

DALEY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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MAR 14 2008

Catherine M. Cook
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5600 Fishers Lane, GCF-1
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Dear Dr. Daley and Counsel:

I have reviewed the record of the regulatory proceeding involving Patrick J. Daley, M.D., including the Center for Biologics and Research's (CBER) Motion to deny Dr. Daley's request for a hearing under 21 C.F.R. § 16.26(a) and to disqualify him under 21 CFR § 312.70, Dr. Daley's Memorandum in Opposition to CBER's Motion, and CBER's Reply Memorandum. Based upon my review, I have concluded that there is no genuine and substantial issue of fact with regard to whether Dr. Daley repeatedly and deliberately violated 21 CFR § 312.70 in connection with an investigational new drug study of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Reassortant Rotavirus Vaccine. I am therefore granting CBER's motion to deny Dr. Daley's request for a hearing and, consistent with 21 CFR § 312.70(b), I have determined that Dr. Daley is no longer entitled to receive investigational drugs. The reasons for this determination are set forth in the enclosed decision.

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

Sincerely,

Janet Woodcock, M.D.
Deputy Commissioner and Chief Medical Officer

Enclosure

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

COMMISSIONER'S DECISION

In this proceeding the Center for Biologics Evaluation and Research (CBER) contends that pursuant to 21 C.F.R. Parts 16 and 312 Patrick J. Daley, M.D. should be disqualified from receiving investigational new drugs. CBER has moved to deny Dr. Daley's request for a hearing under 21 C.F.R. § 16.26(a) and to disqualify him under 21 C.F.R. § 312.70.

Based upon my review of the parties' submissions, I find that there is no genuine and substantial issue of fact with regard to whether Dr. Daley repeatedly or deliberately violated 21 C.F.R. Part 312. I am therefore granting CBER's motion to deny Dr. Daley's request for a hearing and to disqualify Dr. Daley from receiving investigational new drugs.

I. Background

Dr. Daley participated as a clinical investigator in a study titled, "Safety and Efficacy of (b) (4) Vaccine in (b) (4) (b) (4) that was sponsored by (b) (4) The study subjects were (b) (4) (b) (4) CBER Motion, Ex. 1. The purpose of the study was to "study the safety of (b) (4) vaccine and the vaccine's ability to (b) (4) The study also was designed to

look (b) (4) CBER Motion, Ex. 4. (b) (4)

(b) (4) *Id.*

FDA investigators conducted an inspection of Dr. Daley's study site between July 19 and September 6, 2002. CBER Motion, Ex. 11. Based upon the results of this inspection, CBER sent Dr. Daley a Notice of Initiation of Disqualification Proceeding and Opportunity to Explain on June 23, 2003, CBER Motion, Ex. 14, and Dr. Daley responded on August 15, 2003. CBER Motion, Ex. 13. CBER concluded that Dr. Daley's "written explanations fail[ed] to adequately address the violations" and it therefore offered him notice and an opportunity for a hearing (NOOH) pursuant to 21 C.F.R. Part 16 and § 312.70 on the question of whether he is entitled to continue to be eligible to receive investigational new drugs. CBER Motion, Ex.12. On February 20, 2004 Dr. Daley responded to the NOOH by requesting a hearing. CBER Motion, Ex. 15.

This matter is now before the Commissioner on CBER's Motion under 21 C.F.R. § 16.26(a) to deny Dr. Daley's request for a hearing and to disqualify him under 21 C.F.R. § 312.70. CBER's Motion is based upon the following six charges:

- (1) Submission of false information to the sponsor (21 C.F.R. §§ 312.62, 312.64, and 312.70);
- (2) Failure to maintain adequate and accurate case histories recording all observations and other data pertinent to the investigation, including case report forms and supporting data (21 C.F.R. § 312.62(b));
- (3) Failure to ensure that the investigation was conducted according to the investigational plan (21 C.F.R. § 312.60);
- (4) Failure to assure that the Institutional Review Board would be responsible for the continuing review and approval of the study by failing to submit

complete and accurate information regarding the safety of the study (21 C.F.R. § 312.66);

- (5) Failure to obtain informed consent in accordance with the provisions of 21 C.F.R. Part 50 (21 C.F.R. § 312.60); and
- (6) Failure to maintain adequate records of the disposition of the investigational drug (21 C.F.R. § 312.62(a)).

On January 14, 2005, Dr. Daley submitted a Memorandum in Opposition to CBER's Motion for Disqualification Without a Regulatory Hearing. On March 14, 2005 CBER submitted a Reply Memorandum to Dr. Daley's Opposition to the CBER Motion.

Under § 21 C.F.R. 312.70, a clinical investigator will be disqualified from receiving investigational drugs if, after evaluating all available information, the Commissioner "determines that the investigator has repeatedly or deliberately failed to comply with the requirements of [Part 312], Part 50, or Part 56, or has deliberately or repeatedly submitted false information to the sponsor in any required report" Under the terms of this regulation, an investigator who *either* repeatedly or deliberately fails to comply with the investigational new drug regulations must be disqualified. *In the Matter of James A. Halikas, M.D.*, Commissioner's Decision, (January 17, 2001).

The Commissioner may deny a request for a hearing, in whole or in part, under 21 C.F.R. § 16.26(a) if the Commissioner or the FDA official to whom the authority is delegated to make the final decision on the matter determines that no genuine and substantial issue of fact has been raised by the material submitted. It is within my delegated authority to make the final decision in this matter. 72 FR 50112.

The standard for denial of a hearing in 21 C.F.R. § 16.26 reflects the standard in federal court for summary judgment. *See John D. Copanos and Sons, Inc.*, 854 F.2d 510, 523 (D.C. Cir. 1988) (comparing standard under 21 C.F.R. § 314.200, which contains similar language, ("The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact"), to the standard for summary judgment in federal court); 53 Fed. Reg. 4613 (1988). Under Rule 56(c) of the Federal Rules of Civil Procedure, summary judgment is proper when there is no genuine issue as to any material fact and the moving party is entitled to judgment as a matter of law.

As is the case for summary judgment under Rule 56(e), the key criterion for determining whether denial of a hearing is appropriate under 21 C.F.R. § 16.26 is whether there are disputed facts that might affect the outcome of the proceeding. The opposing party may not rest on mere allegations or denials of the moving party's evidence but must present evidence of its own that establishes a genuine issue of fact. However, where, in the first instance, "the evidentiary matter in support of the motion does not establish the absence of a genuine issue, summary judgment must be denied even if no opposing evidentiary matter is presented." Rule 56(e), Advisory Comm. Note. If there are no genuine disputes of fact, denial of the hearing is appropriate.

Based on the evidence presented in and attached to CBER's Motion, Dr. Daley's Opposition to CBER's Motion, and CBER's Reply to Dr. Daley's Opposition, I find that, with respect to certain of CBER's charges, there is no genuine and substantial issue of fact with regard to whether Dr. Daley repeatedly or deliberately violated 21 C.F.R. Part 312. I am therefore granting CBER's motion to deny Dr. Daley's request for a hearing on these charges and, because these charges amount to "repeated" and "deliberate" violation of the regulations, I am granting the motion to disqualify Dr. Daley from receiving investigational new drugs.

II. Analysis

A. Submitting False Information to the Sponsor in Violation of 21 C.F.R. §§ 312.62, 312.64, and 312.70

1. Submitting Case Report Forms (CRFs) containing false information purporting to document the administration of doses of study vaccine/placebo that were not, in fact administered to the infant study subjects.

CBER alleges that Dr. Daley recorded on CRFs the vaccine vial ID numbers and date of vaccination for study vaccine/placebo doses that he did not administer and that he then submitted these CRFs to the sponsor. CBER Motion at 6, NOOH at 2. Dr. Daley responds that "any failure of study subjects to receive documented doses of study vaccine or placebo does not demonstrate a deliberate violation of the regulations" since "[t]here are valid reasons not to administer study material at a scheduled visit" and "[w]here Dr. Daley mistakenly believed that the subject had received the dose of study medication or placebo, or believed that the subject shortly would receive the dose, there was likewise no deliberate violation of applicable law and regulations." Request for Hearing at 4. He further argues that "the failure to administer study material or the incorrect documentation of such posed no safety risk to the patients." *Id.* Finally, Dr. Daley adds that "certain inconsistencies in study data are not material." *Id.*

Dr. Daley's response is an admission that he recorded vaccination information on the CRFs for vaccine doses that were not administered.

As stated above, the standard for disqualification under 21 C.F.R. § 312.70 is repeated *or* deliberate failure to comply with the applicable regulations (21 C.F.R. § 312.70(a)). Thus, even if it is taken as fact that Dr. Daley's recording of false information regarding administration of vaccine/placebo was not "deliberate," since he says in certain instances he "mistakenly believed

that the subject had received the dose of study medication or placebo, or believed that the subject shortly would receive the dose," his acknowledgement that CRFs for multiple subjects contained information falsely documenting administration of vaccine/placebo thus establishes a "repeated" violation.

Dr. Daley's contention that his recording of information that falsely reflects administration of vaccine/placebo doses that were never administered posed no risk to the study subjects is similarly unavailing since the standard for disqualification does not require that the failure to comply with applicable regulations pose a risk to study subjects. 21 C.F.R. § 312.70.

Dr. Daley's final response, that "inconsistencies in study data" were not material, also fails to refute the charge. In arguing that the materiality of his violations is a valid defense, Dr. Daley relies on *United States v. Gaudin*, 515 U.S., 506 (1995), to conclude that, "Materiality is an issue for the trier of fact to decide." Opposition at 5. Unlike Daley's own case, though, *Gaudin* was a criminal case in which materiality was an element of the crime alleged. The Court concluded that the 5th and 6th Amendments to the Constitution "require criminal convictions to rest on a jury determination that the defendant is guilty of every element of the crime with which he is charged," and that the question of "materiality" therefore should have been submitted to a jury for consideration. 515 U.S. at 510. Dr. Daley has not been charged with a crime and there is no issue of his constitutional right to a trial by jury so *Gaudin* is not relevant. In fact, the *Gaudin* Court noted that "civil and criminal juries' required roles are obviously not identical, or else there could be no directed verdicts for civil plaintiffs." *Id.* at 517. Notably, in other contexts, the Court has held that "materiality" is an issue of law. *See Kungys v. United States*, 485 U.S. 759, 771 (1988).

Since the standard under 21 CFR 16.26 is the same as that for summary judgment under Rule 56 of the Federal Rules of Civil Procedure (see supra p. 4), "materiality" enters the analysis in a 16.26 motion to the extent that it would for a motion for summary judgment under Rule 56. In such motions, "the substantive law will identify which facts are material. Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment. . . . materiality is only a criterion for categorizing factual disputes in their relation to the legal elements of the claim and not a criterion for evaluating the evidentiary underpinnings of those disputes." *Anderson*, 477 U.S. at 248. In this case, the substantive law that identifies the material facts is found at 21 C.F.R. § 312.70. This rule prohibits submission of false information to the sponsor. Since the rule does not prohibit submission of false *and material* information to the sponsor, materiality is not an element of the rules Dr. Daley is charged with violating. Under *Anderson*, then, "materiality" is not a "material fact."¹

Because Dr. Daley has admitted submitting CRFs to the sponsor that contain false information, there is no genuine and substantial issue of fact with respect to this charge.

2. Submitting false information to the sponsor documenting the completion of post vaccination follow-up of safety contacts that were never performed

CBER alleges that in CRFs and facsimile transmissions Dr. Daley reported making follow-up safety contacts on days 7, 14, and 42 after administration of each dose of vaccine/placebo when he never made those contacts. CBER Motion at 6, NOOH at 3. When he prepared and signed a "Memo to File" that states, "[t]he majority of the day 7, 14, and 42 follow-

¹ While materiality is not necessary to a finding that a clinical investigator repeatedly or deliberately violated the regulations, "the Commissioner always retains the discretion not to disqualify if the Commissioner believes the violations are insignificant or lesser sanctions would be adequate." *In the Matter of Huibert M. Vriesendorp, M.D.* (2001). The significance of CBER's charges against Dr. Daley is addressed herein in the conclusion.

up phone calls were not made . . .", Dr. Daley admitted the charge. CBER Motion, Ex. 7.

While Dr. Daley responds that "[n]early all of the subjects who were enrolled in the study were regular patients of Dr. Daley, and patient and family contact was therefore ongoing throughout the study," Request for Hearing, at 4, this response does not dispute that the reports he sent to the sponsor contained false information. Because Dr. Daley admitted in the Memo to File that he did not make the follow-up phone calls that he reported having made, there is no genuine and substantial issue of fact with respect to this charge.

3. Entering False Information in the "Contact Survey Information (6 week safety surveillance)" CRF

CBER charges that Dr. Daley entered information in the "Contact Survey Information (6 week safety surveillance)" CRF falsely reporting that he conducted safety monitoring for multiple subjects. CBER Motion at 7, NOOH at 4. Dr. Daley's response to this charge is the same as for the charge above but adds that the difference between ongoing, regular contacts with subjects who were also his patients is not materially different from the telephone contacts required by the study protocol. Request for Hearing, at 5.

As with the charge above, Dr. Daley admitted in his "Memo to File" that he did not make the follow up phone calls on days 7, 14, and 42 after vaccination. And, as explained above, 21 C.F.R. § 312.70(a) calls for disqualification of a clinical investigator for submitting false information, not false and material information. Materiality is therefore not an element of the regulatory requirement for disqualification.

There is no genuine and substantial issue of fact with respect to this charge.

4. Falsely reporting in CRFs that concomitant vaccines were administered when no such vaccines were administered on the dates reported

CBER states that Dr. Daley falsely recorded dates of administration of concomitant vaccines including diphtheria, tetanus, and pertussis, hepatitis B, polio, Haemophilus influenzae type b, and Prevnar. CBER Motion at 7, NOOH at 5. In his response, Dr. Daley does not dispute that the dates recorded in the CRFs were false but says, "It is unclear . . . why the listing of any dates different from the dates that the vaccines were actually administered has any material value in terms of the results collected for this clinical study." Request for Hearing, at 5. As explained above, materiality is not an element of the regulatory requirement for disqualification.

Dr. Daley's response does not raise a genuine and substantial issue of fact with respect to this charge.

5. Submitting false information regarding the absence of serious adverse events

CBER charges that Dr. Daley submitted information to the sponsor falsely reporting that subjects did not experience serious adverse events (SAEs). CBER Motion at 7, NOOH at 7. In particular, CBER states that subject (b) (6) was hospitalized and discharged from the hospital on (b) (6) of follow up after administration of the first dose of vaccine/placebo. While Dr. Daley admits that he did not report to the sponsor that subject (b) (6) experienced an SAE, he responds that "the primary goal of the study was to identify any cases of (b) (4) and subject (b) (6) did not suffer (b) (4). Request for Hearing, at 5.

Determining whether Dr. Daley's report to the sponsor is false depends upon whether subject (b) (6) experience meets the definition of an SAE. CBER says that the protocol defines an SAE, "as an event that, among other things, 'results in or prolongs an existing inpatient hospitalization.'" NOOH, at 7. However, aside from quoting this phrase, CBER offers no evidence to support its allegation that subject (b) (6) experience met the study protocol definition

of an SAE. While CBER has demonstrated that the definition of an SAE encompasses more than (b) (4) (see CBER Motion, Ex. 5, "any serious adverse experiences (SAEs), *including* (b) (4) (emphasis added)), no exhibit is attached to document the protocol definition of an SAE in its entirety. It is therefore unclear whether the elements of the SAE definition that CBER refers to as "among other things" would result in subject (b) (6) experience being excluded from the SAE definition.

Based on the information submitted, there is an issue of fact with respect to this charge.

6. Falsely reporting subjects' temperatures as rectal in CRFs when the subjects' temperatures were taken under the arm

CBER charges that in CRFs for 264 subjects Dr. Daley recorded the subjects' temperatures as "rectal" when he took the temperatures under the arm. NOOH at 7. Dr. Daley responds that "[s]tudy subject temperatures were measured under the arm, converted to what the value would have been if taken rectally, and recorded." Request for Hearing, at 5. He also states that the contract research organization knew that this was his method for taking the subjects' temperature. *Id.*, Daley Opposition, at 3.

To be eligible for the study, subjects were required to have a rectal temperature of less than 38.1°C/100.5°F. CBER Motion, Ex. 5. It is not clear whether this eligibility requirement precluded taking a subject's temperature under the arm and converting the result into a rectal temperature. The requirement does not specify that the temperature be *taken* rectally but just that the rectal temperature *be* less than 38.1°C/100.5°F. *Id.* As a result, based on the information submitted, there is an issue of fact with respect to this charge.

B. Failing to Maintain Adequate and Accurate Case Histories in Violation of 21 C.F.R. § 312.62(b)

1. Failure to document in CRFs the occurrence and follow-up of SAEs

CBER charges that on CRFs for three subjects who were hospitalized for runny stools, abdominal pain, and diarrhea/bloody stools, Dr. Daley falsely answered "none" in response to a question about whether any SAEs occurred and "no" in response to a question about whether the subject had visited a health care facility for a stomach illness such as diarrhea. CBER Motion at 8, NOOH at 8.

For the reasons explained above, in the absence of documentation of the protocol definition of SAE, it is not clear whether subjects suffered SAEs. There is therefore an issue of fact as to whether Dr. Daley's answer of "none" in response to the question of whether any SAEs occurred was false and constituted a failure to maintain an adequate case history under 21 C.F.R. § 312.62(b).

Dr. Daley has admitted that his response to the question of whether the subject visited a health care facility for a stomach illness was false, however. Dr. Daley acknowledges that subjects (b) (6) were hospitalized, although he maintains the hospitalizations were not "material" since the subjects did not suffer (b) (4). Request for Hearing, at 6. Again, "materiality" is not an element of the charge. CBER charges that Dr. Daley failed to maintain adequate and accurate case histories. A subject's CRF is part of the subject's case history. 21 C.F.R. § 312.62(b) ("Case histories include the case report forms and supporting data"). By admitting he provided false information in the CRFs for subjects (b) (6) Dr. Daley admits he failed to keep accurate case histories. There is therefore no genuine and substantial issue of fact as to this charge.

2. Falsely Documenting Administration of Vaccine/Placebo Doses in CRFs

CBER charges that Dr. Daley recorded in multiple subjects' CRFs false dates of vaccine/placebo administration and false vial numbers of vaccine/placebo administered. CBER

Motion at 10, NOOH at 9. Dr. Daley offers the same response as he did for charge A.1. Request for Hearing, at 6. In this response he admits "failure to administer study material or the incorrect documentation of such," but maintains that this failure "posed no safety risk to the patients." Request for Hearing, at 4. When, by his admission, Dr. Daley documented in subjects' CRFs doses of vaccine/placebo that were not administered, he failed to accurately maintain case histories. There is thus no genuine and substantial issue of fact with respect to this charge.

3. Falsely Documenting Administration of Vaccines in "Vaccine Inventory and Label Log" CRF

CBER charges that Dr. Daley affixed to the "Vaccine Inventory and Label Log" CRF tear-off labels from 33 vials of vaccine/placebo that were never administered and recorded in this CRF the date, amount administered, and person administering doses of vaccine/placebo that were never administered. CBER Motion at 10, NOOH at 10.

As with charge A.1., Dr. Daley responds that "any failure of study subjects to receive documented doses of study vaccine or placebo does not demonstrate a deliberate violation of the regulations," and that "[w]here Dr. Daley mistakenly believed that the subject had received the dose of study medication or placebo, or believed that the subject shortly would receive the dose, there was likewise no deliberate violation of applicable law and regulations." Request for Hearing at 4; *see also* *infra* at 5. Dr. Daley thus admits that, although his violation was not "deliberate," he did record false information in the CRFs as a result of what he characterizes as his mistaken belief that patients had already or would shortly receive a dose that had not actually been administered. Since the CRFs are part of the case history, *see infra* at 11, Dr. Daley's admission to recording false information in the CRFs is an admission of recording inaccurate information in subjects' case histories. There is consequently no genuine and substantial issue of fact with respect to this charge.

4. Falsely Documenting Dates of Follow-Up Safety Contacts in “Vaccination Visit [2 or 3] Follow-Up Contact Survey Information (Vaccination follow-up)” CRF

CBER charges that Dr. Daley recorded dates for follow-up safety contacts on days 7, 14, and 42 after administration of vaccine/placebo when the vaccine/placebo doses were not administered. CBER Motion at 11, NOOH at 10-11. Dr. Daley offers the same response as he did for charge A.2. As with that charge, Dr. Daley’s response constitutes an admission. Dr. Daley admitted in the “Memo to File” that he did not make the follow-up calls he reported having made. CBER Motion, Ex. 7. By making this false report in the subjects’ CRFs, he failed to keep accurate case histories. There is no genuine and substantial issue of fact as to this charge.

5. Falsely Documenting Administration of Concomitant Vaccines on the “Concomitant Non-Study Vaccine” CRF

CBER charges that Dr. Daley recorded administration of concomitant vaccines in subjects’ CRFs when the subjects’ medical records do not reflect administration of these vaccines and CBER charges that Dr. Daley failed to record in the CRFs administration of concomitant vaccines that the subjects’ medical records reflect were administered. CBER Motion at 11, NOOH at 12-13. Dr. Daley offers the same response as he did for charge A.4. In this response, Dr. Daley admits that he listed “dates different from the dates that the vaccines were actually administered.” Request for Hearing, at 5. By recording incorrect dates in the subjects’ CRFs, Dr. Daley failed to keep accurate case histories. There is no genuine and substantial issue of fact with respect to this charge.

6. Failure to Prepare and Maintain and Maintain Complete and Accurate “Subject Vaccine Administration Records” (SVAR)

CBER charges that Dr. Daley failed to prepare and maintain SVARs for certain subjects, that the "Time Removed from the Refrigerator" and "Time Administered" columns of the SVARs for certain subjects are crossed out without being corrected, initialed, or dated, and that the number of vaccine/placebo doses listed as being administered in the SVARs does not agree with the number listed in the "Vaccine Inventory and Label" CRF. CBER Motion at 11-12, NOOH at 14.

Dr. Daley responds that "such minor inconsistencies are almost unavoidable in the context of a large clinical study. Such inconsistencies are immaterial in this context." Request for Hearing at 7.

The charge underlying this allegation is the violation of 21 C.F.R. § 312.62(b), failure to maintain adequate and accurate case histories. According to CBER, the investigational plan required the maintenance of SVARs. NOOH at 14. While failure to maintain an SVAR might violate the investigational plan, it is not clear that the lack of an SVAR for a particular subject would render the subject's case history inaccurate by itself. It is similarly unclear whether cross outs on the SVAR would render the case histories inaccurate or inadequate if there were another record of the vaccine administration in the case history that was accurate. With respect to these two issues, there is an issue of fact.

However, the third issue CBER raises, the lack of agreement between the number of vaccine/placebo doses listed in the SVARs and the number listed in the CRFs, does address the accuracy of the case histories. By admitting in his response to "such minor inconsistencies" in the records he kept, Dr. Daley admits that he recorded incorrect information in either the SVARs or the CRFs and, as a result, that he kept inaccurate case histories. Consequently, there is no genuine and substantial issue of fact with respect to this charge.

7. Failure to Maintain Complete and Accurate "Subject Participation Log"

CBER charges that the investigational plan required maintenance of a "Subject Participation Log," and that, in keeping the Log, Dr. Daley did not include entries for some subjects and included false dates of vaccination visits. CBER Motion at 12, NOOH at 14. It is not clear from the information submitted whether the investigational plan required that the "Subject Participation Log" be maintained as part of the subjects' case histories. Since the underlying charge is failure to maintain accurate case histories, if the "Subject Participation Log" is not part of a case history then failure to maintain an accurate Log would not constitute a violation of 21 C.F.R. § 312.62(b). As a result, there is an issue of fact with respect to this charge.

C. Failure to Ensure the Investigation was Conducted According to the Investigational Plan in Violation of 21 C.F.R. § 312.60

1. Failure to Report SAEs Within 24 Hours as Required by the Protocol

CBER charges that Dr. Daley failed to report SAEs to the sponsor within 24 hours as required by the study protocol. CBER Motion at 13, NOOH at 15. As with the previously discussed charges relating to SAEs, in the absence of documentation establishing the protocol's definition of an SAE, it is unclear whether SAEs occurred. The portion of the study protocol establishing the 24-hour reporting requirement is also not attached as an exhibit. There thus is an issue of fact with respect to this charge.

2. Failure to Obtain Subjects' Temperature by Rectal Method as Required by the Protocol

CBER charges that Dr. Daley failed to obtain the study subjects' temperature rectally as required by the protocol. NOOH at 15. As explained previously, it is not clear whether the protocol requirement that subjects have a rectal temperature of less than 38.1°C/100.5°F

precluded taking the subjects' temperature under the arm and converting it to a rectal temperature. See infra at, 10. There is therefore an issue of fact with respect to this charge.

3. Failure to Collect Subjects' (b) (4) as Required by the Protocol

CBER charges that Dr. Daley did not follow the protocol requirement that he collect (b) (4) samples from all subjects hospitalized with potential (b) (4) when he failed to collect (b) (4) samples for subjects (b) (6) "who were hospitalized with symptoms of (b) (4)" NOOH, at 15. Since the portion of the protocol with this requirement is not attached as an exhibit, it is not clear under what circumstances the protocol required collection of (b) (4) samples. CBER represents the requirement as pertaining when subjects are "hospitalized with potential (b) (4)" *Id.* From the information submitted it is not clear whether this would include all subjects who suffered "symptoms of (b) (4)" since it is not apparent that any person hospitalized with (b) (4) symptoms is necessarily hospitalized for potential (b) (4). As a result, there is an issue of fact with respect to this charge.

4. Failure to exclude Subject with (b) (4) in Violation of Protocol Requirement

According to CBER, protocol section I.D.2.g "excludes from the trial subjects with 'clinical evidence of active (b) (4) illness or past diagnosis of severe (b) (4) illness requiring surgery or that is currently controlled through medications such as (b) (4) or (b) (4)" NOOH at 16. CBER charges that Dr. Daley violated this protocol requirement by enrolling subject (b) (6), who had (b) (4) that was treated with (b) (4) *Id.* Dr. Daley responds that he obtained from the sponsor oral permission to enroll subject (b) (6) and a subsequent oral waiver. Request for Hearing at 7-8.

It is not clear from the information submitted whether the sponsor granted an oral waiver permitting Dr. Daley to enroll subject (b)(6). There is thus an issue of fact with respect to this charge.

D. Failure to Assure the IRB Would be Responsible for Continuing Review and Approval of Study, in Violation of 21 C.F.R. § 312.66, by Failing to Submit Complete and Accurate Information Regarding Safety of Study

1. Failure to Report SAEs Within Five Days as Required by the IRB

CBER alleges that Dr. Daley violated an IRB requirement that it be notified "within five days of 'serious adverse events including. . . hospitalizations or prolonging of hospitalization.'" NOOH at 16. Based on the quoted portion of the IRB requirement, it is not clear whether, when read in the context of the entire document, there might be other information that would result in the requirement not applying to the subjects who enrolled at Dr. Daley's study site and who were hospitalized. As a result, there is an issue of fact with respect to this charge.

2. Falsely Reporting to IRB that Subjects did not Experience SAEs

CBER charges that Dr. Daley submitted a "Study Status Report/Reapproval Form" to the IRB on which he falsely answered "no" in response to the question, "Serious Adverse Event(s), Unexpected or Unusual Occurrence(s) in Subject(s) entered into study at your site?" NOOH at 17.

As explained previously, the definition of an SAE is not apparent from the information submitted. In the absence of a complete definition of an SAE, it is not clear whether the experiences of subjects (b)(6) constituted an SAE within the meaning of the study protocol. If no SAE occurred, then Dr. Daley did not provide false information on the "Study Status Report/Reapproval Form." There is consequently an issue of fact with respect to this charge.

3. Failure to Submit to IRB Eligibility Waivers Granted by the Sponsor

CBER alleges that the sponsor instructed Dr. Daley to submit to the IRB eligibility waivers the sponsor granted and that Dr. Daley failed to do so. NOOH at 17.

Dr. Daley responds that he believed the CRO had already submitted the waivers to the IRB. Opposition at 4. He notes that a waiver letter from the CRO states, "If using the Central IRB, ERC, this waiver has already been submitted on your behalf." *Id.*, citing CBER Motion, Ex.16.

Based on the information submitted, it appears that the CRO may have already submitted the waivers to the IRB. If so, and if Dr. Daley understood that the CRO had done so, then he would have fulfilled the regulatory requirement that he assure the IRB be responsible for continuing review and approval of the study. 21 C.F.R. § 312.66. There is consequently an issue of fact with respect to this charge.

4. Failure to Include Witness Signature on Consent Forms

CBER alleges that Dr. Daley forged his study coordinator's signature on the witness signature line of 196 informed consent forms. CBER Motion at 15, NOOH at 17. Dr. Daley responds that "[n]o documentation or citation to documentation is provided . . . to demonstrate that the IRB expressly required a witness signature. Apparently, FDA has inferred this intent on the part of the IRB from the fact that a witness signature line was included on the consent form." Request for Hearing at 8.

CBER's charge is that Dr. Daley's forging of his study coordinator's signature on informed consent forms is a failure to assure that the IRB would be responsible for continuing review and approval of the study under 21 C.F.R. § 312.66. For this and the other alleged violations of this regulation, CBER maintains Dr. Daley violated the regulation "by failing to

submit complete and accurate information regarding the safety of the study." NOOH at 16.

CBER has not explained, however, how failure to obtain witness signatures or forgery of witness signatures on informed consent forms would be a failure to submit to the IRB complete and accurate information on the safety of the study. First, it is not apparent that failure to obtain a witness signature compromised the safety of the study. Second, even if it did, investigators are not required to submit completed informed consent forms to the IRB and CBER has not represented that Dr. Daley did submit the falsified consent forms to the IRB. If Dr. Daley did not submit the falsified forms to the IRB then it is not clear how he failed to assure the IRB's continuing review of the study. Perhaps there are additional factual circumstances that indicate Dr. Daley's failure to obtain a witness signature and his forgery of the study coordinator's signature did interfere with the IRB's continuing review of the study, however, these facts are not apparent from the information submitted. As a result, there is an issue of fact with respect to this charge.

E. Failure to Obtain Informed Consent in Accordance with the Provisions of 21 C.F.R. Parts 50 and 56 in violation 21 C.F.R. § 312.60

CBER alleges that Dr. Daley failed to follow informed consent requirements for subject (b) (6) by failing to have on the informed consent form the signature of the person obtaining consent, the signature of the witness other than the person obtaining informed consent, the child's name, and the date that the parent or legal guardian signed the informed consent form. NOOH at 18. Dr. Daley responds that subject (b) (6) parents signed an outdated version of the consent form on June 13, 2001. When the subject's father subsequently signed an updated consent form, which did not vary substantively from the previous version of the form, the form was not filled out fully. Request for Hearing at 9.

The informed consent regulations require that the informed consent form be signed and dated by the subject or the subject's legally authorized representative. 21 C.F.R. § 50.27(a). Dr. Daley concedes that when the proper informed consent form was filled out, the subject's parent did not date the form. However, he maintains that the date on the form was the only substantive difference between the two consent forms. Request for Hearing at 9. While the failure of the subject's parent to date the second form he signed would seem to violate the rule's requirements, if the two forms he signed, the one with the wrong date and one with the correct date, were maintained together, they might be considered to be one form. Whether subject (b) (6) consent form was properly dated when it was signed is thus an issue of fact.

F. Failure to Maintain Adequate Records of the Disposition of the Investigational Drug in Violation of 21 C.F.R. § 312.62(a)

1. Failure to Maintain "Vaccine Accountability Log"

CBER charges that Dr. Daley failed to complete the "Vaccine Accountability Log" for 36 shipments of investigational drug. CBER Motion at 16, NOOH at 18. Dr. Daley responds that "ministerial omissions" of this type "are not uncommon in the course of conducting a large clinical study." Request for Hearing at 9. Dr. Daley's response fails to raise a genuine and substantial issue of fact.

Investigational drug regulations require that the clinical investigator "maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects." 21 C.F.R. § 312.62(a). The failure to keep accountability records for 36 shipments of investigational drug, whether or not a "ministerial omission," is a violation of this regulation. There is no genuine and substantial issue of fact with respect to this charge.

2. Failure to Sign and Date Packing Slips

CBER alleges that Dr. Daley failed to sign and date packing slips for shipments of investigational drug upon receipt although required to do so by the investigational plan. CBER Motion at 16, NOOH at 18. As with the charge above, Dr. Daley admits to this "ministerial omission" and maintains that such omissions are "not uncommon." Request for Hearing at 9.

Dr. Daley's failure to sign and date packing slips does not by itself constitute a failure to keep adequate records of disposition of the investigational drug under 21 C.F.R. § 312.52(a). If all shipments of the drug were entered in the log along with date, quantity, and use by subjects, Dr. Daley would have a record of the disposition of the drug that fulfills the requirements of the regulation, notwithstanding the failure to sign and date packing slips.

However, CBER also alleges that Dr. Daley violated 21 C.F.R. § 312.60 by failing to follow the investigational plan requirement to sign and date packing slips as well as failing to maintain packing slips that describe the condition of the shipment at the time of receipt. NOOH at 18. Unfortunately, CBER does not document this requirement with a copy of the investigational plan. As a result, based on the information submitted it is not clear what the exact investigational plan requirement was and there is thus an issue of fact with respect to this charge.

III. Conclusion

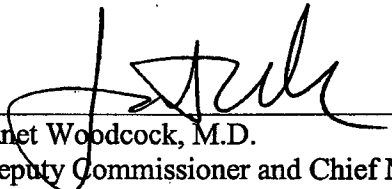
I find that Dr. Daley repeatedly and deliberately failed to comply with the requirements of 21 C.F.R. Part 312 in connection with the clinical investigation of (b) (4) (b) (4) Vaccine. Based on the information submitted, I find that there is no genuine and substantial issue of fact and I am granting the motion to deny Dr. Daley's request for a hearing with respect to: whether Dr. Daley submitted false information to the sponsor by submitting CRFs documenting administration of study vaccine/placebo doses

that were not administered, submitting information documenting the completion of post-vaccination follow-up safety contacts that were never performed, entering false information in the "Contact Survey Information (6 week safety surveillance)" CRF, and reporting in CRFs that concomitant vaccines were administered on certain dates when they were not; whether Dr. Daley failed to maintain adequate and accurate case histories by falsely reporting in a CRF that a subject did not visit a health care facility for a (b) (4) illness, by documenting in CRFs false dates and vial numbers of vaccine/placebo administered, by falsely documenting administration of vaccines in the "Vaccine Inventory and Labeling Log" CRF, by documenting dates of follow-up safety contacts that were never made, by documenting incorrect dates for the administration of concomitant vaccines in CRFs, and by recording inconsistent information in SVARs and CRFs; and whether Dr. Daley failed to maintain adequate records of the disposition of the investigational drug by failing to maintain an accurate Vaccine Accountability Log. Because there is no genuine and substantial issue of fact with respect to these charges, I am granting the motion to disqualify Dr. Daley from receiving investigational new drugs under 21 C.F.R. § 312.70.

Based on the information submitted, there are issues of fact with respect to the remaining charges. However, because I am granting the motion to disqualify Dr. Daley from receiving investigational new drugs with respect to the charges described above, there is no need to proceed with a hearing on the remaining charges.

Dr. Daley has argued that many of CBER's charges are not "material." While the Commissioner retains the discretion not to disqualify a clinical investigator if he believes the violations are insignificant, "this discretion should be exercised only in extraordinary circumstances (e.g., where disqualification would be truly unjust or would accomplish nothing)."

In the Matter of Huibert M. Vriesendorp, M.D., citing 52 Fed. Reg. 8798, 8826 (1987). Given the totality of Dr. Daley's violations of the regulatory requirements for clinical investigations, including the repeated submission of false information to the sponsor, I do not find that there are such extraordinary circumstances here. I therefore conclude that Dr. Daley is no longer entitled to receive investigational drugs. Dr. Daley may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 C.F.R. § 312.70(f).



Janet Woodcock, M.D. Date 3/14/08
Deputy Commissioner and Chief Medical Officer
Food and Drug Administration