

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

To: The Commissioner
Through: The Deputy Commissioner _____

DATE: 10 30 1976

EXHIBIT B

FROM : Associate Commissioner for Medical Affairs

SUBJECT: Investigator, Edward C. Froning, M.D., of San Mateo,
California--ACTION

ISSUE

To propose a course of action on the issue of the disqualification of Dr. Froning as an investigator of investigational use drugs.

BACKGROUND

In a March 28, 1975, telephone conversation with Dr. Edward C. Froning, an investigator of the investigational drug _____, Dr. _____ of _____ confirmed that Dr. Froning had performed a reinjection of a patient. The information had been given to _____ on March 27, 1975, by a San Mateo physician who expressed concern about Dr. Froning's work with _____.

In an April 1, 1975, letter to Dr. _____ confirming a telephone conversation of that date, Dr. _____ informed Dr. _____ that a review of Dr. Froning's case report forms failed to disclose the second injection administered by Dr. Froning to one of his patients. The company viewed such reinjections as being prohibited (Tab A). Dr. _____ also indicated, in a second letter dated April 1, 1975, that Dr. Froning had been suspended as an investigator by his sponsor, and he enclosed a copy of a telegram to Dr. Froning advising him of the decision (Tab B). Dr. _____ further advised Dr. _____ that Dr. Froning had made some comments indicating that more than one patient may have been reinjected.

An investigation of the facts surrounding the conduct of Dr. Froning as an investigator of _____ then took place. By letter of June 2, 1975, Dr. _____ advised Dr. Froning that on the basis of our investigation: "We conclude that you have repeatedly and deliberately violated the conditions of the Investigational Drug Regulations...." Dr. Froning was invited to an informal conference to discuss the charges (Tab C).

At the July 7, 1975, informal conference (Tab D--transcript), Dr. Froning did not deny that he had reinjected four patients nor that he had failed to report the reinjections to the sponsor. He argued that reinjections were not prohibited under the conditions of his approved protocol. He further

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argued that the status of reinjections was confused because there was no single protocol used by all investigators. He also argued that Dr. [redacted] originator of the drug, had advised him to perform a reinjection of one of Dr. [redacted] patients. This was Dr. Froning's first of four patients whom he reinjected. Dr. Froning maintained that he viewed Dr. [redacted] as fulfilling some type of "senior investigator" role in the investigation and that he therefore relied heavily upon Dr. [redacted] advice. Dr. Froning also indicated that Dr. [redacted] had informed him that other investigators were performing second injections and that the company was aware of this fact. Dr. Froning maintained that Dr. [redacted] had advised him not to report the reinjections because [redacted] "could not handle it" at that time. Dr. Froning stated that he discussed each reinjection with Dr. [redacted] and that he assumed that Dr. [redacted] was in contact with [redacted] and was discussing the reinjections with the sponsor. Dr. Froning did not press Dr. [redacted] regarding the apparent discrepancy over reinjections nor did he attempt to verify Dr. [redacted] advice or instructions with the sponsor.

Dr. Froning did deny injecting patients after receiving notification that he was suspended as an investigator. He argued that the mailgram advising him of his suspension arrived in his office the day that he had scheduled three patients for treatment. He maintained that he was not aware of the receipt of the mailgram until the procedures were completed, after which he went to his office. He maintained that he was not advised of his suspension as an investigator in telephone conversations with Dr. [redacted] (March 28, 1975 and March 31, 1975).

Dr. Froning stated, at his informal conference, that he became clearly aware that reinjections were prohibited during 1973 telephone conversations with Dr. [redacted]. At that point, Dr. Froning stated he ceased administering second injections to his patients.

On July 31, 1975, Dr. [redacted] advised Dr. Froning that "...I cannot accept as credible the explanation offered on July 7, 1975." Dr. Froning was further advised that Dr. [redacted] had recommended that he be found ineligible to receive investigational drugs because he had concluded that Dr. Froning had "...repeatedly and deliberately failed to comply with the conditions of our regulations...." Dr. Froning was advised of his right to request an informal hearing before the Commissioner (Tab E).

Dr. Froning was granted his request for an informal hearing, and on November 11, 1975, he and his counsel appeared before me to discuss the charges surrounding his conduct as an investigator of the investigational drug, [redacted]. Representatives of the Bureau of Drugs and of the Office of General Counsel participated in the informal hearing.

CHARGES

At the November 11, 1975, informal hearing, the Bureau of Drugs charged:

- a. Dr. Froning had repeatedly or deliberately failed to comply with the conditions or regulations in that he performed reinjections in four patients after being informed by the sponsor that a second injection of _____ was prohibited.
- b. Dr. Froning submitted false information to the sponsor in required reports in that he did reinject four patients and failed to report the reinjections to the sponsor.
- c. Dr. Froning injected three patients (all on April 2, 1975) after being informed by the sponsor (_____) that he was suspended as an investigator and that he was to do no further injections "...subsequent (sic) to the receipt of this communication."

DR. FRONING'S RESPONSE TO THE CHARGES

Dr. Froning and his counsel submitted exhibits and argued at the November 11 informal hearing in support of his credibility (challenged in Dr. July 31, 1975 letter) and in support of mitigating circumstances surrounding Dr. Froning's conduct as an investigator (Tab F--transcript).

Dr. Froning noted that a draft package insert sent for his comments prior to an August 1970 investigator meeting indicated that "_____ for injection is contraindicated in patients with known sensitivity to _____ and in patients previously treated with _____" (Tab G).

Dr. Froning's counsel argued that "contraindicated" is not synonymous with "prohibited."

Dr. Froning acknowledged that he had received several packets of information from the sponsor prior to and shortly after he became an investigator of _____ in 1970. A May 28, 1970, letter described results of a conference with FDA and listed several agreements reached at that conference, including a statement that: "A second injection of _____ is prohibited until an appropriate skin test has been developed to detect potential reactors" (Tab H). Dr. Froning also received, some time prior to the August 29, 1970, investigator's meeting, a RESEARCH SUMMARY prepared by _____ which stated in the "Contraindications" section, "re-injected 'Patients who have been treated with _____ injections must not be re-injected pending development of a satisfactory screen test to evaluate sensitivity to the enzyme'" (Tab I).

Dr. Froning alluded to early problems he had in communication with and receiving instructions or guidance from He pointed out that several changes in personnel occurred about the time he became an investigator, and these changes led to confusion about whom to contact for help and consultation. Dr. because of his authoritative role at the August 29, 1970, meeting and because of his part in the drug's development, was viewed by Dr. Froning as filling some type of "senior investigator" role in the investigation (Tab J). Based on this perception, Dr. Froning consulted with Dr. and acted upon advice received from him. Dr. Froning maintained that he felt Dr. was reflecting an update on the subject of reinjections gathered following the August 1970 meeting when, in 1972, Dr. asked Dr. Froning to perform a reinjection of a patient originally treated by Dr. Dr. Froning reinjected four patients between June 1972 and March 1973.

Dr. Froning maintained that he became clearly aware that reinjections were not allowed in telephone conversations in early 1973 with Dr. Following these conversations, Dr. Froning maintained that he ceased performing reinjections and he submitted an affidavit to support this contention (Tab K).

Dr. Froning pointed out that his protocol (approved in 1970) did not expressly preclude reinjections. He noted that there was no uniform protocol available until August 1974 (the consent form for this protocol) expressly forbade reinjections with).

Dr. Froning contended that he discussed each reinjection with Dr. and that he assumed that Dr. was then communicating with regarding the reinjections. Dr. purportedly indicated that reinjections could be performed and that the sponsor was aware that reinjections were being made. Dr. Froning stated that Dr. advised him not to report the reinjections, unless an adverse reaction occurred, because the company "could not handle" reinjections at that time. Dr. Froning followed the advice but maintained that he did not prepare or alter his patient records to hide the reinjections.

Dr. Froning contended that he did not perform injections of patients following receipt of official notification of his suspension as an investigator. Dr. Froning stated that the mailgram advising him of his suspension did not arrive in his office until the morning of April 2, 1975 (Tab L). Dr. Froning maintained that he was at the hospital and was in the process of treating one of three patients previously scheduled to receive

the drug (one patient had been rescheduled from April 1 to April 2 in order to allow time for Dr. [redacted] to advise Dr. Froning of his status as an investigator). Dr. Froning did not become aware of the mailgram advising him not to make additional injections "...subsequent (sic) to receipt of this communication, ..." until he reported to his office late on April 2. He stated that he had not performed any injections of [redacted] since receipt of the mailgram.

SUMMARY

Dr. Froning readily admits the reinjection of four patients with the investigational drug, [redacted]. He argues in his defense mitigating circumstances, consisting of his misconception of the "role" of Dr. [redacted] in the investigation, and that his protocol did not specifically preclude reinjection. Dr. Froning does acknowledge receiving a May 28, 1970, letter (Tab H) which stated, in part, "A second injection of [redacted] is prohibited...." He also acknowledges receipt of a 1970 RESEARCH SUMMARY which stated, in part, that "Patients who have been treated with injections must not be reinjected pending development of a satisfactory skin test to evaluate sensitivity to the enzyme." Furthermore, a March 27, 1972, Investigator Communication Record (Tab M), prepared by Dr. [redacted] of Travenol states in part, "Has a patient who deserves reinjection. Informed Dr. Froning it is absolutely contraindicated." This communication was obtained from the records of an FDA investigation of [redacted] investigators conducted by Food and Drug field staff in mid-March of 1975. Neither Dr. Froning nor the Bureau of Drugs referred to this record in either the informal conference or in the informal hearing.

Dr. Froning readily admits that he did not advise the sponsor of the reinjections he performed. He argues that he assumed that Dr. [redacted] was advising of the reinjections and that the reinjections were not being reported because [redacted] could not handle the reports at that time. In 1973 when Dr. Froning became clearly aware that reinjections were prohibited, however he did not inform [redacted] that he had performed reinjections nor did he offer to supply information regarding the reinjections to the sponsor.

FINDINGS

I find that Dr. Froning repeatedly or deliberately failed to comply with the conditions of the exempting regulations in that he performed reinjection of four patients after being informed by the sponsor, in information supplied in 1970 and again in a March 1972 telephone conversation, that a second injection of [redacted] was prohibited. There are, however, possible mitigating circumstances surrounding Dr. Froning's conduct as an investigat

(his misconception of the role of Dr. [redacted] and his reliance upon Dr. [redacted]. I do not doubt that Dr. Froning did view Dr. [redacted] as an expert and that he discussed various aspects of the investigation with Dr. [redacted]. I cannot, however, accept as credible that Dr. Froning felt he was receiving an update on the reinjection issue in conversations with Dr. [redacted] in June 1972. I believe that a responsible investigator, following the March 27, 1972, conversation with the sponsor would have questioned whether reinjection was allowed when he was requested to perform a reinjection only three months later.

I find that Dr. Froning repeatedly or deliberately submitted false information to the sponsor of the investigation in that he did not report the facts of the four reinjections he performed to [redacted]. Even upon becoming clearly aware in 1973 that reinjections were prohibited, Dr. Froning failed to advise the company that he had performed reinjections or to supply his records pertaining to the reinjections. Although Dr. Froning may have viewed Dr. [redacted] as filling a "special" role in the investigation, I believe that a prudent investigator would have questioned any advice leading to his not accurately reporting the facts of his investigation to the sponsor of the investigation.

I find that Dr. Froning ceased performing injections of [redacted] after being officially notified of his suspension as an investigator by the sponsor. The three injections performed by Dr. Froning on April 2, 1975, were completed before he was made aware of Dr. [redacted] mailgram, which officially notified him of his suspension.

CONCLUSION

The findings against Dr. Froning would support a recommendation that he be disqualified as an investigator of investigational drugs. The circumstances however, militate against this action.

A key circumstance in this conclusion is that the drug is no longer available to Dr. Froning or to any other investigator. Disqualification would, therefore, have no meaning in the context of preventing Dr. Froning from continuing to receive the investigational drug, or upon his current status as an investigator because the only investigation in which he has been involved was on [redacted]. Disqualification would be based upon the significance of his actions as they relate to our regulations and would not be "corrective" as in the case of disqualification of an investigator actively engaged in the study of an investigational drug or drugs.

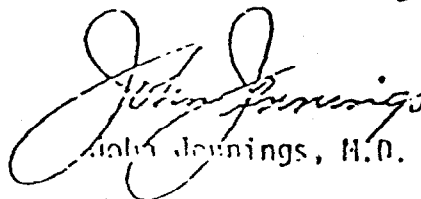
A second fact militating against disqualification is that Dr. Froning ceased performing reinjections when, in 1973, he became clearly aware that such reinjections were prohibited. Dr. Froning, at his informal hearing, submitted an affidavit signed by a patient indicating that he had refused to perform a reinjection of the patient, who in December 1973 and again in February 1974, requested a second treatment with . . . The affidavit was submitted expressly for the purpose of furnishing adequate assurance that the conditions of the investigational study were followed by Dr. Froning after he became aware that reinjections were prohibited. Disqualification is, therefore, not necessary to obtain or to assure corrective action.

Disqualification is considered remedial and not punitive. In this case, there is no longer a need to remedy the possibility of false or inaccurate data being generated as the drug is no longer being investigated. Dr. Froning has, to some degree, demonstrated personal remedial action or rehabilitation, and disqualification would not contribute further to that process. Because disqualification is without a time limitation, it lasts until the investigator applies for reinstatement in relation to an IND. Dr. Froning, who is not a "professional" investigator, might then never have this opportunity available to, and used by, investigators who are routinely or frequently involved in the study of investigational-use drugs.

Finally, the record will show, and Dr. Froning will be so advised, that any request that he be accepted as an investigator of investigational drugs will be carefully evaluated and that his performance and his data will be subjected to close scrutiny to assure that the conditions of the investigation are followed and that he presents adequate assurance that he will employ investigational drugs solely in compliance with the exempting regulations.

RECOMMENDATION

That the Commissioner sign the attached letter to Dr. Froning advising him of the decision regarding his status as an investigator of investigational drugs.


John Jennings, M.D.