DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

. STEVEN K. TEPLICK, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

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REPORT OF THE PRESIDING OFFICER

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I. INTRODUCTION

Pursuant to Title 21 of the Code of Federal Regulations ("C.F.R.")[1] Parts 16 and 312, the Food and Drug Administration ("FDA") conducted a hearing on 12/12-13/91, to consider the proposal of the Center for Drug Evaluation and Research ("Center") to disqualify Steven K. Teplick, M.D. from receiving investigational new drugs ("INDs").[2] The Center contended that

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[1] All references in this report are to Title 21 C.F.R., unless otherwise specified. Although many of the events cited in the charges of the NOOH took place prior to the revision of the investigational new drug ("IND") regulations on 3/19/87, the NOOH referred to the revised IND regulations. However, because the revised regulations are largely consistent with the regulations in place at the time of the events in issue (except as noted in the "Analysis" section), this revision had no effect on the recommended disposition of the charges. Therefore, for purposes of this report, I have used and cited the current form of the regulations for analyzing the Center's charges, unless otherwise noted.

[2] An investigational new drug ("IND") is defined as "a new drug, antibiotic drug, or biological drug that is used in a clinical investigation." [§ 312.3(b).] A new drug is defined in section 201(p) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), Title 21, United States Code ("U.S.C."), and includes an approved drug that is proposed for a new use.

Dr. Teplick should be disqualified as a clinical investigator because he repeatedly or deliberately violated the federal food and drug regulations in a clinical investigation[3] using the investigational new drug, : (" "), in which he participated as a clinical investigator.[4] More specifically, the Center contended that Dr. Teplick failed to comply with the regulations regarding clinical investigations set forth in §§ 312.64(b), 312.66, 312.60, 312.62(b), 312.62(a), 50.27, and 50.25.

For the reasons stated below, it is the recommended decision of the Presiding Officer that Dr. Teplick be disqualified from receiving investigational new drugs. This document constitutes my report on the hearing. [See § 16.60(e).] This report, along with any comments by the Center and Dr. Teplick regarding this report and the administrative record will be referred to the Commissioner for a final determination on this matter. [See § 16.95.]

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[3] A clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." [§ 312.3(b).]

[4] An investigator is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject)." [§ 312.3(b).]

II. BACKGROUND

A Notice of Claimed Investigational Exemption for a New Drug ("IND")[5] was originally requested by the sponsor-investigator,[6] M.D., Department of Gastroenterology, University , for an emergency use[7] of in one subject. [Center Exhibit ("CX") 60 at Tab J.] William Bachrach, M.D., a Medical Officer in the Center's Division of Cardiorenal Drug Products,[8] issued this emergency IND on 3/15/85. [Id. at Tab I.]

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[5] Section 312.20 requires a sponsor to "submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a)."

[6] A sponsor-investigator is defined as "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed . . . ." The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor. [§ 312.3(b).]

A sponsor is "a person who takes responsibility for and initiates a clinical investigation." [§ 312.3(b).]

[7] See § 312.36: "Need for the use of investigational drug may arise in an emergency situation that does not allow time for the submission of an IND in accordance with § 312.23 or § 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone . . . ."

[8] This division is now called the Division of Gastrointestinal Coagulation Drug Products, which is directed by Stephen B. Fredd,

Dr. 's first written communication to the FDA was a letter, dated 5/28/85, in which he reported the clinical experience with the one subject. In reviewing the IND file (IND), Mr. Thomas Hassall, Consumer Safety Officer ("CSO"), noted that Dr. had not received the Center's standard introductory letter and FDA forms. [CX 60 at Tab I.]

Dr. later submitted the necessary forms, including a clinical protocol for the treatment of both gall bladder and common bile duct stones, to the file on 7/22/85.[9] [Id.] William R. Stern, M.D., Medical Officer in the Center's Division of ardiorenal Drug Products, reviewed these documents and found hem to be acceptable, as noted in his Medical Officer's Review report dated 10/11/85. [Id.]

As IND sponsor ("sponsor"), Dr. wrote a letter, dated 1/28/86, to Raymond J. Lipicky, M.D., Acting Director, Division of Cardiorenal Drug Products, requesting:

> that two colleagues . . . be allowed to become co-investigators under my IND. These are Steven K. Teplick, Professor of Radiology at Medical College . . . copies of their curricula vitae and bibliographies are enclosed
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> . . . .

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[9] Dr. Fredd in his testimony incorrectly stated that the IND e was 7/22/86. [Trans. Vol. 1 at 17.] The IND submission date 7/22/85. [See, e.g., CX 60 at Tab F.]

> [e]ach of these individuals has agreed to monitor their patients carefully, although they are not at present in a position to carry out a controlled study comparing with They have agreed to send completed patient report forms on each patient that they treat with They are well aware of its dangers, and they will not initiate clinical studies until their protocol has been approved by their local Institutional Review Boards.[10]
>
> Each of these individuals has agreed to purchase their from , the material being manufactured by .

[CX 55 at 1-2.]

On the second page of Dr. 's letter, a handwritten notation, dated 2/06/86, with Dr. Bachrach's initials read: "The proposed arrangement is agreeable." [Id.] In a record of a telephone conversation or meeting, dated 3/31/86, Mr. Hassal had noted:

> Dr. 's [sic] Jan. 28, 1986 letter requested the addition of Dr. Stephen [sic] Teplick (Medical College) & Professor (U.) as investigators under Dr 's controlled cross-over comparison of and (protocol submitted 7/22/85). Dr. Bachrach noted on 2/6/86 that the additional investigators were ok & asked me to confirm

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[10] An "Institutional Review Board" ("IRB") is "any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research." [§ 50.20(i).] The IRB used by Dr. Teplick was the University Committee for Human Studies. [See CX 36.]

> with the sponsor. I placed this call to notify Dr. [sic] of our acceptance of the Jan 28, 1986 proposal. [Secretary to Division of Gastroenterology, Department of Medicine, University of] said she would notify the investigators (Teplick + [11] and make note of this call in the IND file."

[Id. at 3.]

The record reflected no further communication between the agency and the sponsor until Mr. Peter A. Manilla, a CSO in the Center's Division of Gastrointestinal and Coagulation Drug Products [see n. 8 at 3.], sent a letter to Dr. dated 6/14/88, stating that the agency was "currently performing an administrative eview of all INDs for and [was] asking for a report of the progress of activities being conducted under each IND. Such a report will aid [FDA] in our evaluation of the safety and effectiveness of as a gallstone dissolution agent to date, and provide a basis for future development." [CX 60 at Tab E.] The letter requested the following: identification of the

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[11] According to the regulations, once Dr. notified Dr. Teplick of his status as an investigator, Dr. Teplick was "responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation." [§ 312.60.] In addition, Dr. Teplick was responsible for obtaining the informed consent of each human subject to whom the drug is administered, in accordance with provisions of Part 50, except as provided in § 50.23. [Id.] itional specific responsibilities are set forth in Parts 312, 50, 56, [Id.]

supplier(s) and labeling of product specifications (e.g., certificates of analysis, stability data, additional product testing by hospital pharmacists); any information on comparability studies performed with and synthetic materials (e.g.,); number and characteristics of the subjects and their treatments and outcomes, as well as an outline of further research planned under the IND for the next year.[12] [CX 55 at 4 & 5.]

Dr. responded to Mr. Manilla's request, in a letter dated 8/4/88, stating, "Dr. Teplick and Dr. met with me in Boston in early July, 1988; and both are preparing detailed descriptions of the patients that they have treated . . . ." [CX 60 at Tab D.] In response to Mr. Manilla's inquiry regarding testing of with synthetic materials, Dr. also stated: "We have had no difficulty with any destruction of this material [ ] during infusion." Only Dr 's name was listed as being copied at the bottom of the letter. [Id.]

In his response, however, Dr. had not provided all the information requested by Mr. Manilla, and on 12/15/88 the agency resent the 6/14/88 letter to Dr. . [CX 60 at Tab C.]

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[12] Under § 312.33, an Annual Report containing this information equired to be submitted within 60 days of the effective versary date of the IND.

Dr. responded to the agency's second request in a letter, dated 4/20/89, by submitting what constituted the first Annual Report to the IND file. [See n. 12 at 7.] The report included Case Reports Forms ("CRFs") from subjects treated by Dr. Teplick, and stated:

> Dr. Teplick, at Medical Center, is an interventional radiologist who has developed a referral practice for [common bile] duct stones. His success is less because the incidence of resistant bile duct stones is greater than with gallbladder stones. The patients received a much larger volume of than that used for gallbladder stones in the other two centers. The patients were generally quite ill, and treatment was not always satisfactory. Some sedation occurred. was often used to obtain partial dissolution and then followed by further lavage with . My impression is that dissolution of duct stones by lavage with under circumstances where leaks into the small intestine is dangerous and should be done only as a last resort. Every effort should be made to obtain information on stone composition before dissolution, and I have advised Dr. Teplick to do this. One patient (TE-3) died after therapy, but the attending physician did not believe that played a role in the patient's demise.

[CX 60 at Tab B.] Dr. Teplick's name was listed as "carbon copied" at the end of this letter. [Id.] In response to this report, Stephen B. Fredd, M.D., Director, of the Center's Division of Gastrointestinal and Coagulation Drug Products, sent a letter, dated 5/25/89, stating: "We request that you not enter any more patients into the common duct portion of the study until have reviewed the details on the patient (TE-3) and notify you

that it is safe to proceed with the study . . . ." [CX 40 at 1.] This letter effectively placed a clinical hold[13] on further entry of common bile duct stone subjects onto Dr 's protocol.

Dr. responded in a letter dated 6/01/89, stating: "I have notified Dr. Teplick . . . that is not to be used for treatment of duct stones until we receive permission from your office." [CX 41 at 2.] In addition, Dr. explained that the subject's death had not been reported sooner to FDA, because Dr. Teplick had not considered responsible for the subject's demise. [Id.]

In accordance with § 312.68, Dr. Fredd requested a directed inspection of Dr. Teplick's activities conducted under IND in a memorandum dated 6/23/89:

> I am concerned about the delay in reporting the death [of patient TE3], the use of company [sic] as supplier, the lack of our having the current protocol for Dr. Teplick's procedure with the unknown (to us) qualifications of the individuals administering the , the inadequate informed consent form, the question of charging raised by the consent form, and the question of what the and

[13] Section 312.42(a) defines clinical hold as "an order issued by FDA to the sponsor [of an IND] to delay a proposed clinical investigation or to suspend an ongoing investigation . . . When a proposed study is placed on clinical hold, subjects may not be given the investigational drug . . . ." The grounds for the imposition of a clinical hold, which include safety reasons as well as deficiencies in the protocol for the investigation, are addressed at § 312.42(b).

> IRBs know of the conduct of the study. Dr. Teplick has used on 25 patients at , and several had adverse reactions, mainly sedation. I cannot assess the extent of the problem with this portion of the study without your assistance in investigating all cases at the IRBs role there, and the reporting procedures in place from Dr. Teplick to Dr. . I am also concerned about Dr. 's procedures to fulfill his responsibilities as monitor in reporting the study to us, particularly adverse reactions, under 21 CFR 312.32(c)(2), 21 CFR 312.33, and 21 CFR 312.53.

[CX 60 at Tab A.]

FDA investigator, Ms. Ann deMarco, of the Philadelphia District ontgomeryville resident post, conducted an audit of Dr. eplick's clinical trials with the medical advice of Bette Lee Barton, M.D., Medical Officer of the Center's Division of Scientific Investigations, at University and reported her findings in an FDA Form 483, dated 7/17/89 - 8/21/89, which was hand-delivered to Dr. Teplick in Arkansas by FDA Investigator Ray McCullough, on 8/28/89. [CX 31; Trans. Vol 1 at 208.]

In accordance with § 312.70, by letter dated 4/12/90, the Center offered Dr. Teplick an opportunity to respond to the violations at an informal conference or in writing. [CX 32.] Dr. Teplick responded by letter dated 5/02/90, in which he stated: "I believe that there were some flaws in the study, but I think I can now that most of the allegations are not accurate." [CX 33 at

1.] His letter included an attachment which addressed the concerns raised in the FDA Form 483. [See CX 31 & CX 33 at 8-15.]

In a letter dated 6/22/90, the Center responded: "We have reviewed your letter of 2 May 1990 in detail and conclude that the explanations offered are not supported by the study records available to the FDA, and are not adequate to satisfy our concerns . . . ." [CX 34 at 1.] The letter advised Dr. Teplick that the Center would recommend to the FDA Commissioner that Dr. Teplick be disqualified from further receiving investigational ew drugs. The letter also provided Dr. Teplick with an pportunity to end the administrative process by his signing a consent agreement. [Id. at 3.]

On 3/22/91, Mr. Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, issued a "Notice of Opportunity for a Hearing" ("NOOH") pursuant to Part 16 procedures and outlined the Center's charges. [NOOH, attached, & CX 35.]

On 4/08/91, Saul H. Krenzel, Esq., Dr. Teplick's attorney for this matter, requested a hearing on behalf of Dr. Teplick. On 7/10/91, Dr. Teplick and counsel for the Center, Ms. Cathy Grimes-Miller, Esq., were contacted to arrange a date for the earing. Through a number of telephone calls, the date of

11/04/91 was mutually agreed upon. On 9/24/91, the Center requested an extension of the hearing date, due to the unavailability of a key witness. As the Presiding Officer, I granted the Center's request, and the hearing was rescheduled and held on 12/12-13/91.

I permitted the hearing record to remain open until close of business, 2/14/92, to allow each party to comment on the transcript, to submit a post hearing summary brief, and to submit any additional information I had specifically requested during the hearing. Both parties submitted timely briefs, which I considered in my analysis of the Administrative Record.

III. CHARGES

The Center made the following charges in the NOOH in support of its proposal that Dr. Teplick be disqualified from receiving investigational new drugs:

Charge I: Dr. Teplick violated § 312.64(b) by

A. failing to report alarming adverse effects immediately to the sponsor for subjects TE3, TE19, TE4, TE7, TE8, TE10, TE11, TE15, TE21, and TE25; and

B: failing to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, the investigational drug for subjects TE13, TE6, TE9, TE14, TE16, TE22, TE23, and JM.

Charge II: Dr. Teplick violated § 312.66 by

A. failing to have continuing IRB approval of the study;

B: failing to report promptly all changes in research activity to the IRB;

C: failing to report promptly to the IRB all unanticipated problems involving risk to human subjects; and

D: failing to obtain IRB approval before making changes in research.

Charge III: Dr. Teplick violated § 312.60 by

A: failing to conduct the investigation in accordance with the Investigator Statement; and

B: failing to follow the investigational plan.

Charge IV: Dr. Teplick violated § 312.62(b) by

failing to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug.

Charge V. Dr. Teplick violated § 312.62(a) by

failing to maintain adequate records of the disposition of the investigational drug.

Charge VI: Dr. Teplick violated § 50.27 by

failing to document informed consent.

Charge VII: Dr. Teplick violated § 50.25 by

failing to satisfy all of the requirements of informed consent.

To support the charges against Dr. Teplick, the Center presented three witnesses: Stephen B. Fredd, M.D., current Director of the Center's Division of Gastrointestinal and Coagulation Drug Products [see n. 8 at 3; Trans. Vol. 1 at 16-132]; Ms. Ann

deMarco, FDA investigator in the Philadelphia District Office [Trans. Vol. 1 at 136-242]; and Bette Lee Barton, M.D., Medical Officer of the Center's Division of Scientific Investigations [Trans. Vol. 1 at 242-322].

To defend the charges against Dr. Teplick, Mr. Krenzel presented two witness on Dr. Teplick's behalf: Steven K. Teplick, M.D., professor and Vice Chairman, Department of Radiology at the University of ,[12] [Trans. Vol. 2 at 4-86 & 130-358]; and , M.D., Staff Radiologist, and Chief of Lithotripsy, at the University of [13] [Trans. Vol. 1 at 86-129].

IV. REGULATORY FRAMEWORK

Section 355(i) of the FD&C Act authorizes FDA to issue regulations permitting qualified experts to investigate the

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[12] Dr. Teplick is also currently the Director of Diagnosis and the Director of the Radiology Residency Training Program at the University of . He served as a professor of radiology and Director of the Divisions of Computerized Tomography, Gastrointestinal and Interventional Radiology and Co-Director, Division of General Diagnosis at Hospital from 7/82 until 6/89. He assumed his current position at the University of on 7/1/89. [See Teplick Exhibit ("TX") B.]

[13] Dr. was a resident in diagnostic radiology from 83-86 at Hospital, where he served as abdominal imaging fellow from 86-87, and as a staff radiologist, from 87-88. [See TX H.]

safety and effectiveness of drugs that are intended solely for investigational use. Section 355(i) provides that FDA may enact such regulations necessary to ensure that the public health is protected during studies using investigational drugs. The regulations may include, among other things, provisions requiring that records of the investigation and drug use are established and maintained so that FDA may evaluate the safety and effectiveness of the drug to support approval of the drug under section 355.

FDA's regulations governing the clinical evaluation of investigational new drugs are set forth in Part 312. Regulations governing informed consent and institutional review boards which are applicable to clinical investigations are set forth in Parts 50 and 56.

Section 312.70 of the regulations provides for the disqualification of investigators. That section provides in relevant part:

> 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 56, . . . 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.

[§ 312.70(b).]

V. ANALYSIS

In preparing my report, I have carefully reviewed each charge alleged by the Center in the NOOH[14] in light of the information in the administrative record.[15] As stated above, I find that Dr. Teplick repeatedly violated the regulations in Parts 312, 50 and 56. Therefore, pursuant to § 312.70(b), I recommend that Dr. Teplick be disqualified from further receiving investigational drugs. Each charge, and my findings on that charge, will be discussed separately below.

* * *

[14] Part 16 provides: "FDA will give to the party requesting the hearing reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the decision or action taken or proposed that is the subject of the hearing and a general summary of the information that will be presented by FDA at the hearing in support of the decision or action." [§ 16.24(f).] Accordingly, any charges made outside of the NOOH, e.g., during the hearing, were not considered, because such charges would not present the clinical investigator with reasonable notice of the matters to be considered at the hearing.

[15] I did not consider information submitted after the hearing except that information for which I specifically permitted additional time for submission, pursuant to § 16.80(b).

Charge I: Dr. Teplick violated § 312.64(b) by:

A. failing to report alarming adverse effects immediately to the sponsor for subjects TE3, TE19, TE4, TE7, TE8, TE10, TE11, TE15, TE21, and TE25; and by

B: failing to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, the investigational drug for subjects TE13, TE6, TE9, TE14, TE16, TE22, TE23, and JM.

The Center alleged that Dr. Teplick failed to report alarming adverse effects immediately to the sponsor for ten subjects, and that he failed to report adverse effects caused by, or probably caused by, the investigational drug promptly to the sponsor for eight subjects, in violation of § 312.64(b).

For the reasons to be discussed below, I find that Dr. Teplick violated § 312.64(b) by failing to report immediately to the sponsor the alarming adverse effects experienced by subjects **TE3, TE4, TE8, TE21, and TE25**, and by failing to report promptly to the sponsor the adverse effects experienced by at least subjects **TE15, TE19, TE16, TE22, and TE23.**

Section 312.64(b) of the regulations provides that "[a]n investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably

caused by, the drug.[16] If the adverse effect is alarming, the investigator shall report the adverse effect immediately."[17]

While the regulations do not specifically define "adverse effect" beyond the above definition, "serious adverse experience" and "unexpected adverse experience" are defined. "Serious adverse experience" is defined in § 312.32(a) as:

> any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose

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[16] A "drug" is defined in relevant part as follows:

(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease [in] man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C) . . . .

[21 U.S.C. § 201(g)(1); see also n. 2 at 1.]

[17] The Center argued in its brief received February 14, 1992, that all alarming adverse effects must be reported to the sponsor regardless of whether the effects "may reasonably be regarded as caused by, or probably caused by, the investigational drug." [§ 312.64(b).] Section § 312.64(b) distinguishes between adverse effects and alarming adverse effects only in that an investigator should report all adverse effects promptly to the sponsor, and alarming adverse effects should be reported immediately to the sponsor. Thus, alarming adverse effects, still must be reasonably or probably caused by the investigational drug.

. . . .

"Unexpected adverse experience" is defined as:

> any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

[§ 312.32(a).]

Dr. Barton testified, as follows:

> alarming adverse events include things like death of the patient temporally related to treatment of the drug; life-threatening problems. It would also include previously unanticipated events, either in type, severity, or in frequency . . . we would expect these alarming events to be reasonably associated[18] with the test article, and the test article includes not only the chemical but the delivery system . . . it does not only include the ether, it would include the tract, the catheter, the TE-tube, the balloon that occludes, et cetera. If it is part of the delivery system, as is defined in the Food, Drug, and Cosmetic Act, it is the drug under the condition of use. Therefore, it is considered a part of the investigational drug or the new drug.

[Trans. Vol. 1 at 253-4.]

Also, according to Dr. Barton, "[a]n alarming adverse effect,

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[18] According to § 312.32(a): "Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug."

immediately we expect the investigator to report to the sponsor these events as soon as he can safely leave the side of the patient . . . ." [Trans. Vol. 1 at 248-9.]

However, the Center did not cite any regulations or agency guidelines to support the broad interpretation of the phrase "alarming adverse effect" to include an effect of the delivery system in the absence of the drug. Accordingly, I find that under FDA's regulations, an adverse effect includes effects of the drug delivery system only when the adverse effect was observed with or following the administration of the investigational drug. If the adverse effect occurred before the administration of the drug, it will not be considered as an adverse experience of the drug. [See § 312.32(a).] Finally, all adverse effects must be temporally related to the drug therapy to be properly considered reasonably associated with that drug and called an adverse effect of the drug.

The subjects entered onto Dr. Teplick's protocols received an investigational drug, and (, a drug approved for dissolution of bile stones. [Trans. Vol. 2 at 62-3.] Regarding the administration of , Dr. Teplick's clinical protocol stated:

> Surgery is still considered to be the treatment of choice for symptomatic gallbladder stones and stones obstructing the common bile duct. However, high-risk

> patients or in those who refuse surgery, other modalities are offered, including endoscopic papillotomy . . . or lithotripsy and extraction percutaneously . . . or per T-tube.
>
> In the occasional patient, all the above methods may fail either because of technical difficulties or large stone size. Hence, alternative therapy in such patients, who may have either gallbladder and/or bile duct stones, is the infusion of gallstone solvents for direct contact dissolution.

[TX E at 3; see also CX 45 at 1.]

According to the protocol, subjects were eligible to receive only after they were assessed to be ineligible for other herapeutic modalities. For this reason, many of the subjects in Dr. Teplick's study had pre-existing medical conditions that were either serious or life-threatening, which excluded them from receiving surgical intervention. [Supra; see also CX 60 at Tab B.] In my deliberations, I have considered that the subjects' pre-existing medical problems may have interfered with Dr. Teplick's ability to assess whether played a role in the alarming and serious adverse effects experienced by the subjects.

For subject TE3, the Center alleged that Dr. Teplick delayed reporting her death for more than six months to the sponsor and that this subject's death was an alarming adverse effect that should have been reported immediately to the sponsor.

The Center presented documents which identified subject TE3 as a 61 year old woman who died on 6/07/88 several hours following an infusion of to dissolve common bile duct stones. [CX 20 at 5-8.] The medical record showed that the subject had a history of end-stage renal disease requiring hemodialysis, hemophilia [a bleeding disorder], and congestive heart failure associated with chronic atrial fibrillation. She had been admitted to the Hospital (" ") from the emergency room on 5/25/88 with acute cholangitis and gram negative sepsis. Further tests demonstrated that she had a dilated common bile duct due to two large stones. An attempt was made physically to remove the tones. The hospital record reflected that the subject was considered "a poor surgical candidate," and the subject underwent chemical dissolution of the stones with drugs, and On 6/07/88, following catheter manipulation and infusion of , she was transferred to the Intensive Care Unit (ICU) because of hypotension and an apparent gastrointestinal bleed. Several hours after the infusion, she vomited, aspirated, and expired from a cardiac arrest. [Id. at 8.]

Dr. , a staff radiologist at who had performed the procedure on TE3, testified that he had had difficulty placing the balloon catheter used to administer "When she had her melanotic stool, that pretty much confirmed that I probably lashed a bit of a pancreatic or duodenal arcade artery, which is

not an uncommon thing . . . ." [Trans. Vol 2. at 93.] Dr. Teplick and Dr. . agreed that the apparent complication occurred prior to the administration of the The CRF, dated 1/06/89, six months after the event, noted Dr. Teplick's statement: "This physician thinks her hypotension was mainly due to a significant GI bleed from our catheter manipulations + [and] not due to --but we'll never be sure what role played in her demise." [CX 20 at 3.]

Dr. Teplick testified: "I'm not saying I shouldn't have reported this, but at the same time that this happened, I really did not believe this had anything to do with . . I still don't believe it really had anything to do with ." [Trans. Vol. 2 at 64-6.]

Subject TE3 had a number of serious medical problems that could have contributed to her death. Death was an unexpected adverse effect, because neither the study protocols of Dr. Teplick or Dr. , nor Dr. Teplick's informed consent form for , listed death as an adverse effect of administration. [See CX 30, 45, and 54.] **TE3 died within several hours after the cessation** of the treatment with ; the date of her death was 6/07/88, and the date of the CRF was 1/06/89. [See CX 20 at 3 and 5.] In summary, the death of **TE3 within several hours of** administration **was an alarming** adverse effect, because it was

both a serious and unexpected adverse experience, as well as temporally associated with the investigational drug. [See n. 19 at 19.] Moreover, since the alarming adverse effect of the death of this subject was not reported immediately, i.e., it was reported six months after the event occurred, I find that the Center proved its subcharge that Dr. Teplick failed to report immediately the alarming adverse effect of TE3's death to the sponsor. Therefore, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report immediately alarming adverse effects.

For subjects TE15 and TE19, the Center alleged that Dr. Teplick failed to report the breakage of the occlusive balloon used in the administration of and that this adverse effect was alarming and should have been reported immediately to the sponsor. [Trans. Vol. 1 at 159; CX 4 at 4; CX 5 at 14.]

Dr. Teplick testified that some of the device products used in the administration of "dissolved" or broke upon contact with the product. He testified that he experimented with several kinds of device products to determine which ones would not break in the presence of [Trans. Vol. 2 at 164.] He had written that the occurrence "did not result in any subject complications. This was interesting to me, but I saw no need to put it on the CRF." [TX J at 2.] When a balloon would break,

Dr. Teplick testified that he would change the balloon and use another type. [Trans. Vol. 2 at 163.]

The dissolution or "breakage" of the balloon device used to administer the was a recognized adverse event, as evidenced in a report by Dr. , which he had submitted to the IND. [CX 60 at Tab G.] The report stated: "Three side effects occurred with , though none caused the discontinuance of its use . . . [O]ne of the catheters we used (material) was significantly destroyed by the in vivo effect; in vitro, no effect had been observed." The report concluded by stating " material cannot be used as a double lumen catheter with , as it can with other biliary, urinary, or enzyme solvents." [Id.] In addition, Dr. had discussed the problem of dissolution in a letter addressed to Mr. Manilla, dated 8/4/88, [supra] in which he stated: of course, will dissolve syringes, but we are using it with catheters composed of . We have had no difficulty with any destruction of this material during infusion." [CX 60 at Tab D.]

It was unclear from his testimony whether Dr. Teplick had been aware of 's effect on some of the catheter materials. He testified that "some of the balloons broke when they came into contact with the " [Trans. Vol. 2 at 163.] He stated that

he had first become aware of the drug's interaction with the device when he noticed "the minute touches a syringe it's frozen solid . . . As we became a little more sophisticated, and then started to put balloons into the system, we found that there's certain material that the balloons are made out of . . . ." that apparently caused them to break in vivo. [Id.] This information was not reflected in the clinical protocol of Dr. Teplick. [See CX 45.] The protocol and consent form submitted by Dr. to the IND, however, did discuss the use of syringes to administer the [CX 54 at 1; TX A at 13.] The consent form used for Dr. Teplick's protocol did not discuss these issues. [See CX 30.]

Dr. Teplick testified that the occlusive balloon was used to block the egress of the from the common bile duct or gall bladder in order to reduce the systemic absorption of the drug. [Trans. Vol. 2 at 161.] He also testified that a balloon was not essential to the administration of the drug, since in Europe the was administered endoscopically directly into the common duct. [Trans. Vol. 2 at 165-6.] Although he did not consider it essential, Dr. Teplick used the device to administer to his subjects. In my opinion, the malfunction or misuse of the device might have resulted in greater absorption of the drug, thereby producing adverse effects.

Dr. Teplick affirmed that the breakage of the balloon occurred only in the presence of the investigational drug. [Trans. Vol. 2 at 163.] The possibility of such an event was not discussed in either his clinical protocol or the consent form. [Supra; CX 30; CX 45.] Since the use of the balloon was not without risk, and the breakage of the balloon introduced unknown risks to the subject, the occurrence of breakage should have been reported as an adverse event for both **TE15** and **TE19** on the CRF. However, since the destruction of the balloon did not result in any clinical sequelae for these two subjects [see TX J at 2], the event, while "unexpected," was not "alarming." Therefore, this adverse effect did not require immediate reporting to the sponsor. However, as an adverse effect, it should have been reported promptly. The CRFs for subjects **TE15** and **TE19** failed to mention that the balloons had dissolved during treatment. [See CX 4 at 1-3 and 5 at 1-3.] For **TE15** and **TE19**, I find that while the Center was unable to prove that the breakage of the balloon was an "alarming adverse effect that was not reported immediately," it did prove that the breakage of the balloon was an "adverse effect that was not reported promptly;" indeed, the effect was not reported at all. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report promptly this adverse effect.

Regarding subject **TE4**, the Center alleged that Dr. Teplick failed

to report the alarming adverse events of severe hypertension and lethargy following administration of

Subject TE4 was a 62 year old woman, who had a history of "malignant hypertension," severe valvular heart disease, and congestive heart failure. She had been taking multiple medications to control both her hypertension and cardiovascular disease at the time of her admission on 12/13/87. [CX 17 at 6.]

A radiology note on the hospital chart stated: "The BP [blood pressure] paradoxically increased during study to approximately 240/110, so decision made to hold today." [CX 17 at 30.] The subject's hospital record reported that the "Patient became sedated, was] held and then restarted. No significant effect on BP." [Id. at 4.]

Dr. Teplick testified that he did not report the elevation of this subject's blood pressure, because in view of her significant past medical history of hypertension, he did not believe that the elevation observed during the administration of was clinically significant, or that contributed to the hypertension. [Trans. Vol. 2 at 181-2.] A note by the Cardiology attending the day following admission, stated: "Suggest: Need better BP control . . . ." [CX 17 at 28.]

Hypertension, however, was not listed as a known adverse effect of in the protocol or in the study consent form. [See CX 30, 45, & 54.] For this reason, hypertension should have been considered an unexpected reaction. TE4's blood pressure prior to was recorded as 220/90, which "paradoxically increased during study to [approximately] 240/110 . . . ." Dr. Teplick had characterized this adverse event as a "minor" side effect. [See CX 17 at 3.]

I consider a change in the diastolic blood pressure from the normal range of 90 to the hypertensive range of 110 mm Hg, in the presence of a high baseline systolic blood pressure (220), occurring during the administration of an investigational agent, to be an "alarming" event. [CX 17 at 28.] Moreover, this elevation in blood pressure formed the basis of the treating physician's decision to withhold further administration of [Id. at 4.] Given that the change in the subject's blood pressure was "associated" with the administration of , and the change that occurred was an alarming adverse experience, TE4's severe hypertension should have been reported immediately to the sponsor.

The Center alleged that Dr. Teplick failed to report the alarming effect of lethargy for TE4. Sedation, which might also be characterized as "lethargy," "sleepiness," or "narcosis," was

experienced not only by TE4, but by many other subjects who received (e.g., TE8, TE21, TE25, TE15, TE16). [See CX 60 at 27-30.] However, the only reference to sedation in Dr. Teplick's protocol stated: "Recently, [ ] has been successfully infused into the biliary tract in 4 patients at , without toxicity or narcosis." [CX 45 at 1.] The protocol submitted by Dr. to the IND listed "absorption of with systemic effects," but did not state that "sedation" was one of those effects. [See CX 54 at 5.] Sedation is not mentioned in the informed consent form. [See CX 30.] However, subjects often received analgesics and other medications during the procedures to which sedation, or "lethargy," could also be attributed. Therefore, while I find that TE4's lethargy should have been reported as an adverse effect, it should not have been characterized as an alarming adverse effect. [See CX 17 at 3.]

On TE4's CRF, Dr. Teplick noted the subject's adverse effect sedation, but he failed to mention the subject's alarming adverse effect of severe hypertension. [CX 17 at 1-3.] Specifically, the CRF listed "mild sedation" for three of the four treatments, and "heavily sedated" for one of the treatments. [Id. at 2.] This subject's overall adverse effects were reported as "minor" side effects. [Id. at 3.]

erefore, I find, that although Dr. Teplick adequately recorded

TE4's "lethargy" as "sedation" on the CRF, he failed to record the severity of TE4's "hypertension" as an alarming adverse experience associated with the administration of . For these reasons, I find that the Center proved the subcharge that Dr. Teplick failed to report immediately TE4's alarming adverse effect of severe hypertension to the sponsor. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report immediately this alarming adverse effect.

The Center alleged that "Subject TE21 experienced chest pain, PVC's, hypotension, atrial fibrillation, and occlusive balloon deflation during treatment with in October and November 1986. You [Dr. Teplick] reported only PVCs and chest pain on the CRF." [CX 35 at 2-3.] I interpreted this charge to mean that the Center alleged that Dr. Teplick failed to report immediately the alarming adverse effects of hypotension, atrial fibrillation, and occlusive balloon deflation to the sponsor.

Subject TE21 was an 86 year old woman, who was transferred to on 11/18/86 for pain due to a common bile duct stone. She was also noted on admission to have chronic obstructive pulmonary disease and cardiac disease, i.e., atrial fibrillation, for which she was receiving several cardiac medications. [CX 6 at 6 & 4.]

According to the discharge summary: "Attempt was done to dissolve the stones 3 times but the patient would complain of right upper quadrant pain and chest pain and she went into rapid atrial fibrillation and had to be transferred to 12 West for monitoring requiring digitalization and high dose [sic] of Inderal IV." [Id.] The Diagnostic Request and Report of the Department of Diagnostic Radiology, read: "Six (6) cc's of were instilled. The patient then experienced runs of etat [sic = "V-tach" ventricular tachycardia] and multifocal PVC's [premature ventricular contractions]. The was then withdrawn after two minutes of therapy. No appreciable effect could be seen at this time. The patient's cardiac symptoms promptly subsided . . . ." [Id. at 8.]

In his testimony, Dr. Teplick stated that he did not report atrial fibrillation as an adverse experience of , because TE21 had this condition prior to her hospitalization. He also stated that he did not report hypotension, because he found no evidence for it.

However, the subject's pain and cardiac arrhythmias worsened during the administration of and improved following cessation of the investigational drug. Also, a Cardiology note in the hospital progress notes dated 11/03, commented that the subject had a "diapheresis [sic] with biliary manipulation. BP

decreased to 100 systolic--now increased to 110 . . . ." which was reflected in the monitoring record of the subject's vital signs during the procedure of the same date. [CX 6 at 14, 24-5.]

With respect to the balloon deflation, Dr. Teplick previously testified that the dissolution of the balloon on contact with the ether did not produce an adverse effect, and he replaced any of these devices which failed during the investigation. [Trans. Vol. 2 at 232-4.]

Neither the clinical protocol nor the consent form listed hypotension, atrial fibrillation, or occlusive balloon deflation as known adverse effects of [See CX 45 & CX 30.] Despite the statement on the CRF that the subject was in "poor medical condition" as a "reason to avoid surgery," she finally underwent surgical removal of the stones under general anesthesia on 11/04/86. [CX 6 at 5.] The CRF listed "minor side effects," including a statement that "the chest pain was probably due to underlying cardiac disease and catheter manipulation . . . ." [Id. at 3.]

Since the cardiac events experienced by TE21 during the administration of were both unexpected and potentially life-threatening, I consider them alarming. Since they were

associated with the administration of the investigational agent, as discussed above, they should have been reported immediately to the sponsor. In addition, although not an "alarming" adverse experience, as an adverse event, the balloon's deflation should also have been reported promptly. [Supra.] For these reasons, I find that for TE21 the Center proved that Dr. Teplick did not report the alarming adverse effects of hypotension and atrial fibrillation and the adverse effect of occlusive balloon deflation. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report immediately the alarming adverse effects of hypotension and atrial fibrillation and failing to report promptly the adverse effect of occlusive balloon deflation.

The Center alleged in the NOOH: "In September, 1987, subject TE25 developed hypotension during, and cyanotic nails following, treatment with You did not report these alarming effects on the CRF." [CX 35 at 3.]

Subject TE25 was a 94 year old man with a past medical history of chronic obstructive pulmonary disease and emphysema. He had been transferred from another hospital with a diagnosis of "septic shock and obstructive jaundice." [CX 14 at 3 & 11.]

Dr. Teplick admitted that hypotension or cyanotic nail beds were

not recorded as adverse events, because he believed these effects resulted from the subject's heavy sedation or his history of chronic obstructive pulmonary disease and pneumonia. [Trans. Vol. 2 at 240; see also CX 14.]

The hospital report noted the administration of the investigational drug on 9/14/87: " was instilled into the common bile duct around several biliary calculi . . . The odor or [sic] was noted on the patient's breathand [sic] the procedure was subsequently stopped due to blood pressure diminishing to 100/50." [CX 14 at 17.] On 9/16/87, was administered again: "The study was stopped due to evidence of patient sedation and mild hypotension with a blood pressure of 90/50. The patient was discharged from the department in stable condition." [Id. at 18.] Since infusion was discontinued as a result of the subject's combined hypotension and sedation, the hypotension was an adverse experience "associated" with the investigational drug and, therefore, should have been reported promptly on the CRF as an adverse effect. [See § 312.64(b).] TE25's hypotension was not reported on his CRF. [CX 14 at 2 & 3.]

Although the subject had significant pulmonary disease which commonly produces cyanosis of the nail bed, no documentation of cyanotic nail beds was produced by the Center in either its

exhibits or testimony. In fact the hospital progress notes following the infusion on 9/16/92 specifically stated that the subject did not exhibit "clubbing" [thickening of the nail-bed, thought to be due to hypoxemia] or "cyanosis" of the nail beds. [CX 14 at 58.]

The subject's CRF recorded sedation on both procedural dates, with a notation of "heavily sedated" for 9/16/87, but failed to mention hypotension as an adverse effect. The final page noted that the subject experienced "minor" side effects. [CX 14 at 2 & 3.]

.herefore, as stated above, Dr. Teplick should have reported promptly hypotension as an adverse effect to the sponsor in the CRF. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report promptly the adverse effect of hypotension for subject TE25.

The Center charged that subject TE8 developed chest pain, atrial fibrillation, and junctional rhythm, and that the occlusive balloon dislodged during treatment with It alleged that only the chest pain had been noted on the CRF, and that Dr. Teplick delayed in reporting all of the above listed alarming adverse effects to the sponsor.

TE8 was an 83 year old woman with a past medical history of congestive heart failure, three myocardial infarctions, and atrial fibrillation, "who had developed sudden epigastric pain on 3/22/87" [actually 3/02/87]. [CX 9 at 12.] She had recovered from cholangitis, and because she had refused surgery for the removal of common bile duct stones, TE8 was transferred from another hospital to on 3/05/87 for nonsurgical removal of the stones. At the time of admission to she was on multiple cardioactive medications.

A procedural sheet stated that on 3/11/87, the subject had an "episode of chest heaviness. '7' on a 1-10 scale. QRS changes on the [EKG] monitor . . . ." which resolved with two doses of sublingular nitroglycerin ("NTG"). [Id. at 26 & 38.] An "unsuccessful" attempt to infuse was made the next day; however, the subject again experienced chest pain, which was relieved by NTG and lidocaine. The CRF reported "The pain on 3/12/87 was probably cardiac and not related to ." The records did show that the was discontinued: "3 1/2 hrs of MTBE . . . ↓ [decreased] level of consciousness forced halt to study . . . ." [Id. at 8.] Another procedural sheet for 3/12/87 noted: "much CP [chest pain] → some relief c ["cum" = "with"] NTG → junctional rhythm. Stopped . . . ." [Id. at 10.]

The Center produced the subject's CRF, which had been signed and

dated by Dr. Teplick on 11/24/88, more than 18 months following the subject's 3/17/87 discharge from [CX 9 at 3 & 12.] Although the subject underwent five infusions of on 3/06, 3/09, 3/10, 3/11, and 3/12/87, the Center noted that the CRF had omitted the 3/11/87 infusion. [Id. at 2; infra Charge IV.4.] The CRF stated: "Because of chest pain -- probably cardiac and arrhythmia [,]therapy [with] was D/c [discontinued]. Pt [Patient] was discharged c ["cum"- with] 1 remaining GB stone." [Id. at 3.]

Even though **TE8** had a significant history of cardiac disease prior to the administration of , the subject experienced an exacerbation of her serious cardiac abnormalities, which was temporally related to the infusion of the investigational product and which caused the infusion of to be halted on more than one occasion. For these reasons, this adverse experience was "alarming." I, therefore, find that not only did Dr. Teplick fail to report the adverse event adequately on the CRF, he also failed to report it immediately to the sponsor. For these reasons, I find that the Center proved its subcharge. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b) by failing to report immediately the alarming adverse effects of at least the chest pain for subject **TE8**.

Regarding subject **TE16**, the Center alleged that Dr. Teplick

failed to report promptly the subject's adverse effects of lethargy, sedation, and pain.

TE16 was a 67 year old woman with a past medical history of recurrent biliary tract stones, insulin-dependent diabetes, and two myocardial infarctions; she had also undergone a pancreatic resection for chronic pancreatitis. [CX 2 at 7.]

Regarding sedation, the subject's medical record stated: "The patient had either [sic] dissolution [sic] on June 2 for the common duct stone. The patient became increasingly somnolent during the administration of and it was terminated after one hour due to increased somnolence." [CX 2 at 7.] In addition, the diagnostic request and report stated: "During the administration of the patient became increasingly somnolent but was arousable at all times. The administration was terminated after 1 hour due to increasing somnolence." [CX 2 at 14.]

Regarding the subject's pain after treatment, the diagnostic request and report stated: "Following the procedure, the subject complained of lower chest or upper abdominal pain. The primary Service was called and an EKG was performed. The EKG showed no acute changes or any change from the previous exam." [CX 2 at 14.]

Dr. Teplick responded in writing that "The patient became sedated from . This was reported on the CRF. No pain occurred from the infusion." [TX J at 5.]

However, according to the subject's CRF, which was signed on 1/09/89 (two and one half years after she had received), sedation was reported, but lethargy and pain were not. This cannot be regarded as "prompt" notification of the adverse effects to the sponsor. In addition, since the evidence showed that the source of pain was undetermined, and the drug was temporally related to the subject's pain, this adverse effect of pain should have also been reported promptly to the sponsor.

For the above reasons, I find that the Center presented sufficient evidence to support its subcharge that Dr. Teplick failed to report promptly the adverse effects experienced by TE16 to the sponsor in the CRF. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b).

Regarding subject TE22, the Center alleged that Dr. Teplick failed to report promptly to the sponsor that was discontinued due to the adverse effects of severe pain and nausea.

TE22 was an 81 year old woman who was transferred from another

hospital with a two-week history of "vomiting, nausea, abdominal pain, shaking chills and fever, having been found by the family to be a bit lethargic . . . ." [CX 26 at 12.] Her hospital record showed that she had a temperature of 104°F upon admission to [Id.]

The subject received two infusions of A diagnostic report dated 3/16/89 stated: " installation was attempted via the pigtail catheter but this was only tolerated for approximately 10 minutes at which point the subject developed severe abdominal pain and nausea." [Id. at 22.] On the following day, TE22 received a second infusion of lasting up to 1 hour and 15 minutes, during which she experienced no nausea. [Id. at 23.] In his written response, Dr. Teplick stated that the subject's nausea was not related to the . [TX J at 5.]

Regarding TE22's pain during the treatment, the CRF stated that her pain was recorded as "+3" on a scale of 1 to 4, with an added: "The pain on 3/16 was probably due mostly to catheter manipulations sans [without] adequate anesthesia." [CX 26 at 2.] Subsequently, she had epidural anesthesia. [Id. at 3.] As noted above, the 3/16/89 diagnostic report also stated that TE22 could tolerate the treatment for only 10 minutes due to both nausea and pain. In his written response, Dr. Teplick stated: "This patient [TE22] experienced pain with the first dose of

which was reported on the CRF." [TX J at 5.]

While the CRF for TE22 did mention pain, it did not reflect that the initial infusion of was discontinued as a result of the severity of the pain and nausea. [CX 26 at 1-3.] In fact, the CRF did not record that the subject had experienced nausea for the infusion on 3/16/89. [Id.]

Although TE22 had a history of pain and nausea, these adverse experiences were temporally noted in association with the drug and were severe enough to cause cessation of the infusion. [Id. at 12 & 22.] Given these facts, even though analgesics or anesthetics were administered to prevent the adverse effects, I find that these events should have been reported to the IND sponsor. Therefore, I find that the Center proved the subcharge for TE22, because Dr. Teplick failed to report promptly the adverse effects of pain and nausea to the sponsor. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b).

Regarding subject TE23, the Center alleged that Dr. Teplick failed to report that was discontinued due to extreme nausea and decreased blood pressure.

This subject was an 84 year old man, with a history of

hypertension and diabetes, as well as "pain with shakes and fever . . . Hydration and antibiotics would relieve his pain . . . ." [CX 25 at 10.]

A radiology note, dated 3/15/89, stated, " installation performed for approximately 30 minutes at which time patient became extremely nauseous with slight drop in blood pressure. It was decided to terminate the procedure at this point." [Id. at 18; see also id. at 6, 10 & 52.] In addition, the Anesthesia Record showed TE23's blood pressure decreased from 138/75 to 90/60 during the infusion. [Id. at 23.]

In his written response, Dr. Teplick stated that TE23 had "received a short course of which was discontinued by the anesthesiologist because he thought we were using '

.'" [TX J at 5.]

However, the subject experienced nausea and fluctuations in blood pressure during the administration of resulting in the termination of drug. As discussed for TE22, the effects experienced by TE23 should have been reported promptly to the sponsor. [See supra.]

On the CRF, nausea was recorded as "0" on a scale of 1 to 4 [CX 25 at 2], and the comments section stated "PT [Patient] received

short course of because anesthesiologist present during procedure was concerned about his cardiac status." [Id. at 3.]

Therefore, I find that for TE23 the Center proved its subcharge that Dr. Teplick failed to report promptly to the sponsor that was discontinued due to extreme nausea and decreased blood pressure. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.64(b).

* * *

I find that the Center sufficiently supported the above subcharges. However, I also wish to note that for a variety of reasons, the Center presented insufficient evidence to support a number of its subcharges listed under Charge I. One example of such subcharge was subject TE7, in which the Center alleged: "On June 5, 1987, subject TE7 returned to her hospital room very lethargic and with low blood pressure. This subject also had periods of apnea and was transferred to the ICU. You failed to report these alarming adverse effects on the CRF." [CX 35 at 2.]

TE7 was an 82 year old woman with a history of insulin-dependent diabetes mellitus and heart disease. She had been transferred to for the "radiologic removal of the [common bile duct] stone." CX 11 at 6.]

The discharge summary denied any adverse experiences: "The patient remained stable throughout her postoperative course with no complaints." [Id.] However, the nursing notes stated "some apnea" had occurred upon the subject's return from the radiology department, following the administration of on 6/5/87. [Id. at 14.] Prior to the administration of TE7's blood pressure was recorded to be in the range of 118/75, and she remained stable throughout the procedure. [Id. at 11.] When she returned to the floor, her blood pressure was recorded as "110/58 - 98/48"; Narcan(a narcotic antagonist) was administered and the subject "became more responsive . . . ." [Id. at 14.] She was then transferred to the ICU where her blood pressure was recorded as 154/60. [Id. at 15.]

In a written response, Dr. Teplick stated: "My records indicated that she was mildly sedated questionably from questionably from narcotics. She was awake and alert in several hours." [TX J at 3.] The records showed that the subject experienced a rapid response to the narcotic antagonist, Narcan, indicating that the likely cause of her adverse effects was a result of a narcotic agent, rather than the investigational drug. Therefore, the Center failed to prove that this adverse effect resulted from the administration of the investigational drug which, therefore, should have been reported. Thus, this subcharge failed to support the Center's charge that Dr. Teplick violated § 312.64(b)

by failing to report immediately the alarming adverse effects of lethargy, low pressure, and apnea for subject TE7.

* * *

Throughout the hearing Dr. Teplick testified that he was unaware of many of FDA's regulations affecting clinical investigators of investigational new drugs. This fact does not absolve him from responsibility under FDA's regulations. I find for the reasons stated above that Dr. Teplick violated § 312.64(b), by failing to report immediately the alarming adverse effects experienced by subjects TE3, TE4, TE8, TE21, and TE25, and by failing to report promptly the adverse effects experienced by at least subjects TE15, TE19, TE16, TE22, and TE23.

* * *

Charge II: Dr. Teplick violated § 312.66 by:

A. failing to have continuing IRB approval of the study.

The protocol approval form issued by the Committee for Human Studies ["CHS"], the "IRB" at Dr. Teplick's institution read, as follows:

> This approval is given subject to the committee's absolute right to monitor this project at any time it sees fit. Any failure to fully cooperate with this Committee on this aspect will result in the immediate

> withdrawal of approval and prompt notification to the proper agencies or authorities. You are responsible for advising the Committee for Human Studies of the date of activation. If the Committee does not hear within one year, it will be assumed that the project was not activated and approval is automatically withdrawn. If it is activated, there will be a review by the Subcommittee of the Committee for Human Studies concerning the progress and continuity of the project at least annually, but more often if the Committee so directs. Forms will be sent to you which must be immediately filled out and returned to the Subcommittee. Failure to do so will make the project ineligible for reapproval and no other projects will be considered by the CHS until compliance is complete. Also note that any radical changes once the project has begun, must be submitted in writing to the OGC ["Office of Grants and Contracts"] and adverse reactions must be reported to the CHS. All signed consent forms must be retained and available for CHS review for a period of five years following the termination of a project. Further, a final progress report must be provided to OGC for their records.

[CX 38; CX 42 at 2; CX 43 at 2.]

1. The Center alleged that Dr. Teplick failed to modify his consent form[19] to conform to his IRB's requirements.

An internal memorandum from the Office of Grants and Contracts of University, dated 3/12/86, stated that the IRB "tabled" Dr. Teplick's protocol until he had, among other things, deleted the reference to the possible effectiveness of the in

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[19] See also infra, Charge VII.

paragraph 3 of the "Purpose of Research" section of his protocol. [CX 36 at 1 & 2.]

Dr. Teplick submitted a response to the Office of Grants and Contracts, dated 3/27/86, which stated that he had "deleted the sentence concerning the effectiveness of the " [CX 37 at 2; see also CX 38 at 5.] The Center, however, presented 14 consent forms, dated from 5/19/86 to 4/10/89, all of which still contained the statement: "We feel that the drug will probably be effective in your case." [CX 30.]

Although the Center demonstrated that Dr. Teplick failed to comply with this requirement from the IRB for approval, the Center records showed that IRB had sent Dr. Teplick an annual report form and approved his study on both 5/6/87 and 8/10/88, thereby continuing his IRB approval until 8/10/89.[20] The Center, thus, failed to substantiate its charge that Dr. Teplick did not have continuing IRB approval for his study. In fact, Dr. Teplick had IRB approval even after his IRB audited his study and examined his consent forms on 1/23/87. [See CX 53.] Therefore, I do not find that this subcharge supported Charge II.A.

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[20] As discussed below, the Center placed Dr. Teplick's clinical trials on clinical hold for the reasons expressed in a letter from Dr. Fredd, in a letter dated 5/25/89. [CX 40.]

2. The Center alleged that Dr. Teplick failed to report back to his IRB after five subjects, as required by the terms of his IRB approval.

The Center presented a document of the IRB dated 4/09/86, which stated: "the protocol is then approved with the condition that Dr. Teplick report back to the Committee after completing five patients before proceeding with the study." [CX 38 at 2.] Dr. Teplick responded in a memorandum to Mr. in the Office of Grants and Contracts, dated 4/21/86, by stating "Yes, we will be glad to report back to you after five cases." [Id. at 3.]

Dr. Teplick's IRB reviewed his project, and the Subcommittee for Continuing Review of Projects of the Committee for Human Studies (part of the IRB) site visited him on 01/23/87 at 10:30 a.m. [CX 53 at 2.] The minutes for the Subcommittee for Continuing Review of Projects stated on 02/11/87: "Six subjects were enrolled in this study . . . Dr. Teplick was reminded that the Committee stipulated that he was to submit a written report to the Committee after he had seen five patients. This report is now due. There were no adverse reactions seen." [Id.]

From the hospital record, it appeared that Dr. Teplick administered to a seventh subject, TE9 between 11 a.m. and 3 p.m. directly following the IRB site visit. [CX 7 at 15 & 17;

see also id. at 29.] No documentation of the initial five subjects was submitted to the IRB prior to the administration of to two additional subjects. For this reason, I find that the Center substantiated its subcharge that Dr. Teplick failed to report back to the IRB after five subjects, as required by the terms of his IRB approval.

However, as with the previous subcharge, the Center did not demonstrate how this subcharge supported the charge that Dr. Teplick failed to have continuing approval of his study. As stated supra, Dr. Teplick did have continuing IRB approval. The act that his IRB already knew that he had violated his stipulation to report back after five patients, as noted in the audit by his IRB on 1/23/87 [see CX 53], but still continued to approve his study, demonstrated that Dr. Teplick did not violate § 312.66 as alleged.

Since neither of the subcharges under Charge II.A. supported the Center's charge as stated, I find that the Center failed to prove that Dr. Teplick violated § 312.66 by failing to have continuing IRB approval of his study.

* * *

Charge II: Dr. Teplick violated § 312.66 by:

B: failing to report promptly all changes in research activity to the IRB.

The Center alleged that Dr. Teplick failed to report to the Human Research Advisory Committee of the University of (also an IRB), the following: 1) that FDA had placed the protocol for common bile duct stones on clinical hold due to unreasonable and significant risk to human subjects; 2) that FDA had specifically suspended the proposed study of the dissolution of the common bile duct stones with and (3) that the FDA had required all of the consent forms to inform potential subjects that a death had occurred.

Neither the Center, nor Dr. Teplick addressed this charge during the hearing. Prior to the hearing, the Center had submitted a letter dated 5/25/89 addressed to the sponsor, Dr. in reference to the "Clinical Hold" on the common duct portion of the study:

> We ask that you not enter any more patients in the common duct portion of the study until we have received the details on the patient (TE-3) and notify you that it is safe to proceed with the study . . . In addition we believe that you should modify your consent form for all protocols to advise potential subjects that a death has occurred . . . .

[CX 40 at 1.]

The sponsor responded to the agency in a letter, dated 6/1/89, providing the following assurances:

> [W]hen I spoke to him [Dr. Teplick] on the telephone yesterday, it was his last day at . . . I have notified Dr. Teplick . . . that is not to be used for the treatment of duct stones until we receive permission from your office.
>
> I have also sent them [Dr. Teplick and the other investigators] a copy of your letter, indicating the necessity of notifying your office quite promptly if there are any side effects.

[CX 41 at 2.]

Dr. Teplick, however, had signed an affidavit on 7/31/89, stating:

> On 7/27/89, Inv. Wilson [FDA investigator who obtained the affidavit] informed me that FDA has instructed that no more patients be entered into the study that involves the dissolution of bile duct stones with
>
> As of 7/27/89, I had not received any written communication from , MD, Sponsor/Investigator, regarding this "clinical hold" on subject entry. He telephonically told me, but I cannot recall exactly when.

[CX 41 at 1.]

In a written response submitted at the hearing, Dr. Teplick stated:

> The protocol [for submitted to the University of IRB is specifically limited to GB ["gall bladder"] calculi.
>
> The IRB at the University of ["] is aware that the

> use of in the ductal system has been suspended. (If you wish I will have them call you). I was not aware that the consent form required a statement that "a death occurred". My understanding was that the cause of death was under investigation and that it had not been established that was the cause.

[TX J at 11; see also n. 20 at 48.]

Dr. Teplick also provided an addendum:

> Dr. and the IRB at were informed that could no longer be used in the common bile duct. I informed them of this personally in a meeting and should there be any question of this please contact Dr. in the department of medicine. That the FDA required all consent forms to inform subjects that a death had occurred: I had no knowledge that the FDA required this information on the consent form. Furthermore, we can only use in the gallbladder and this was a death that had nothing to do with the gallbladder.

[TX V at 21.]

The Center did not produce any additional evidence to demonstrate that Dr. Teplick had received notice that the agency required his consent forms to mention the occurrence of a death on the protocol. In addition, the wording in the Center's letter to the sponsor--"we believe that you should modify you consent form . . . ."--might be interpreted that Dr. Teplick had the option not to include such information. [CX 40 at 1.] Dr. Teplick's :tions, however, demonstrated that he had been aware of the linical hold" the agency had placed on the common duct portion

of the protocol. Since a "clinical hold" represented a change in the research activities on his clinical study, he was required, and he proceeded to convey this information to the new institution's IRB. [See § 312.53(c)vii.] Dr. Teplick's presentation at a meeting of the new institution's IRB constituted reasonable notification of the required information.

Under § 312.56(d), when a sponsor determines that an investigational agent poses an undue safety concern, which was addressed in the agency's letter to Dr. , it is the sponsor's responsibility to notify all IRBs and the investigators who have at any time participated in the investigation of the discontinuance of an investigation. [See § 312.56(d).] Nevertheless, Dr. Teplick seemed unaware that the subject's death should be included in the consent form, and the Center failed to establish that Dr. Teplick had been dutifully informed of this requirement by the sponsor.

For the above reasons, I find that Dr. Teplick adequately informed the IRB of the University of of the clinical hold on his study, and that he was unaware of a requirement to modify his consent forms indicating that a death had occurred. Therefore, I find that the Center did not prove this subcharge. Thus, this subcharge did not support the Center's charge that Dr. Teplick violated § 312.66 by failing to report promptly all

changes in research activity to the IRB.

* * *

Charge II: Dr. Teplick violated § 312.66 by:

C: failing to report promptly to the IRB all unanticipated problems involving risk to human subjects.

An unanticipated problem involving risk, as explained above, is an adverse experience which is not mentioned in the study's protocol or informed consent form that could be potentially life-threatening or have serious health consequences. [See § 312.32(a).] Dr. Teplick's protocol in the "Risk Management Procedures" section listed instances where infusion would be discontinued: severe pain, intractable nausea and vomiting, evidence of a leak around the catheter, no stone dissolution, on demand of the patient, and at the recommendation of the attending physician. [CX 45 at 6.] Dr. Teplick's informed consent form listed the following possible side effects: discomfort from venipuncture in the blood tests (excessive bleeding, bruise, blood clot, infection), and nausea and vomiting. [CX 30 at 3.]

1. "There is no documentation that the death of subject TE3 was reported to the IRB." [CX 35 at 5.]

I interpreted this subcharge to mean that the Center alleged that Dr. Teplick violated § 312.66 by failing to report promptly to the IRB the unanticipated event of a death of a study subject that was temporally associated with the administration of the investigational drug. For this reason, death was an adverse event and represented a risk to human subjects that was not mentioned in the protocol or the informed consent form. [See CX 45 at 6; CX 30 at 3.] The Center presented records to substantiate that subject TE3 died on 6/07/88. The circumstances leading up to this subject's death have been described, under Charge I. [Supra.] In addition, the annual "Survey Sheet of the Subcommittee for the Continuing Review of Projects of the Committee for Human Studies," dated 8/10/88 to 8/10/89, was presented which failed to show the reporting of TE3's death. [CX 44.] Although the Survey requested information regarding "toxicities, idiosyncrasies, side effects, etc. . . .", this section of the survey had been left blank. [Id.]

In his written response to the Center, Dr. Teplick stated: "It is true that I did not report TE3's death. But, as stated previously, we did not consider that her death was due to —" [TX J at 5.] No additional information was produced by Dr. Teplick at the hearing.

While may not have been a direct cause of TE3's death, it

was at least temporally related. As discussed in Charge I, supra, the death should have been reported to the IRB. Therefore, I find the Center proved that Dr. Teplick failed to report TE3's death to the IRB, as required. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to report promptly to the IRB all unanticipated problems involving risk to human subjects.

2. "On January 23, 1987, you reported verbally to the IRB that 'no adverse reactions had occurred.' Medical records show that on September 26, 1986, an occlusive balloon dissolved (TE19); on August 18, 1986, a t-tube and two occlusive balloons dissolved (TE15); on October 31, 1986, subject TE21 had PVCs; and on November 3, 1986, subject TE21 had atrial fibrillation and PVCs" [CX 35 at 5.]

I interpreted this subcharge to mean that the Center alleged that Dr. Teplick made an oral misrepresentation to the IRB, stating that no adverse effects had been observed, when in fact several had. The Center, however, presented no documentation to demonstrate that Dr. Teplick had in fact made this oral misrepresentation to the IRB. The minutes for 2/11/87 meeting of the Subcommittee for Continuing Review of Projects (which apparently acted for the IRB) reported that for Dr. Teplick's study "There were no adverse reactions seen." [CX 53 at 2.] On the second page, the minutes of the IRB stated: "Dr. Teplick reported that no adverse reactions had occurred." [Id. at 3.] However, the minutes of the IRB meeting did not list Dr. Teplick

as physically in attendance at the meeting, and the circumstance surrounding the Center's allegation remained unclear. [Id.]

Therefore, I find that the Center failed to support adequately this subcharge that Dr. Teplick made oral misrepresentations to his IRB, and this subcharge then did not support the Center's charge.

3. The Center charged that Dr. Teplick's "first annual report, covering the time period from May 14, 1986, to March 27, 1987, reported that nine subjects had participated in the clinical study and that there were no side effects "other than the odor of on [the] breath of three subjects and one patient who became slightly sedated . . . ." In addition, the Center charged that the following subjects experienced adverse reactions which were also not reported to the IRB: TE15, TE19, TE21, TE5, TE8, TE9, and TE16. [CX 35 at 5 and 6.]

I interpreted this subcharge to mean that the Center alleged that Dr. Teplick violated § 312.66 by failing to report promptly to the IRB the unanticipated problems involving risk to the above listed subjects. The Center presented Dr. Teplick's written response to the IRB's survey to support this subcharge. [CX 42 at 1.] In this survey, which was received by the IRB on 3/27/87, Dr. Teplick reported in the form's section, "Toxicities, Idiosyncracies, Side Effects:" "Other than the odor of on breath of (3) pts. [patients], and (1) pt. [patient] who became slightly sedated - No side effects," and he concluded, under the section "remarks" to report: "No complications encountered."

[Id.]

In his written response to the agency addressing this allegation, Dr. Teplick stated: "My first annual report [to the IRB of the clinical trial] was on February 8, 1987, after we had used in a total of 6 patients . . . ."[21] [TX J at 6.]

In an earlier version of his written response, Dr. Teplick wrote:

> [The IRB] approved my project but never sent me any guidelines about how and when to report to them. Except, they did ask me to report after my 1st 5 patients - I did this (actually after the 1st 6 patients), and then again after the 1st 9 patients which I did . . . I believe I reported the complications accurately. We did not consider odor on the breath as a complication unless it caused sedation. We were not sure how it got to the lungs since egress into the duodenum was blocked . . . The PVC's and chest pains were not considered to be due to . . . .

[CX 33 at 4.]

In reviewing the study records, had been administered to 6

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[21] The "first annual report," to which Dr. Teplick referred in his written response to the agency, was dated 2/09/87 and was addressed to Dr. , Chairman of the IRB. The report stated: "We have used in a total of 6 patients with common bile duct stones. In three of these patients the was detectable on the patient's breath. One of these three patients became mildly sedated but recovered quickly once the was discontinued. No other complications were encountered." [CX 39.]

subjects, **TE17, TE16, TE18, TE15, TE19,** and **TE21**, between 5/20/86 and 11/03/86. [CX 1 - CX 6.] From the Minutes of the Subcommittee for Continuing Review of Projects [part of the IRB]:

> This site visit was held on January 23, 1987, at 10:30 A.M. Six subjects were enrolled in this study . . . Dr. Teplick was reminded that the Committee stipulated that he was to submit a written report to Committee after he had seen five patients. This report is now due . . . .

[CX 53 at 2.]

On the same day, it was noted that a seventh subject, **TE9**, received on 1/23/87, apparently following the site visit. [CX 7 at 2, 5 & 15-17.]

The clinical significance of on the breath of the subjects was not addressed in the protocols of either Dr. Teplick or the sponsor, Dr. [See CX 30, 45 & 54.] In addition, the informed consent form used by Dr. Teplick also failed to mention this experience. [CX 30.] The IRB approval of Dr. Teplick's clinical protocol had been contingent upon his response to questions regarding the systemic absorption of the through the gall bladder. [CX 36 at 2.] At the hearing, Dr. Teplick stated: "When is systemically absorbed, 90% is rapidly excreted by the lungs and consequently would be detectable on the breath. Considerably higher doses of than are used to dissolve gallstones would result in more systemic absorption and

patient sedation . . . ." Dr. Teplick testified that higher doses were used in the subjects who had common bile duct stones, than had been proposed in Dr. 's original protocol for subjects with gall bladder stones. [Trans. Vol. 2 at 135-8; infra at **Charges II.D.2., III.B.4. & IV.1.**] Dr. testified that the odor of could be taken up by clothing, and that the smell would dissipate within several hours following administration of the [Trans. Vol. 2 at 119-20.] However, the only way of discerning whether was on the breath or in the room, would be to put one's nose right up to a subject's nose. [Id.]

Regarding the charges of failing to report the unanticipated adverse reactions involving risk to human subjects experienced by subjects **TE8, TE9, TE15, TE16, TE19, TE21**, the substantive issue of adverse effects for subjects **TE8, TE15, TE16, TE19,** and **TE21** were already discussed in **Charge I.**, supra. For most of these subjects, I found that Dr. Teplick should have considered the events described in the subcharges to be adverse events reportable to the IRB. For this particular subcharge, I found that several of the adverse events had not been reported, and that the events were unanticipated and involved risk to human subjects. For example, subjects **TE15, TE19,** and **TE21** had either the t-tube or the occlusive balloon dissolve during infusion, which, as previously discussed in **Charge I.A.**, was

documented by the Center. T-tube or occlusive balloon dissolution was an unanticipated adverse event involving risk to human subjects, because the possibility of these events was not discussed in Dr. Teplick's protocol [see CX 45 at 6] or his informed consent forms [see CX 30 at 3] and such events could have serious health consequences if, for example, the t-tube or catheter dissolved within the body of the subject. Another unreported example of unanticipated events involving risk to human subjects was the atrial fibrillation and PVCs experienced by subject TE21, which was not mentioned in Dr. Teplick's protocol [see CX 45 at 6] or his informed consent forms [see CX 30 at 3] and was potentially life-threatening because the subject could have died from complications of either of these cardiac effects. Both the t-tube or catheter dissolution and the cardiac events were not addressed in Dr. Teplick's first annual report. [See CX 42 at 1.]

For these reasons, I find that the Center proved its subcharge that Dr. Teplick did fail to report a number of these adverse events to the IRB. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to report promptly the unanticipated problems experienced by at least TE15, TE16, TE19, and TE21.

4. The Center charged that Dr. Teplick's second annual report, covering the time period from May 6, 1987 to May 6, 1988, did

not properly document all of the unanticipated adverse effects involving risk to human subjects observed and overstated the number of subjects treated as 14 instead of 13. Specifically the Center charged that the following subjects experienced side effects which were not reported to the IRB: TE13, TE7, TE12, TE4, TE14, TE10, TE3, TE2, and TE11.

The Center charged that Dr. Teplick failed to document properly all of the unanticipated adverse effects of the above subjects. In addition, it charged that he misreported the number of subjects on the study, and that he failed to report some adverse reactions altogether. To support this subcharge, the Center presented an IRB annual survey sheet dated 7/14/88, as representing Dr. Teplick's second "annual report" of his tudy. [CX 43.] In this exhibit, the section on "Toxicities, diosyncrasies, Side Effects, etc." was reported as: "None major. One patient experienced slight sedation. Infusion stopped." [CX 43 at 1.]

In a written response to the agency, Dr. Teplick wrote: "I have no record of a second annual report (May 1987 to July 1988). Please send me a copy. You are correct. Only 13 patients were treated between 3/27/87 and 7/14/88." [TX J at 6.]

In contrast to the reported occurrence of sedation in only one subject, nine of the 13 subjects who received , during this time period (TE13, TE7, TE12, TE4, TE14, TE10, TE3, TE2, and 11) experienced unanticipated problems involving risk to human

subjects which should have been reported to the IRB.

For example, the substantive issues of adverse effects for at least subjects TE3 and TE4 were already addressed in Charge I. The death of subject TE3 was temporally associated with the infusion. [See supra, Charge I.A.] Death as an adverse event was an unanticipated event involving risk to human subjects, because the possibility of such an event was not discussed in Dr. Teplick's protocol [see CX 45 at 6] or his informed consent forms [see CX 30 at 3], and death would obviously be considered a very serious event. Subject TE4's severe lethargy and hypertension [see supra, Charge I.A.] were also unanticipated events involving risk, because both lethargy and hypertension were not addressed in Dr. Teplick's protocol [see CX 45 at 6] or his informed consent forms [see CX 30 at 3], and such events could have serious health consequences. The events of death and the lethargy and hypertension were not mentioned in Dr. Teplick's second annual report. [See CX 43 at 1.] For the above reasons, I find that the Center proved its subcharge that Dr. Teplick did fail to report a number of these adverse events to the IRB. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to report promptly the unanticipated problems experienced by at least TE3 and TE4.

5. The Center alleged that Dr. Teplick's third and final report, covering July 14, 1988 to June 5, 1989, reported the project

> **"terminated" and failed to provide any information regarding the number of subjects (GL, TE20, TE23, TE22, JM, TJ, and ES [TE26]) or the side effects observed.**

I interpreted this charge to mean that the Center alleged that Dr. Teplick violated § 312.66 by failing to report promptly the unanticipated problems involving risk to above listed human subjects. The Center presented this "third and final report," covered the IRB approval period from 8/10/88 to 8/10/89, but the report was stamped as received by the IRB on 6/05/89. [CX 44.] Under the section labeled "Changes" the word "terminated" was written, and aside from the name of the study, the investigator, and the above-referenced dates, the remainder of the form had been left blank. [Id.]

In a written response to the agency, Dr. Teplick stated:

> I have no copy of the final report. In addition, I had no knowledge that the project was terminated. Who terminated it? . . . We received no notification from IRB . . . The IRB survey sheet was blank because whoever terminated the project had no knowledge of the number of participants or any of the complications . . . .

[TX J at 7.]

More importantly, however, Dr. Teplick testified that he had "tried to . . . delegate some of the paperwork" required in the conduct of the clinical study and had given the task of submitting the annual survey reports required by the IRB to his

secretary. [Trans. Vol. 2 at 44.] Dr. Teplick testified: "I gave her all my raw data and I said, 'Okay. Could you do me a favor and go through this, and fill this [the annual report, CX 42] in, and send it to the IRB . . . ." [Id.] According to Dr. Teplick's testimony, his secretary had a high school education i.e., no formal medical training. [Id. at 48.] He further stated that he had not checked the reports she had prepared and submitted to the IRB, although he considered this to be his responsibility. [Id. at 47-8.]

Although Dr. Teplick stated that he had signed the first two annual report surveys [see CX 42; CX 43; Trans. Vol. 2 at 44-6.], he disavowed knowledge about this third report. [CX 44.] In fact, at the hearing Dr. Teplick denied that he had signed the above referenced report (i.e., "annual survey"). [Trans. Vol. 2 at 48.] Mr. Krenzel entered into the record a report of a handwriting expert who confirmed Dr. Teplick's statement. [Id. at 51-2; TX F; see also TX G.]

The seven subjects referenced in the Center's subcharge received during the months of November 1988 to May 1989. [See CX 23-29.] Several of these subjects experienced unanticipated adverse effects involving risk to such subjects, which should have been reported to the IRB. For example, TE23 received a short course of which was discontinued by the anesthesiologist because of

fluctuating blood pressure and nausea. [CX 25 at 6, 10 & 52.] TE23's fluctuating blood pressure was an unanticipated adverse event involving risk to human subjects, because the possibility of this event was not discussed in Dr. Teplick's protocol [see CX 45 at 6] or his informed consent forms [see CX 30 at 3]. Such an event could have had serious health consequences, as evidenced by the attending physician's decision to discontinue the infusion of for this subject. [See CX 25 at 6, 10 & 52.]

Regardless of who prepared the annual report to the IRB, Dr. Teplick was responsible for the accurate reporting to the IRB of all unanticipated adverse effects involving risk to human subjects. For this reason, I find that the Center proved this subcharge. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to report promptly to the IRB all unanticipated problems involving risk to human subjects.

* * *

Since I found that Dr. Teplick violated several of the subcharges raised by the Center in support of Charge II.C., I find that the Center proved that Dr. Teplick violated § 312.66 by failing to report promptly to the IRB all unanticipated problems involving risk to human subjects.

* * *

Charge II: Dr. Teplick violated § 312.66 by:

D: failing to obtain IRB approval before making changes in his research.

1. The Center charged that Dr. Teplick failed to obtain IRB approval before using in conjunction with his investigation in at least 19 out of the 26 subjects.

Although the informed consent form used by Dr. Teplick [CX 30 at 3.] discussed the use of as one of the alternative treatments and procedures in the removal of ductal stones, the clinical protocol for did not mention the use of this approved drug. [CX 45.] The Center submitted the CRFs of 19 subjects to demonstrate that subjects received the drug in addition to the investigational drug . [Trans. Vol. 1 196-7.]

Dr. Teplick admitted to using in conjunction with the investigational agent, . [See Trans. Vol. 2 at 236-9.] He testified that during the period of time that was used for his subjects, was an approved drug indicated for the dissolution of common bile duct stones. [Id. at 238-9.] Dr. Teplick explained that he used the two agents mainly because of differences in delivery systems: required more nursing care and had to be administered during the day, while required minimal nursing care and could be administered during hours when

nursing supervision of the subject was minimal. [Id. at 236-7.] He testified that he did not himself perform or know of any preclinical studies of the interactions of and combination therapy. [Id. at 234.] He continued by stating that he was unaware that the protocol needed to address the use of since it was being used for its approved indication. [Id. at 237.] Dr. Teplick testified that he used both agents together without getting approval from his IRB to modify the protocol, because "[t]here was nothing in the protocol that said that I shouldn't do this, and, as far as I was concerned, we could observe the positive and negative effects of while we were doing the procedure." [Id. at 238.]

Although no adverse reactions or other side effects occurred as a result of the sequential use of the approved drug and the investigational agent, it was possible that the use of the two products together would produce unexpected toxicities, as well as alter the efficacy of each product. Such a result could have obscured the evaluation of the investigational agent alone. Therefore, this modification in the original investigational plan should have been documented in both the study protocol and the consent form. This change should have also been reported to the IND sponsor and the IRB.

ıerefore, I find that the Center substantiated this subcharge,

and Dr. Teplick should have amended his protocol to address the use of in conjunction with the investigational drug, In addition, continuing IRB approval of the protocol was based on his agreement that "any radical changes once the project has begun, must be submitted in writing to the OGC [part of the IRB]." [CX 38; CX 42 at 2; CX 43 at 2.] Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to obtain IRB approval before making changes in his research.

2. The Center charged that Dr. Teplick routinely employed infusion volumes of in excess of the 5 cc limit specified in Dr. Teplick's protocol.

The protocol used by Dr. Teplick stated: "Twenty-four hours after the placement of this [cholecystostomy] tube, continuous infusion and aspiration of from 1 to 5 cc of will be performed to create uninterrupted stirring of the gallbladder . . . Once complete dissolution is documented, the infusion will be stopped . . . ." [CX 45 at 4.] Common bile duct stones would be treated in the same manner. [Id. at 5.] The protocol continued: "No infusion will be continued for more than 72 hours." [Id.] In the background section of the protocol, a discussion of the use of in dogs stated that "instillation of into the gallbladder, common duct, or duodenum in volumes of 10 to 20 cc/hr . . . ." did not produce toxic metabolites,

such as . and did not pose an hazard in the air. [Id. at 2.]

To support the Center's subcharge, Ms. deMarco presented numerous examples where the protocol limit of 5 cc was exceeded by Dr. Teplick. For example, **TE16** and **TE15** were given 10 cc [CX 2 at 5; CX 4 at 4]; **TE9** received 15 cc [CX 7 at 5]; **TE19** received 20 cc [CX 5 at 14]; and **TE5** received 50 cc [CX 8 at 5].

Dr. Teplick admitted that he used more than 5 cc . [Trans. Vol. 2 at 306.] He testified that "the amount of that we used was based on the size of the [common bile] ductal system. [Id. at 134.] He continued by explaining "the reason that we changed the amount . . . of that we were injecting [from the volumes specified in the protocol] was because it seemed that the amount that we put into the ductal system to dissolve the stone in most cases was grossly insufficient to actually have any effect on the stone at all." [Id. at 135-6.] He explained that the increase in the volume of would improve the contact between the drug and the stone, which was required for stone dissolution. [Id.] He continued by stating that Dr. had revised his protocol to address the issue, modifying the dose of to "20 percent less than the volume of the gallbladder." [Id. at 137-8.] He later testified that he did not believe that he had violated the protocol by either increasing the volume or

the infusion rate of the as specified in the protocol, so it did not occur to him to report this to his IRB. [Id. at 269-70.]

While it may have been necessary for Dr. Teplick to increase the amount of used, this constituted a change in the investigational plan which could have incurred additional risks to the subjects. For this reason, he should have amended his protocol and submitted it for approval to both the IND sponsor and the IRB, as required by the regulations. In addition, continuing IRB approval of the protocol was based on his agreement that "any radical changes once the project has begun, must be submitted in writing to the OGC [part of the IRB]." [CX 38; CX 42 at 2; CX 43 at 2.] Therefore, I find that the Center proved this subcharge that Dr. Teplick routinely used volumes of in excess of the amounts specified in the protocol approved by the IRB. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.66 by failing to obtain IRB approval before making changes in research.

* * *

Since the Center proved both of these subcharges and both subcharges supported the Center's Charge II.D., I find that the Center proved that Dr. Teplick violated § 312.66 by failing to obtain IRB approval before making changes in his research.

* * *

The Center produced sufficient evidence to support the majority of the subcharges, and thus, I find that Dr. Teplick did violate § 312.66. At the hearing, Dr. Teplick claimed that the IRB provided no oversight of his work. [Trans. Vol 2. at 45-9.] However, the IRB sent information to Dr. Teplick regarding its annual reviewing requirements, which clearly stated: "Also note that any radical changes once the project has begun must be submitted in writing to the OGC ["Office of Grants and Contracts"] and adverse reactions must be reported to the CHS [part of the IRB]." [CX 38; CX 42 at 2; CX 43 at 2.] For this reason, I find that Dr. Teplick had received sufficient information from the IRB to permit him to meet his responsibilities as an investigator with respect to his reporting requirements to the IRB. [Supra, **Charge II.A.**]

* * *

Charge III: Dr. Teplick violated § 312.60 by

A: failing to conduct the investigation in accordance with the Investigator Statement.

The Center charged Dr. Teplick with violating §312.60 by failing to follow the agreement in the "Investigator Statement" [i.e., FDA Form 1572 or FDA Form 1573] to notify the sponsor prior to

making changes in the protocol.[22] Section 312.60 "General responsibilities of investigators" states: "An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations . . . ."

The Center did not produce any evidence to demonstrate that Dr. Teplick had signed an FDA Form 1572. The Center did not prove that the agency or the sponsor had ever requested that Dr. Teplick complete an FDA Form 1572. Instead, the Center presented a copy of Dr. s investigator statement. [CX 48.]

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[22] The FDA FORM 1572 includes the commitments from the clinical investigator participating in a study conducted under an IND. Section 312.60 requires the investigator to ensure that the investigation is conducted according to the signed investigator statement. Some of the pertinent commitments to these proceedings are, as stated:

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in the protocols after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s)
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64.
- I agree to maintain adequate and accurate records in accordance with § 312.62 and to make those records available for inspection in accordance with § 312.68.

[See CX 48.]

When Dr. Teplick was asked whether he had signed an FDA Form 1572 or 1573, he replied, "I don't know what those forms are . . . No, I don't recall doing that [seeing or signing FDA Form 1572 or 1573]." [Trans. Vol. 2 at 148-9.]

Dr. Teplick testified that he had met Dr. , who had asked Dr. Teplick if he wanted to "use his IND [for for the purpose of dissolving biliary stones in subjects. When asked whether Dr. , the sponsor, had provided any written information to Dr. Teplick, Dr. Teplick testified "No. He sent me his protocol and consent form." [Id. at 26.] When questioned later during the hearing, Dr. Teplick denied knowledge of Title 21, Part 312 or that Dr. had ever mentioned the pertinent regulations. [Id. at 148.]

Under § 312.50: "**Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND . . . .**"[23] Although Dr. Teplick claimed to have been unaware of the pertinent regulations

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[23] Section 312.53(c) delineates what information and surances the sponsor must receive from the investigator prior the initiation of clinical trials under the sponsor's IND.

governing his responsibilities, and although he had not signed the investigator statement, he acknowledged that he was an investigator and that the investigation that he was conducting was under the aegis of Dr. 's IND which was regulated by the agency.[24]

In summary, while the Center did not present evidence to document that Dr. Teplick had signed or was aware of the "Investigator Statement," I find that Dr. Teplick was, and acted in a way that evidenced that he understood himself to be, an investigator. For example, among other things, Dr. Teplick submitted a protocol for the study to his IRB, enlisted patients in the study, and filled our case report forms on those patients. Since § 312.60 requires that an investigator follow the Investigator Statement, the requirements of the Investigator Statement are, in effect, required by § 312.60, whether or not an Investigator Statement was actually signed by the investigator. I find that Dr. Teplick failed to notify the sponsor prior to making changes in the protocol as specifically addressed, infra, in Charge

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[24] Although Dr. Teplick had not signed an investigator statement, he confirmed his intent to act as an investigator:

Mr. Krenzel: "What was your first experience with FDA-regulated research?

Dr. Teplick: "Basically, "

[Trans. Vol 2. at 9-10.]

III.B. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to conduct the investigation in accordance with the Investigator Statement.

* * *

Charge III: Dr. Teplick violated § 312.60 by

B: failing to follow the investigational plan[25].

As stated above, § 312.60 requires investigators to ensure that an investigation is conducted according to the investigational plan. The investigational plan is described in the clinical protocol. [See § 312.23(a)(6).] As new information is acquired about an investigational agent, it is often necessary to revise or modify the current clinical protocol. Under § 312.30 "Protocol Amendments":

> b) Changes in a protocol. (1) A sponsor shall submit a protocol amendment describing any change in a Phase I protocol that

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[25] The investigational plan is a requirement of the IND application, under § 312.23(a)(3) "Introductory statement and general investigational plan.": "(i) . . . the broad objectives and planned duration of the proposed clinical investigation(s) . . . (iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) the rationale for the drug or the research study; (b) the indication(s) to be studied; (c) the general approach to be followed in evaluating the drug; (d) the kinds of clinical trials to be conducted . . . ; (e) the estimated number of patients to be given the drug . . . ; (f) any risks of particular severity or seriousness anticipated . . . ."

> significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

[§ 312.30(b).] Therefore, the investigator must inform the sponsor of any protocol amendments in order for the sponsor to notify FDA of such amendments.

The IRB also required written notification of significant changes in the investigational plan.[26]

1. The Center charged that Dr. Teplick violated his own protocol by not limiting his subjects to individuals who were poor surgical candidates or who refused surgery.

The Center submitted a copy of Dr. Teplick's protocol which required for subject selection: "Patients with symptomatic biliary stones (gallbladder stones or ductal stones) who are poor operative candidates or who refuse surgery." [CX 45 at 3.] Dr. Barton testified that, regarding TE21:

> [W]e found a quotation in the records for this patient as follows: "Surgeons are pressuring us to take her to surgery." We also found the quotation, "Went to surgery next day." Neither of these would look like a patient that is not an operative candidate

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[26] The IRB stated in their protocol approval form: "any radical changes once the project has begun, must be submitted in writing to the OGC and adverse reactions must be reported to the S." [CX 38; 42 at 2; 43 at 2; supra, Charge II.A.]

> . . . We also would say for Subject TE25 [actually, subject TE5], in the records for that subject we found quotations like, "Surgeons very anxious to operate." . . . We also have for the same subject, "Patient whisked to surgery." So these are direct quotes from the records for these two subjects.

[Trans. Vol. 1 at 265-6.]

As discussed in the protocols of both Dr. and Dr. Teplick: "Surgery is still considered to be the treatment of choice for symptomatic gall bladder stones and stones obstructing the common bile duct. However, in high-risk patients or in those who refuse surgery, other modalities are offered . . . ." [TX E at 3; see also CX 45 at 1; see supra, Charge I.]

Dr. Teplick had also responded to the Center's charge in writing:

> Both TE5 and 21 were sent to us from another institution where the referring physicians did not think it was safe for them to undergo surgery. They were referred specifically for stone dissolution/extraction. When admitted to these patients were seen in consultation by our surgeons. Our surgeons felt that they were operable candidates. Therefore, they really did not give us adequate time to treat the stones nonsurgically, but they pressured us and the referring physicians to allow them to take these patients to surgery after only a brief attempt at dissolution/extraction.

[TX J at 8; see also Trans. Vol. 2 at 312.]

Dr. Teplick testified that: "I think if a boarded physician

. . . [who] sent in their [sic] patients, said, 'I don't think this patient is a good surgical candidate, I would like you to do one of these procedures on him,' I would." [Trans. Vol. 2 at 313.]

As previously discussed [supra, Charge II.C.3.], TE5 was a 77 year old critically ill man who was transferred to the emergency room with ascending cholangitis in septic shock on a ventilator with "multiple system failure." [CX 8 at 9.] The subject's course was complicated with a series of events, including a right pulmonary artery tear secondary to an arterial catheter placement, which were life-threatening in nature. [See CX 8 at 9-12.] The subject's CRF indicated, under the section entitled "Reason to avoid surgery": "Considered too high risk for surgery by referring surgeons." [CX 8 at 2.] The hospital notes on 2/10/87 stated: "[E]valuation by Dr. Teplick as to feasibility of removal of stones and decompression of biliary tree into GI tract. If unable to accomplish this, he will need surgical decompression in spite of high risk of general anesthesia." [Id. at 127.] The subject received an infusion of on 2/11/87, which was unsuccessful. [Id. at 27.] The notes continued to state that due to the life threatening complications caused by the stones, "On 2-13-87 the patient underwent exploratory laparotomy, common bile duct exploration, removal of common duct stones, intraoperative cholangiogram . . . The

patient tolerated the procedure well and was taken to the SICU in stable condition. His postoperative course was very stormy. The patient had severe malnutrition, continued septic shock, acute respiratory failure, acute renal failure, wound infection, and a cardiopulmonary arrest on 4-1-87. The patient expired on that date." [Id. at 10.]

Based on these discoverable records, **TE5** was deemed critical upon arrival to and was, therefore, considered a poor surgical candidate. The nonsurgical removal of the biliary stones was considered life saving. Only upon the unsuccessful resolution of the stones using did the subject undergo surgical manipulation. Moreover, shortly following the operative procedure the subject died, corroborating the initial assessment of the subject's unsuitability for general anesthesia. **Thus, I find that the Center failed to substantiate that Dr. Teplick violated his study protocol by accepting this individual who otherwise would have been a surgical candidate.**

Regarding **TE21**, the CRF noted "She did not get adequate exposure to either The surgeons were anxious to operate." [CX 6 at 3.] However, the CRF described the subject, as follows: "Poor medical condition. Decision [to avoid surgery] of referring M.D. and pt. [patient]." [Id. at 2.] The surgical notes stated:

> In view of the patient's age [86 years] and medical condition, she was transferred here . for initial attempt at dissolution of the stones percutaneously . . . Attempt was done to dissolve the stones 3 times but the patient would complain of right upper quadrant pain and chest pain and she went into rapid atrial fibrillation and had to be transferred to 12 West for monitoring requiring digitalization and high dose of Inderal IV. This resolved but the patient was unable to tolerate medical treatment for her stones and therefore it was decided to bring the patient to the OR to treat her choledocholithiasis."

[Id. at 4-5; see also supra, Charge I.] Again, this subject only went to surgery after conservative medical treatment (i.e., drug dissolution of the stones) was not feasible.

Therefore, I find that the Center failed to demonstrate its subcharge that Dr. Teplick violated his protocol by including subjects who were either poor operative candidates or refused surgery, namely TE5 and TE21, both of whom were acceptable by his protocol's selection criteria on this basis. Thus, this subcharge does not support the Center's charge.

2. The Center charged that Dr. Teplick violated his own protocol by treating TE3, TE4, TE5, TE13, and TE20 who displayed evidence of acute cholecystitis, cholangitis, or septicemia.

The Center charged that Dr. Teplick included five subjects who should have been excluded from the protocol, based upon the protocol's selection criteria. The Center emphasized that the

protocol selection criteria used by Dr. Teplick specifically stated: "The patient will show no evidence of acute cholecystitis, cholangitis, or septicemia."[27] [CX 45 at 3.] Neither the protocol nor the Center defined further what would constitute "evidence" of these conditions. Dr. Teplick stated that in his opinion, some of the "evidence" would be fever, upper abdominal tenderness, "Murphy's sign," and lack of a patent cystic duct. [Trans. Vol. 2 at 183.]

For purposes of this discussion, acute cholecystitis or cholangitis are usually characterized by the presence of signs and symptoms, such as fever, elevated leukocyte counts, right upper quadrant pain, and jaundice, in conjunction with a positive radiologic examination for the presence of biliary stones. Septicemia is diagnosed by a positive growth of a microbial organism from a properly obtained blood culture.

Dr. Teplick addressed the Center's charge in response to the Form FDA 483: "[T]hese patients were sent to me to treat these

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[27] Cholangitis is defined as "inflammation of a bile duct or biliary tree." [Stedman's Medical Dictionary, 25th Ed., at 294 (1990).] Cholecystitis is defined as "inflammation of the gall bladder;" in acute inflammation, "congestion and or hemorrhagic necrosis, with variable infection, ulceration, and neutrophilic infiltration of the gallbladder wall; usually due to impaction of a stone in the cystic duct." [Id.] Septicemia is a "systemic disease caused by the spread of microorganisms and their toxins via the circulating blood." [Id. at 1405.]

conditions because the referring physician felt they might die if they were treated surgically." [CX 33 at 5.] While Dr. Teplick's statement may be true, his protocol clearly excluded all subjects who displayed evidence of acute cholecystitis, cholangitis, or septicemia. [CX 45.] If the treatment of these subjects was deemed essential, an emergency IND or a protocol amendment should have been submitted to both the sponsor and the IRB. [See n. 7 at 3.]

According to the hospital records submitted by the Center, TE4 was admitted with a diagnosis of "cholecystitis" and "cholelithiasis" [gallbladder stones] and "choledocholithiasis" common bile duct stones]. Although she had a history of right upper quadrant pain one week prior to admission, her abdomen was non-tender, and her temperature was normal at the time of admission to , in the absence of antibiotics or antipyretics. [CX 17 at 6.] Although antibiotics were instituted for a temperature of 101°F on the second hospital day [id. at 31 & 33], the subject became afebrile and remained so during the rest of her hospital course. For the above reasons, no definitive evidence was produced that the subject was experiencing an acute episode of cholecystitis at the time she was admitted to the protocol. Therefore, she would have been eligible for the protocol.

TE13 had been admitted to on 3/13/87, for what appeared to be an assessment of his previously diagnosed Hodgkin's lymphoma. On admission the subject had anemia, evidence of lymphoma, and angina. [CX 10 at 11-2.] Although the Center did not submit the subject's complete records, the discharge summary described the subject as becoming icteric on 3/25/87, stating: "On 3/28/87 the patient had an ultrasound of the right upper quadrant which showed gallstones with [an] obstructing common bile duct stone. The patient was placed on antibiotic therapy prophylactically and had infusions . . . ." [Id. at 12.] Again, this subject failed to demonstrate fever, pain or infection commensurate with an acute process at the time of administration and would have been, therefore, eligible for the protocol.

The Center alleged that Dr. Teplick ignored the protocol's selection criteria by including subject TE3 because she had been diagnosed with "acute cholangitis" and because "cholangitis" had been listed as a contributory cause to her death. [CX 20 at 5 & 12.] As described earlier, TE3 had been admitted to on 5/25/88, with a diagnosis of "gram negative sepsis" and "acute cholangitis." [Id. at 5; see also supra, Charge I.A.] She had been symptomatic with fever, dyspnea, and diarrhea, and she was administered antibiotic therapy for septicemia, which was diagnosed by positive blood cultures on 5/27/88.

Dr. Teplick testified that he believed the hospital records demonstrated that TE3 had recovered from her acute episode of cholangitis prior to her entry onto the study. [Trans. Vol. 2 at 61.] Although the subject did not receive until 6/07/88, more than 24 hours after she had defervesced, the subject remained on antibiotics throughout her hospital course. For this reason, it was impossible to assess whether her initial septicemia or cholangitis had been adequately resolved at the time of administration. For this reason, she was ineligible for the protocol and should have been excluded from the protocol.

TE20 had been "recently treated for ascending cholangitis" at another hospital from which he had been discharged 5 days prior to his admission to on 1/16/89. He was admitted to for complaints of fever and jaundice of one-day duration. [CX 24 at 8.] He had continued to take an antibiotic and was afebrile on admission to A transhepatic cholangiogram was performed the same day, and the subject was noted to have "one stone in the common bile duct." [Id. at 9.] Although the bile culture taken during the procedure grew out "heavy Enterococcus, Group D," the subject remained afebrile on antibiotics during his hospital course. [Id.] From the above information, this subject may have been experiencing an acute episode of his previously diagnosed cholangitis and, therefore, should have been excluded from the

protocol.

As discussed earlier, **TE5** was a critically ill subject transferred to from another hospital on 2/10/87, with a diagnosis of ascending cholangitis in septic shock and multisystems failure requiring assisted ventilation. [CX 8 at 9.] His history of cardiac disease, liver and renal failure made him inoperable at the time of admission. [See id.; see also supra, **Charges II.C.3 & III.B.1.**] The dissolution of the biliary stones by was considered to be a life saving procedure by the treating physicians. However, since he had ascending cholangitis on admission to TE5 was ineligible for the protocol and should have been excluded from the study.

Thus, although the Center failed to document that TE4 and TE13 had evidence of active acute processes that would have excluded them from the protocol at the time of their entry onto the protocol, the hospital records of subjects TE3, TE20 and TE5 did show definitive evidence of acute cholecystitis, cholangitis, and/or septicemia at the time of their entry onto the protocol. Although **TE3** and **TE20** defervesced on antibiotics, no attempt was made to ascertain whether their active infections would have shown recrudescence in the absence of antibiotics. For the above reasons, I find that the Center provided sufficient documentation to conclude that at least three of the subjects experienced

"evidence" of acute infectious processes which rendered them ineligible for Dr. Teplick's protocol. [See CX 45.]

As discussed above, changes to the protocol must be reported to both the IRB and the sponsor, who is required to file them with the agency. [See § 312.30; see supra, Charge III.B.] Neither party introduced any evidence to show that Dr. Teplick notified the sponsor, the IRB or the agency regarding the protocol modification. Therefore, I find that Dr. Teplick violated his protocol selection criteria by admitting subjects who displayed evidence of cholecystitis, cholangitis, or septicemia, as alleged in this subcharge. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

3. The Center charged that Dr. Teplick violated his own protocol by treating ES(TE26) and GL as outpatients.

The Center presented Dr. Teplick's protocol, which stated under "Patient Selection" criteria: "No outpatient studies will be performed." [CX 45 at 3.] Dr. Teplick testified that he was unaware that his outpatient administration of was in violation of the clinical protocol he had submitted to the IRB. [Trans. Vol. 2 at 259-60.]

During the hearing, Dr. Teplick admitted that subject **ES(TE26)**

was an outpatient. [Trans. Vol. 2 at 305.] Regarding subject GL, Dr. Teplick testified: "Actually, I don't recall this particular patient, but I want it to be stated that it's quite possible this patient could be admitted to the short procedure unit, have a procedure done, and then be admitted overnight . . . [J]ust because he went to the short procedure unit initially doesn't mean he wasn't admitted [to the [Id. at 305.]

The Center referred to Dr. Teplick's previous admission to this charge by reviewing the charges made in the EIR: "No outpatients were permitted under this protocol. This exclusion criteria was not followed. Subjects ES and GL were both outpatient participants." [CX 31 at 4.] Dr. Teplick had responded in writing: "This is true and was my error" [CX 33 at 5]; he also wrote: "This is true, but I believe that GL went back to a nursing home where medical supervision was available." [TX J at 9.] Although Dr. Teplick claimed that he did not have his records when he prepared his response to this charge [id.], as discussed earlier, the records submitted by the Center for subjects GL and ES(TE26) demonstrated that they were outpatients at the time of administration. [See supra, Charge II.D.; see also CX 23 at 10; CX 29 at 3.] Therefore, on this subcharge, I find that Dr. Teplick violated his protocol selection criteria by administering the investigational drug to at least two individuals as outpatients. Thus, this subcharge supported the

Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

4. The Center charged that Dr. Teplick violated his protocol by infusing volumes of exceeding the 5cc limit set by his protocol for 23 subjects TE3, TE4, TE5, TE7-TE19, TE21-TE26, and GL.

This charge has been addressed in an earlier discussion for **Charge II.D.2.** [See supra, **Charge II.D.2.**] The clinical protocol limited the infusion volume of to a maximum of 5cc. [CX 45 at 4.] As stated above, Dr. Teplick has admitted that he infused volumes greater than 5cc, which he deemed necessary to dissolve common bile duct stones. For example, TE9 received 200cc, 40 times the maximum volume specified in the protocol. [CX 7 at 5; see CX 45 at 4.]

Although Dr. Teplick found it necessary to increase the volume of the investigational drug infused into subjects with common bile duct stones, he did not file a "protocol amendment"[28] which would modify the dose of the investigational product, as required by the regulations. [See § 312.30; see supra, **Charge III.B.**]

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[28] Specifically, the IND sponsor is required to submit to the IRB changes in a protocol, which include: "Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study." [§312.30(b)(i).]

No evidence was produced by either party to suggest that Dr. Teplick notified the IND sponsor, the IRB, or the agency regarding the protocol modification. Therefore, I find that the Center demonstrated that Dr. Teplick violated the protocol by infusing volumes of exceeding the 5 cc limit set by his protocol. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

5. The Center charged that Dr. Teplick violated his protocol by failing to perform the required cholangiograms at 1, 24, and 48 hours after stone dissolution.

The Center presented the protocol used by Dr. Teplick, which required the following monitoring of the subjects: "Patient will receive follow-up cholangiogram at 1,24 [sic] and 48 hours after stone dissolution . . . **When complete stone dissolution is established, the access tubes will be removed at the discretion of the principle investigator (Steven K. Teplick, MD).**" [CX 45 at 5.] Dr. Barton testified that the Center was unable to locate documents to demonstrate that these tests had been performed. [Trans. Vol. 1 at 266.]

Dr. Teplick responded in writing: "It was not always possible to get follow-up studies in this group of patients, particularly long range follow-up. 24 and 48 hour cholangiograms were

obtained when possible." [TX J at 9.] In a written addendum, he also submitted:

> Concerning follow-up cholangiograms: Follow-up cholangiograms were performed when possible. Most, if not all, patients had follow-up cholangiograms at 1 +-24 hours after the stones were dissolved or removed. These would be in our x-ray files at However, once the biliary drainage catheter is removed, it is not [sic] impossible to get a follow-up cholangiogram since the cholangiogram is performed by injecting contrast through the catheter. The biliary drainage catheters were and should be removed as rapidly as possible once we felt the stones are gone. (usually the next day). The larger [sic--longer?] the biliary drainage catheter is left in the patient, the higher the incidence of complications."
>
> [TX V at 15.]

It was apparent from the records that the cholangiograms were performed inconsistently, in violation of the requirements of the current protocol. Withholding this testing may have been for valid safety concerns, but it may also have significantly affected the "safety of the subjects, the scope of the investigation, or the scientific quality of the study." [See § 312.30; see supra, Charge III.B.] However, Dr. Teplick did not file a "protocol amendment" to decrease or eliminate these tests. In addition, neither party produced evidence to suggest that Dr. Teplick notified the IND sponsor, the IRB, or the agency regarding the protocol modification. Therefore, I find that the Center demonstrated its subcharge that Dr. Teplick violated his

protocol by failing to perform the required cholangiograms at 1, 24, and 48 hours after stone dissolution. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

6. The Center charged that Dr. Teplick violated his protocol by failing to perform the required ultrasound examinations of the gallbladder and bile ducts. The consent form incorrectly stated that the examinations were optional.

The Center presented the protocol requirement: "Ultrasound examination of gallbladder and bile ducts will be done at 4 month intervals after stone dissolution, for a period of 3 years, to determine stone recurrence." [CX 45 at 5.] The informed consent form stated: "We would like you to return every 4 months for an ultrasound study of the gallbladder and bile ducts to see if any stones recurred. This is optional but would be appreciated." [CX 30 at 2 .] According to the protocol, however, the ultrasound testing was a requirement, not an option.

Dr. Teplick acknowledged that his protocol required these ultrasound tests, but he thought that tests were not useful to detect common bile duct stones. [Trans. Vol. 2 at 320-1; see also TX V at 15-6.]

If the ultrasound tests were considered unnecessary, the protocol should have been amended to reflect the change. As stated above,

changes to the protocol must be reported to the IRB and to the IND sponsor, who is required to file them with the agency. [See § 312.30; see supra, Charge III.B.] In addition, neither party produced evidence to suggest that Dr. Teplick notified the IND sponsor, the IRB or the agency regarding the protocol modification. Therefore, I find that the Center proved its subcharge that Dr. Teplick violated his protocol by failing to perform the required ultrasound examinations of the gallbladder and bile ducts. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

7. The Center charged that Dr. Teplick violated his protocol by failing to analyze bilirubin, alkaline phosphatase, SGOT, SGPT, and amylase every 24 hours.

The Center presented the protocol, which stated: "Baseline blood analysis will include CBC, PT, PTT, platelet count, serum electrolytes, bilirubin, alkaline phosphatase, SGOT, SGPT, and amylase. The latter five analysis [sic] will be measured every 24 hours." [CX 45 at 4.] Ms. deMarco testified that, during he investigation, she found that none of the studies had been performed at the frequency specified by the protocol. [Trans. Vol. 1 at 191-5.]

When Dr. Teplick was questioned at the hearing as to how the

blood tests had been obtained, he stated:

> Poorly? No, what I did was -- this was another one of those instances that I had tried to delegate to other people. For example, if a referring clinician called me up and said he was going to send in such-and-such a patient for stone extraction procedure, and I had an inkling that we might use , I would ask would he please, himself, or have his resident draw all the appropriate blood studies.
>
> And then, sometimes I would ask, try to delegate it to either -- to our nurses, or call the nurses on the floor, and I failed to check up on it to see whether it was actually done as it was supposed to be done. Otherwise, I would have had to do it myself.

[Trans. Vol. 2 at 261-2.]

When questioned further regarding the inconsistencies between the reported dates the blood tests and the actual dates the tests were obtained, he affirmed his previous statement:

> It seems, listening to the reports, that they [those who drew the blood work] were always several days off from when the actual study was performed, and this is [sic] probably just simply reflects the fact that when they actually did do as I had asked them to, they didn't do it when I had asked them to do it.

[Trans. Vol. 2 at 263.]

Dr. Teplick commented on the value of these tests:

> I think some of the clinical studies that I've done, we way over-utilize blood stu[dies] -- we get a lot of unnecessary blood studies . . . And it's my own personal impression that unless there's a clinical counterpart to it, just having a blood study

> probably does not contribute significantly to these studies.

[Trans. Vol. 2 at 264.]

In his written response to the agency, Dr. Teplick stated: "Some of the patients did receive the appropriate blood studies, but it seems we did not obtain the appropriate blood samples on many of the patients. Unfortunately, I no longer have access to the patient's [sic] charts to verify the accuracy of the lab values." [TX J at 9.] In his written addendum, Dr. Teplick stated:

> There is no question that we were remiss in obtaining some or even the majority of the blood studies. As explained previously, this was one aspect of the study that I delegated either to the referring clinician, or to the nurse on the floor, or to our radiology nurses and I did not follow-up to see that these blood values were actually obtained."

[TX V at 16.]

As discussed in the previous subcharges, if the testing was deemed unnecessary, the protocol should have been amended to reflect the change. As stated above, changes to the protocol must be reported to the IRB and to the IND sponsor, who is required to file them with the agency. [See § 312.30; see supra, Charge III.B.] In addition, neither party produced evidence to suggest that Dr. Teplick notified the IND sponsor, the IRB, or the agency regarding the protocol modification. Therefore, I find that the Center proved this subcharge that Dr. Teplick

violated his protocol by failing to analyze bilirubin, alkaline phosphatase, SGOT, SGPT, and amylase every 24 hours. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

In addition, as discussed in Charge II.C.5., it was the responsibility of Dr. Teplick, as the principal investigator at

to "personally conduct or supervise the described investigation(s)," which included the obtaining of all test results, as required by the protocol.

Therefore, since I found that the Center proved its claims in subcharges 2 - 7, and these subcharges supported Charge III.B., I find that the Center sufficiently supported its charge that Dr. Teplick violated § 312.60 by failing to follow the investigational plan.

To summarize, I find that the Center sufficiently supported its allegations in Charges III.A.and III.B., which demonstrated that Dr. Teplick violated § 312.60.

* * *

Charge IV.: Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the

investigational drug.

1. The Center charged that Dr. Teplick failed to report accurately the volume of used, the duration of the treatment, and the side effects for all subjects.

I interpreted this charge to mean that the Center alleged that if Dr. Teplick failed to report accurately the volume of used, the duration of the treatment, and the side effects for at least one subject, he violated § 312.62(b) by failing to maintain adequate and accurate records of this observation pertinent to the study. The Center, however, did not present specific evidence for this subcharge; it discussed this subcharge in the context of the earlier charges. [See supra, **Charges I, II, and III.**] For example, the FDA Form 483, stated:

> **SSi[TE19]** 9/26/86 100 cc reported on CRF; 160cc in subject records [CX 5 at 2 and 14]
>
> **MDel[TE9]** 1/23/87 CRF reports 200cc for 1 1/2 hrs; records state 300 cc over several hours [CX 7 at 2 and 15]
>
> **MC [TE8]** 3/9,10/87 no volume reported in subject records; 3/9/87 3 hrs reported on CRF; 2 1/2 hrs in patient records 3/10/87 5 hrs reported on CRF; 3 1/2 hrs in patient records. [CX 9 at 2 and 6-10].

[CX 31 at 7.]

In his written response to the agency, Dr. Teplick stated: "I

have records of the volume and duration for at least most of the patients." [TX J at 10.] In his written addendum of 1/22/92, he stated: "To the best of my knowledge, either in the patient's [sic] charts or in my own records, I have both the volumes of used and the duration of treatment for all subjects." [TX V at 17.]

The above examples demonstrate some of the inconsistencies between the CRFs and other hospital records regarding the volume and duration of the infusion. This information was important to retain as evidence on which to determine the effectiveness of . In addition, since I have already found that Dr. Teplick was often remiss in reporting the "side effects" for at least some of the subjects [see, e.g., Charge I.], I find that the Center established that Dr. Teplick failed to report accurately the volume of used, the duration of the treatment, and the side effects for subjects in his study. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug.

2. The Center charged that Dr. Teplick failed to prepare CRFs for subjects TJ, JM, and GM.

During their inspection of Dr. Teplick's records, the FDA investigators were unable to locate the CRFs for the three subjects, **TJ, JM** and **GL.** [See CX 28, 27; 23.]

In his written response to the agency, Dr. Teplick stated: "TJ was treated for a retained CBD stone mainly with [sic] and basket extraction. On 4/17/89 she received 2 doses (5-8 cc) of . . . As far as I know, all CRF[s] were sent to Dr. but I will check this." [TX J at 10.] However, in his written addendum of 1/22/92, he stated: "If TJ did not receive there is no reason to have a CRF form on her. Dr. [sic] should have received case forms on all patients including JM and GL." [TX V at 17.]

According to the hospital records, **TJ,** a 64 year old woman, had been diagnosed with a common bile duct stone. [CX 28 at 1.] Since she was afebrile and in no acute distress when she was admitted to on 4/12/89 for removal of the stone, she would have been eligible for the protocol. The hospital chart did not address whether the subject had been considered for the trial, or why she instead received the infusion, rather than surgical removal of the stone. [Id.] The Center failed to produce additional evidence that she had been considered for the MTBE study. In the absence of further information an fact that this subject did not participate in the study, the need

for a CRF could not be assessed.

However, subjects JM and GL did receive which was noted in their respective records. [Supra, Charge II.C.5; see CX 27 & CX 23.] For each of these subjects, a CRF should have been completed and submitted to the sponsor. Therefore, since he was unable to provide evidence that CRFs had been completed for two subjects, I find that Dr. Teplick failed to prepare and maintain adequate study records for JM and GL, and that the Center proved this subcharge. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare adequate and accurate records on each individual treated with the investigational drug.

3. The Center charged that Dr. Teplick reported to his IRB at the University of that he had treated approximately 35 subjects when the records available to FDA indicate that only 27 individuals were treated with

The Center presented a copy of a letter Dr. Teplick wrote to the University of IRB, dated 7/21/89, which stated: "Since the beginning, I have been involved with helping to get FDA approval and have used in approximately 35 patients at [CX 51 at 1 .]

According to Center's review of the study records, Dr. Teplick had treated only 27 subjects. [See CX 1 - CX 29.] Two of these

subjects, **TE9=TE14** and **TE19=TE2**, had been assigned more than one study identification number, apparently because they had received at two different times. [See CX 7, CX 18 & CX 5, CX 21.]

In his written response to the agency, Dr. Teplick stated: "At the time I submitted this letter, I had just moved to the University of I did not have access to my raw data or my computer." [TX J at 10.] He reaffirmed this statement in his written addendum of 1/22/92. [TX V at 17.]

Dr. Teplick acknowledged that the number of subjects he had mentioned was only an approximate number. In addition, he had maintained CRFs on the subjects that had actually participated in the study. For this reason, although I find that the Center proved the subcharge that Dr. Teplick reported an inaccurate number of subjects treated on the protocol, I also find that the Center has failed to establish how this subcharge supports the charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate and accurate records of data pertinent to the investigation on each individual treated with the investigational drug.

4. The Center charged that the CRF for TE8 did not report that the subject had received on 3/11/87, and that the treatment was discontinued due to chest heaviness and EKG changes.

For TE8, the Center demonstrated that a discrepancy existed between the subject's medical record [CX 9 at 26 and 38] and the CRF, i.e., the CRF [CX 9 at 2] failed to mention treatment on 3/11/87. The Center substantially presented the argument in support of this subcharge in conjunction with a previous charge. [Supra, Charge I.]

In his initial written response to the agency, Dr. Teplick stated: "TE-8 received no on 3/11/87. The chest pain and EKG changes were due to the catheter manipulation in the gallbladder." [TX J at 10.] However, he substantially revised his answer in an addendum of 1/22/92, where he stated that his personal notes had not reflected that this subject received on the day in question:

> The FDA has a copy of my personal records and can verify this. The chest pain that she developed on 3-12 is reported on the CRF form. My notes also state that on 3-12, that the gallbladder manipulations resulted in significant pain and that the pain was relieved by nitroglycerine. It was and still is my opinion that it was the gallbladder manipulations that caused the pain. Had I known that she had received on 3-11, I certainly would have reported it on the CRF form. Also noted on patient TE-8 was that she had chest pain on admission and four weeks prior to the procedure had a myocardial infarction. She has other significant cardiac disease such as atrial fibrillation and an abnormal sinus.

[TX V at 18.]

While I cannot ascertain the accuracy of Dr. Teplick's statements based on the records submitted, infusion was discontinued due to this subject's chest heaviness and EKG changes which were at least temporally associated to the infusion on 3/11/87. [See CX 9 at 34.] As discussed above under **Charge III.A.**, Dr. Teplick was responsible for reporting to the sponsor adverse experiences that occur in the course of the investigation in accordance with § 312.64. [See n. 22 at 74.] In addition, he was responsible for maintaining "adequate and accurate records in accordance with § 312.62 and to make those records available for inspection in accordance with § 312.68." [Id.] It was, therefore, his responsibility to monitor these records and to resolve any discrepancies in the study records.

For the above reasons, I find that the Center proved this subcharge that Dr. Teplick did not report TE8's infusion and related adverse effects on 3/11/87. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain the records of data pertinent to the investigation for subject TE8's treatment on 3/11/87.

5. **The Center charged that the hospital records reported that TE3 received 142cc of over two hours and fifty minutes while the CRF reported that the subject received 360 cc of over six hours.**

I interpreted this subcharge to mean that the Center alleged that Dr. Teplick failed to prepare and maintain accurate records of infusion amount and duration for subject TE3, as evidenced by the unresolved discrepancy between the record of infusion in the hospital records and his CRF. This subcharge, along with the discrepancies noted in FDA Form 483 [CX 31 at 7], is essentially a specific example of Charge IV.1. The Center submitted the record that revealed this discrepancy between the CRF [CX 20 at 2] and radiology report [id. at 16].

Dr. Teplick explained in his written response that his records showed the subject had received 360cc over 6 hours. [TX J at 10.] He continued by stating: "I do not know why the discrepancy with medical records, I no longer have access to the records." [Id.] He reaffirmed this statement in his written addendum of 1/22/92. [TX V at 18-9.]

As discussed above, Dr. Teplick was responsible for maintaining "adequate and accurate records in accordance with § 312.62 and to make those records available for inspection in accordance with 21 C.F.R. 312.68." [See n. 22 at 74.] It was also his responsibility to monitor these records and to resolve any discrepancies in the study records. The unresolved discrepancy regarding the amount and duration of infusion was an example of data pertinent in the study to evaluate the effectiveness of

infusion. For the above reasons, I find that the Center proved its subcharge that an unresolved discrepancy regarding the amount and duration of infusion existed between the hospital records and the CRF for subject TE3. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate and accurate records of all observations and data pertinent to the investigation on each individual treated with the investigational drug.

6. The Center charged that Dr. Teplick failed to maintain adequate records of x-rays performed on the subjects in his study.

In a previous discussion, the Center presented information to document that Dr. Teplick failed to comply with some of the modifications requested by the IRB that reviewed his protocol. [Supra, **Charge II.A.**] One of the modifications requested by the IRB when the study was initially tabled stated: "Please address the radiologic risks from x-rays every 2 hours. The Committee recommends that such exposure be limited to 5 x-rays." [CX 36 at 2.] Dr. Teplick had replied in a document received by the university's Grants and Contracts office on 3/27/86, stating: "In our opinion a radiograph every 2 hours is not excessive. However, we can reduce the radiographic exposure to comply with your wishes without compromising the study." [CX 37 at 1.]

Nevertheless, Dr. Teplick's protocol still stated: "Cholecystograms [the radiographs referred to by the Center in this subcharge] will be performed at 2-hour intervals until stones are no longer evident." [CX 45 at 4.] Since the radiological examinations were included in Dr. Teplick's protocol as a part of the study, Dr. Teplick was required to keep records of such tests as data pertinent to the study.

Dr. Teplick testified during the hearing that although he did limit each subject's exposure to five x-rays, he had not documented his compliance. [Trans. Vol. 2 at 267.] When questioned: "Is [sic] there any records that are obtainable that will demonstrate that you took or limited yourself, to five exposures, pursuant to the IRB committee's requirements?", he replied: Yes. You'd have to go to the radiology department to get the x-rays." [Id.]

The parties failed to prove or disprove that more than "five x-rays" were taken for any subject. Dr. Teplick provided study records that documented his written acceptance of the IRB's request for the limitation in the number of radiologic examinations. However, he failed to submit any documentation to support his compliance. As discussed above, Dr. Teplick was responsible for maintaining "adequate and accurate records in accordance with 21 C.F.R. § 312.62 and to make those records

available for inspection in accordance with 21 C.F.R. § 312.68." [See n. 22 at 74.] Therefore, I find that this subcharge is established by Dr. Teplick's inability to produce adequate and appropriate records to substantiate his compliance. Thus, this subcharge supported the Center's charge that Dr. Teplick failed to prepare and maintain adequate and accurate records of all observations and data pertinent to the investigation on each individual treated with the investigational drug.

7. The Center charged that Dr. Teplick did not make available the CRF or medical record for the fourteenth subject referred to in Dr. Teplick's second annual report (the Center had information for thirteen).

I interpreted this charge to mean that the Center alleged that Dr. Teplick failed to keep adequate and accurate records of the observations and other data pertinent to the investigation for the unaccounted for fourteenth subject referred to in Dr. Teplick's second annual report. The Center substantially addressed this subcharge in its presentation in support of Charge II.C.4. [Supra; see also CX 43 at 1.] As stated above, Dr. Teplick affirmed in his written response to the agency that only 13 subjects had been treated during the dates of the report, and that he had no record of the second annual report and requested a copy be sent to him by the Center. [TX J at 6.]

As discussed above, Dr. Teplick was responsible for maintaining

"adequate and accurate records in accordance with 21 C.F.R. § 312.62 and to make those records available for inspection in accordance with 21 C.F.R. § 312.68." [See n. 22 at 74.] It was also his responsibility to monitor these records and to resolve any discrepancies in the study records. Since there was no fourteenth subject, Dr. Teplick did not violate this subcharge by failing to provide a CRF or medical record for a non-existent subject. Thus, this subcharge did not support the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug.

However, Dr. Teplick should have maintained records of his correspondence to both the IRB and the sponsor, and his inability to locate study documents supported the Center's allegation of his generally poor record-keeping.

8. The Center charged that at least 16 of the 26 CRFs reported false dates with respect to the SGOT and alkaline phosphatase values obtained.

The Center presented information related to this subcharge in its presentation of **Charge III.B.7.** For this subcharge, the Center presented testimony explaining how the date discrepancies were discovered and documented. [Trans. Vol. 1 at 198-203.]

In his response to the charge, Dr. Teplick testified that he had delegated the responsibility for collecting the specimens, and he admitted that he was lax in checking on whether his staff completed all of the tests. He also testified that his staff may have not reported the proper dates when the tests were done. [Trans. Vol. 2 at 261-3; see supra, Charge III.B.7.]

Dr. Teplick was responsible for maintaining "adequate and accurate records in accordance with 21 C.F.R. § 312.62 and to make those records available for inspection in accordance with 21 C.F.R. § 312.68." [See n. 22 at 74.] It was also his responsibility to monitor these records and to resolve any discrepancies in the study records. For this reason, I find that the Center proved this subcharge that Dr. Teplick reported false dates with respect to the SGOT and alkaline phosphatase values obtained for subjects, whether because of poor record-keeping or deliberate false reporting. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 312.62(b) by failing to report these test values accurately for the investigation on each individual treated with the investigational drug.

9. The Center charged that Dr. Teplick failed to submit a CRF for subject LM [TE3] which showed treatment for common bile duct stones one year prior to the subject's May 25, 1988 admission.

The Center presented no information to substantiate this

allegation. The Center, however, suspected this prior treatment based on a May 31, 1989 letter to the sponsor stating that this had occurred.

Dr. Teplick, however, addressed the subcharge in his written response to the agency:

> This is an error. I probably confused her with one of several patients who I treated and who had recurrent common bile duct stones. On 2/6/85 LM[TE3] presented with jaundice. We did a biliary drainage procedure and found she had a large common bile duct stone which was removed surgically. We never used on her until 1988.

[TX J at 10.]

In his addendum of 1/22/92, Dr. Teplick stated:

> On 2-6-85, a patient (LM) who was subsequently known as exhibit 20(TE-3) presented to [sic] hospital with jaundice and evidence of cholangitis. I treated her with antibiotics and by inserting a biliary drainage catheter. At that time, she had one large common bile duct stone. The stone was removed surgically. There was no attempt to dissolve the stone and in 1985 we had only for dissolution purposes. We did not start to use until 1986. Consequently, no CRF form was sent or should have been sent to Dr.

[TX V at 20.]

Dr. Teplick clearly admitted that the 5/31/89 letter existed by describing the reason for his error. Dr. Teplick, however,

failed to document accurately to the sponsor the actual treatment of TE3 of the time of her 1985 admission. The inaccuracy of his 1989 letter, again, demonstrated the poor quality of his record-keeping. As discussed previously, the Center was able to demonstrate inaccurate statements made about subjects reported to both the IRB and the sponsor.

Dr. Teplick was responsible for maintaining "adequate and accurate records in accordance with 21 C.F.R. § 312.62 and to make those records available for inspection in accordance with 21 C.F.R. § 312.68." [See n. 22 at 74.] He was also responsible for monitoring these records and for resolving any discrepancies in the study documents. In this case, however, the Center's subcharge focused on Dr. Teplick's lack of submitting a CRF for a suspected infusion of with subject TE3 that apparently never occurred. Therefore, the Center was unable to support its subcharge that Dr. Teplick failed to submit a CRF for infusion with TE3 one year prior to the subject's May 25, 1988 admission. Thus, this subcharge did not support the Center's charge that Dr. Teplick violated § 312.62(b) by failing to prepare and maintain adequate records of all observations and data pertinent to the investigation on each individual treated with the investigational drug.

* * *

Of the above subcharges under **Charge IV.**, I found that the Center proved that Dr. Teplick violated **Charges IV. 1-6 and 8** and that of these subcharges, all but **Charge IV.3.** supported the **Charge IV.** Therefore, I find that Dr. Teplick did violate § 312.62(b) by failing to maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug.

* * *

Charge V. Dr. Teplick violated § 312.62(a) by failing to maintain adequate records of the disposition of the investigational drug.

The regulation under 312.62(a) states: "Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects . . . ."

The Center charged that Dr. Teplick failed to maintain drug accountability records. The Center presented testimony on this charge. Ms. deMarco testified:

> No drug accountability records were available. I telephoned Dr. Teplick because, as I said, he wasn't present and I thought maybe I was just overlooking them. And he confirmed by telephone that he had not kept drug accountability records. He did not know who purchased the drug. He didn't know technically how it was paid for within the

> University. And I was not even able to track down more than one receiving record for it. So there were no drug accountability records maintained.

[Trans. Vol. 1 at 205.]

Dr. Teplick testified that the pharmacy wanted control of the drugs purchased for studies. He stated that the pharmacy[29] would ask him how much he needed, and he would then tell his secretary to order more He stated that the department [of Radiology] would pay for and then keep the until it was needed. [Trans. Vol. 2 at 167-70.]

Dr. Teplick claimed that all of his communications with the pharmacy were conducted by telephone. For this reason, he stated that he could not produce written evidence of the above transactions concerning the investigational drug. [Trans. Vol. 2 at 173.] Finally, Dr. Teplick admitted that he had not maintained drug accountability records. [Trans. Vol. 2 at 311.] Dr. Teplick's CRFs did note the source of as which differed from the source the IND sponsor had named in the IND. [See, e.g., CX 20 at 1; CX 55 at 1-2.]

Dr. Teplick clearly stated that he had not maintained this type

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[29] Dr. Teplick testified that he dealt with the "Head of the Pharmacy." [Trans. Vol. 2 at 171.]

of records. [See Trans. Vol. 2 at 311.] Therefore, I find that Dr. Teplick did violate 312.62(a), by failing to maintain adequate records of the investigational drug

* * *

Charge VI: Dr. Teplick violated § 50.27 by failing to document informed consent for two subjects, TJ and JM.

Under § 50.20: "Except as provided in § 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." Section 50.27 requires that "[e]xcept as provided in § 56.109(c),[30] informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form." The IRB also required documentation

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[30] Section 56.109(c) states: "An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context."

and maintenance of consent forms for periodic review.[31]

The Center charged that Dr. Teplick failed to obtain informed consent from TJ and JM. As discussed previously [supra, Charge IV.2.], TJ did not receive ; for this reason, Dr. Teplick argued, she did not have a CRF. Therefore, I find that Dr. Teplick did not violate § 50.27 with respect to subject TJ. Dr. Teplick admitted that JM received although infusion was discontinued after one dose. [TX V at 17; see also Charge II.C.5.; CX 27 at 7.] Dr. Teplick stated in both of his written responses to the agency, that consent forms were obtained from all subjects treated with [TX J at 12; TX V at 22.] However, no proof of a signed consent form from JM was submitted for review. Also, Dr. Teplick did not provide any evidence that the IRB waived the informed consent requirement for JM, in accordance with § 56.109.

Therefore, I find that Dr. Teplick violated § 50.27, by failing to document a signed consent form (i.e., informed consent) for subject JM.

* * *

[31] All signed consent forms must be retained and available for CHS review for a period of five years following the termination of a project. [CX 38; 42 at 2; 43 at 2.]

Charge VII: Dr. Teplick violated § 50.25 by failing to satisfy all of the requirements of informed consent. The Center charged that Dr. Teplick's consent form:

1. **Did not adequately describe the purpose of the research.**

2. **Did not adequately disclose the foreseeable risks and discomforts to the subjects.**

3. **Did not contain an adequate explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.**

Section 50.25(a) requires that eight "basic elements of informed consent" be provided to each research subject. These include:

> (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
> . . . .
>
> (2) A description of any reasonably foreseeable risks or discomforts to the subject . . .
> . . . .
>
> (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject . . .
> . . . .

[§ 50.25(a).]

In his written response to the agency, Dr. Teplick addressed this charge: "I used the consent forms sent by Dr. My

understanding is that each institution has its own additions or deletions to a specific consent form.[32] I used the consent form that was approved by 's IRB." [TX J at 12.] He affirmed this position in a written addendum, dated 1/22/92:

> I gave this [Dr. 's] consent form to 's IRB. They made certain changes and I abided by the changes that they made. I assumed that the IRB was familiar with the FDA requirements for investigational informed consents. Consequently, I used basically Dr. 's consent with some modifications from our own IRB.

[TX V at 22.]

The Center charged that the consent form used by Dr. Teplick in his study failed to address the three required elements listed above. Regarding the form's statement of purpose of the research **(Charge VII.1.)**, Dr. Barton testified that Dr. Teplick's informed consent:

> **would not be acceptable to the Food and Drug Administration. The regulations are very specific that the purpose of the study is to determine the safety and efficacy of the drug. That is the purpose of the study. A nice fringe benefit would be that it benefits the patient also, but the purpose of the study is to evaluate the new drug, evaluate**

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[32] Dr. Teplick was partly correct. Section 56.109(b)(emphasis provided) states: "The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects." Dr. Teplick was incorrect to believe that an IRB could delete or remove certain required sections based on § 50.25.

> its safety and efficacy. And that should be clearly stated to the patient. They know the purpose is to study the drug, not to treat the patient.

[Trans. Vol. 1 at 270.]

The Center objected to the section of the consent form entitled, "Purpose of Research," alleging that it failed to sufficiently inform the study participants that the use of was investigational. Specifically, this section of the form stated:

> The purpose of this study is to attempt to dissolve biliary stones using a drug called . We feel that the drug will probably be effective in your case, and, if so, our study will help establish its use as an accepted agent for dissolving biliary stones.

[CX 30 at 1.]

In its review of the consent form, the IRB required Dr. Teplick to remove the reference to the possible effectiveness of the in the "Purpose of the Research" section. [CX 36 at 2.] Although Dr. Teplick informed the IRB that he had deleted the sentence concerning the effectiveness of the [CX 37 at 2], this sentence was not removed from the document, as previously discussed in Charge II.A.1. [See also CX 30.]

However, the concept that infusion was "investigational" was apparent in numerous locations throughout the consent form document. For example:

> I understand that because of the investigational nature of the treatment or procedure there may be some unknown risks or results and that, therefore, there can be no guarantee of any results or outcome of same."

[CX 30 at 1.]

> I accept the personal risks of this treatment or procedure with the full understanding that it is for my possible benefit, the advancement of science, and in the interest of humanity.

[Id.]

Based on this information, I find that while Dr. Teplick's informed consent form could have perhaps more clearly identified the investigational nature of the purpose of the research, the consent form adequately explained the purpose of the research as investigational in accordance with § 50.25(a). Therefore, the Center did not prove its subcharge that Dr. Teplick's informed consent form did not adequately describe the purpose of the research. Thus, this subcharge did not support Charge VII.1. that Dr. Teplick violated § 50.25 by failing to satisfy all of the requirements of informed consent.

Dr. Barton also testified that the consent form inadequately described the foreseeable risks and discomforts to the research participants (Charge VII.2.):

> [Y]ou'll recall from the adverse events that I've already listed that there were many problems that should have been reported to the patient. The patient should be aware of

> these adverse events before they sign a consent form. And they are not adequately described here.

[Trans. Vol. 1 at 270.] She went on to describe specific adverse events which the consent form did not address. [Id. at 270-2.]

The consent form used by Dr. Teplick addressed adverse effects, as follows: "There are some minor discomforts associated with the venipunctures need [sic] for blood tests. In addition, occasional patients may experience nausea and, at times, vomiting, which can be controlled medically, as well as temporarily reducing the injection of

[CX 30 at 3.]

As discussed above, the Center presented information regarding the adverse experiences which should have been reported to the IND sponsor, the IRB, and the agency. [See supra, **Charges I. & II.C.**] These adverse experiences should also have been addressed in the consent form. Such adverse experiences included a temporally-associated death, exacerbation of previous cardiac conditions, and severe nausea and sedation observed in the subjects with common biliary duct stones, who required higher doses of In particular, the consent form should have been modified to address the complications that required the product to be discontinued for some subjects. [Id.] In addition, because the procedural risks associated with the placement of the

catheter to deliver the investigational agent were significant (e.g., breakage of the occlusive balloon, pain, bleeding, and death), the consent form should have provided a description of these risks as well. [See Trans. Vol. 2 at 93; TX C at 6.] For these reasons, I find that the Center demonstrated **Charge VII.2.** that Dr. Teplick's informed consent form did not adequately disclose the foreseeable risks and discomforts to the subjects. Thus, this subcharge supported the Center's charge that Dr. Teplick violated § 50.25 by failing to satisfy the requirements of informed consent.

Finally, Dr. Barton addressed the subcharge that the consent form inadequately identified a contact person to address pertinent questions about the research and the research subject's rights, and to answer questions in the event of a research-related injury to the subject (**Charge VII.3.**):

> [F]or the case of physical injury, and it merely states, "I should contact the investigator." No, we do not consider that to be adequate. The regulations require that the investigator be identified and the subject be informed how to contact this individual . . . At least a name and a phone number.
>
> . . . .
>
> [F]or questions about rights it says that they may obtain this from the Office of Grants and Contracts. Grants and Contracts is a large something. The regulations require that the subject be informed whom to contact and how to contact. Again, a name and a number are required.

[Trans. Vol. 1 at 273.]

The consent form used by Dr. Teplick, which had been approved by the IRB provided the following:

> I hereby agree to permit Dr. Steven K. Teplick and such Associates and Assistants as he/she may designate (each of whom is hereafter called 'the investigator'), to perform upon me (or upon the participant) the investigational treatments or procedures . . . .

[CX 30 at 1.]

> I have been advised that if I experience any physical injury due to this treatment or procedure, I should contact the Investigator, who is prepared to provide or obtain appropriate medical treatment . . . Further information on the foregoing as well as information regarding this research and my rights may be obtained from the Office of Grants and Contracts.

[Id. at 1.]

Although no specific telephone number was listed, the consent form did identify "Dr. Teplick," as the "Investigator," as well as identifying the "Associates and Assistants" stipulated by Dr. Teplick to conduct the clinical trial, as the contacts. Because all patients were supposed to be treated as inpatients in each subject would presumably know or be able to find out the telephone number of which in turn could locate Dr. Teplick. Also, although a specific individual was not named as a contact regarding research subject's rights, the consent form did

identify an office within the institution to which such concerns could be directed. [Id.] In the absence of an IRB policy statement requiring the inclusion of information such as the telephone number or name of the contacts, I do not find that the level of detail desired by Dr. Barton is required by the regulations for informed consent regarding whom to contact for answers to questions about the research, research subjects' rights and research-related injury. For this reason, I conclude that Dr. Teplick adequately explained whom to contact for answers to the above information. Thus, this subcharge (**Charge VII.3.**) did not support the Center's charge.

Nevertheless, the Center sufficiently supported the allegation that the consent form was incomplete, because it did not contain accurate information regarding the risks of the product or procedures (**Charge VII.2.**). The consent form had not been appropriately updated to include new information regarding the nature and severity of adverse experiences of subjects who were receiving for common biliary duct stones.[33] I, therefore, find that the Center demonstrated that Dr. Teplick violated

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[33] In previous charges, the Center had argued that Dr. Teplick had not stated the correct number of subjects who had received Regarding Dr. Teplick's consent form, it stated: "To the best of our knowledge only two patients have been reported in the medical literature as having received this treatment in the United States" [CX 30 at 2] and was never updated, even though Dr. Teplick was aware that additional subjects had received the product at his own institution.

§ 50.25 by failing to provide a consent form which addressed all of the required elements (specifically, element § 50.25(a)(2)) of informed consent.

VI. CONCLUSION

I conclude that Dr. Teplick failed to report alarming and unanticipated problems involving risk to human subjects in a timely manner to the agency, in violation of § 312.64(b) (**Charges I.A. & I.B.**). In addition, he failed to report promptly such problems to the IRB, or to obtain IRB approval prior to making changes in his research plan, in violation of § 312.66 (**Charges II.C. & II.D.**). Dr. Teplick failed to follow the investigational plan, as required under § 312.60 (**Charges III.A. & III.B.**); to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual treated with the investigational drug, under § 312.62(b) (**Charge IV.**); and to maintain adequate records of the disposition of the investigational drug, under § 312.62(a) (**Charge V.**). Finally, I find that Dr. Teplick failed to provide an adequate consent form or to document properly informed consent, in violation of §§ 50.27 (**Charge VI.**) and 50.25 (**Charge VII.**). Since Dr. Teplick repeatedly violated the regulations in Parts 50 and 312, I conclude that Dr. Teplick should be

disqualified from receiving investigational drugs.

VII. RECOMMENDATION

I recommend that the Commissioner disqualify Dr. Teplick from receiving investigational drugs.

JUN 21 1993

Freddie Ann Hoffman, M.D.

Presiding Officer