for confirmation; Dr. Gentry confirmed the evaluation. NIDPOE Response Attachment 4 (Clinical Data Correction Form). The sponsor again asked for reconsideration, citing the FDA guidelines. This time, Dr. Gentry assigned "improved" to the patient. CDER MSD Exhibit 33; NIDPOE response pp. 3-5. (2) "Evaluability is assigned by the sponsor ... and is based upon prospective criteria described in the study protocol. Administration to the patient of effective concomitant therapy is identified in protocol [ ] as precluding the patient from being evaluable for efficacy (citing p. 20 of the protocol). Accordingly, patient #801 was not presented by the sponsor to FDA as evaluable for the analysis of efficacy." NIDPOE Response p. 5.

that CDER's assertion that Dr. Gentry did not document this contention[210] is not sufficient to justify summary decision; he asserts that CDER does not deny there was an agreement to reclassify this subject, and that he will prove this point at a hearing.

Dr. Gentry further claims that the FDA reviewer understood that the clinical response rating of "unable to evaluate" would be assigned only where a subject was lost to follow-up.[211] Although the subject was given a clinical rating of "Improved" the subject was not evaluated for efficacy; thus the reclassification was not material.

Finally, Dr. Gentry argues that the protocol did allow for "departure from protocol" so long as the investigator contacted the monitor "to discuss the situation and agree on an appropriate course of action."[212] Dr. Gentry asserts that the requirements for protocol departure were met in this case, as documented on the Clinical Data Correction Form and in a letter from the sponsor.[213] The letter confirmed that the sponsor requested that "a clinical response be assigned."

CDER responds[214] that guidance documents do not relieve an investigator of his obligation to follow the study protocol. The Center further asserts that the "points to consider" document applies only where there was a resolution of symptoms and the subject did not receive additional antimicrobial treatment,[215] but that this subject received additional treatment.

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[210] It is not clear which "contention" Dr Gentry is referring to.
[211] NIDPOE Response p. 4, attachment 3.
[212] Protocol [ ] Amendment # 3 (5/21/92) at 11-12, cited in NIDPOE Response p. 5.
[213] NIDPOE Response attachments 4 and 5.
[214] CDER's response is to Dr. Gentry's pre-motion arguments; see CDER MSD pp. 24-5.
[215] CDER refers to Exhibit 34 to the CDER MSD, and states that exhibit 34 is a page from the guidance document; it actually is a page from the medical review.

The Center argues that there is no documentation of Dr. Gentry's claim that the sponsor instructed him to make the change.[216] In fact, the sponsor only asked Dr. Gentry to verify his original response.[217]

Finally, CDER asserts that the change did not meet the requirements for departure from the protocol. Protocol departure can be done only in writing and with mutual agreement between sponsor and investigator.[218] CDER claims that Dr. Gentry has presented no evidence of such an agreement, and that a protocol amendment was required, citing 21 C.F.R. § 312.30.

This charge raises a number of questions that I am unable to answer based on the record, and therefore I will deny CDER's motion for summary decision with respect to this charge.

First, did the FDA guideline apply? CDER says "no" because it only applies where there was a resolution of symptoms and the subject did not receive additional antimicrobial treatment. However, the guideline is not in the record, so CDER's assertion could not be affirmed. 21 C.F.R. § 16.95(b).

Second, if the guideline did apply, was a protocol revision required? CDER argues that the protocol for study [ ] supports its position that modification of the protocol was necessary, but the protocol is not in the record. Therefore, Dr. Gentry's argument that he followed protocol rules for departure from protocol cannot be verified.

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[216] Dr. Gentry does not explicitly make this argument in the briefs, but CDER concluded that he made the argument in the pre-motion submissions.
[217] Clinical Data Correction Forms, Exhibits 31 and 33.
[218] CDER states that "the relevant section for protocol [ ] is attached as Exhibit 35." However, the language referred in the pages included in Exhibit 35 to governs changes to the protocol, not departures from the protocol.

Third, is Dr. Gentry's explanation that the patient was not evaluated for efficacy relevant and, if so, was the patient in fact not evaluated for efficacy? The parties did not adequately develop the first part of the question. Further, there is no documentation of Dr. Gentry's claim that the patient was not evaluated for efficacy; the sponsor's letter addressed the subject only in general terms.

Fourth, did the sponsor instruct Dr. Gentry to change the clinical response? If so, is that a de facto revision of the protocol? The sponsor letter states that the sponsor requested that "a clinical response be assigned." Arguably, this was a de facto revision of the protocol, but the clinical correction forms in the record seem to indicate otherwise.

In conclusion, I will deny CDER's motion for summary decision on this issue because the record is incomplete on a number of points, and factual issues remain for resolution.

VII. RECOMMENDATIONS

For reasons given in the previous section, I have denied CDER's motion for summary decision on several of the charges that it brought. However, I have also found that Dr. Gentry repeated and deliberately violated a number of regulations as enumerated in section VI.C.1.

The violations are pervasive in that they involve transgressions of several different kinds of requirements including record retention, record authentication, preparation of accurate records, obtaining institutional review board approval for a research site, and supervision of the study. The violations are significant in that they

involve the kinds of deviations from ordinary care that can jeopardize the integrity of clinical studies.

I find that there are no genuine issues of material fact for hearing on any of the charges for which I have found repeated and deliberate violations.

Based on my findings, I recommend that the Commissioner disqualify Layne O. Gentry from being eligible to receive investigational new drugs.

Henry N. Startzman III, M.D.

Henry Startzman, M.D.
Presiding Officer

Date: 9/12/01