MEMORANDUM 11 November 1977

SUBJECT: Report of FDA Inspection

TO: SAM/CC

1. On 8 November, Dr. Gurston Turner, HFD-180, Bureau of Drugs, Federal Drug Administration, Washington, and Mr. Dave Forrestor, of the San Antonio FDA Regional Office, presented themselves, their credentials, and a letter of notification of inspection to Dr. John Triebwasser, Internal Medicine Branch, Clinical Sciences Division. They wished to review our files pertaining to the 201 Thallium Myocardial Imaging Study; this was conducted in the Clinical Sciences Division with isotopes supplied by the New England Nuclear Corp. under the auspices of FDA, during the time that the isotope was under restricted use as an investigational new drug (IND). The NG study was completed on 19 January 1976 and subsequent to that time the drug has been approved by the FDA for full utilization.

2. Background information: On approximately December 1974 New England Nuclear Corp. was queried as to the availability of 201 Thallium for evaluation of the effectiveness (sensitivity, specificity and accuracy) of the isotope for myocardial imaging to non-invasively determine the presence or absence of coronary artery disease. The prime consideration and basic hope was that this isotope, technically superior to others (e.g., potassium and rubidium), could be an effective go/no-go procedure prior to cardiac catheterization and coronary angiography. The Company advised the drug was available provided an application was made to the FDA because of it's IND status. This was complied with. According to the information supplied, our reporting would be direct to New England Nuclear and it was their responsibility to comply with FDA reporting requirements. Essentially, New England Nuclear was not interested in the clinical evaluation of the drug but rather documenting numbers of patients to whom the drug was given to establishing the safety of the medication. They emphasized (on more than one occasion) to the investigators that reports of patient administration should be submitted to them as promptly as possible and not be held until scan analysis was complete in each case and definitely not be held until the entire study was completed. Very little detailed guidance was received from New England Nuclear regarding clinical data to be included, format, etc. Per FDA requirements during the study, New England Nuclear representatives offered to furnish additional isotope at no cost (almost $14,000 worth) for our use in additional patients since we had been so prompt in submitting the required patient data reports to them. This was the only significant communication from the Company between the start of the study and March 1977.

In March 1977, Dr. Triebwasser received a letter requesting certain additional information on various patients. At that time, he reviewed all of the patient data, did find and did correct some administrative

discrepancies on the patient reporting forms, and so advised New England Nuclear by letter 6 April 1977. At the same time, he updated each patient's reporting form with information which had evolved between the time of the initial (in effect preliminary) report and the conclusions of the study. Over the life of the study considerable experience was gained with the Thallium scans which did affect interpretations to some degree. Additionally, patient scans were independently reviewed by the Chief of Nuclear Medicine from Wilford Hall Medical Center and re-reviewed by Dr. Tom Loecker and Dr. Triebwasser. All of these interpretations were compared with prior ones and with catheterization data. The additional information (which in some cases reflected minor-to-major change from the preliminary interpretation) was also annotated on the patient reporting forms. These updated forms were provided to New England Nuclear. No written or verbal comments subsequent to that time were received from New England Nuclear.

3. From the FDA point of view, a number of factors combined to give them the impression of at least questionable reporting practices. They did review the initial report forms provided to them by New England Nuclear. When they received the annotated, updated reports, they were unable in some instances to determine what the chronological sequence of events was in a particular patient. Additionally, our manner of assigning patient case numbers was confusing since if a patient had his evaluation and returned to home base, and then returned to SAM days or weeks later for the scan and cath, he was given a new case number. In some instances, there was confusion as to whether different case numbers represented different patients or the same patients. There were also some administrative oversights such as not dating every signature/entry. Perhaps the most significant point is that New England Nuclear did not provide the April 1977 additional data explanations and patient study summary which they had received from NG. According to the FDA inspectors, New England Nuclear was asked for additional data two or three times in the nine months prior to October 1977 and FDA received no response. All this combined to raise flags and suspicions which triggered the investigation.

4. Considerable time was spent the first day of the investigation briefing the inspectors on the organizational structure and nature of the mission of the Clinical Sciences Division, USAFSAM and AMD. Particular emphasis was placed on the nature of the Consultation Service patient population. This, as it turned out, was quite significant because one of the major red flags raised in the medical review at FDA was the peculiarity of our patient population. There were a number of studies (actual number unknown) by other investigators utilizing this drug/isotope. In all cases, these were essentially hospital based studies and the study populations represented a spectrum of cardiovascular disease from mild to severe.

Our group of patients stood out as a discordant note since they all were either "no disease," or mild disease, and all were asymptomatic. Another factor was the absence of some data on each patient which they expected to see and we did not know should have been submitted; also procedural or format inadequacies or discrepancies which FDA expected as a matter of routine. Presumably New England Nuclear knew of these requirements, however, specifications and criteria were never provided to the investigators nor were these discrepancies ever pointed out at any time by New England Nuclear during the course of the study. As a matter of policy and routine the FDA does not ever query the investigators directly when such questions arise but always seeks explanations from the "sponsor," i.e., the drug company (in this case New England Nuclear). Based on considerable discussion it can easily be stated that these FDA reviewers have considerable reason and past experience to be suspicious. In essence, they have to rely on patient data from investigational studies to determine or assess the safety of a drug. They have many bad experiences of fictitious patients, "graphited data," etc. This background, coupled with no communication between our investigators and their medical reviewers, and no knowledge by their reviewers of our structure, mission or patient population, understandably caused them to be concerned. The final item which prompted the investigation was the failure of New England Nuclear to provide additional explanatory data as requested by FDA.

5. In the outbriefing, Dr. Turner clearly stated that he, himself, was completely satisfied that the study had in fact been done, that scientifically it was valid, that the patient data was accurate, and he felt he could answer all of the questions which had been raised by his superiors/medical reviewers. Both inspectors felt there were lessons to be learned from this; these were discussed and include the following:

a. Extreme care should be taken to insure that all reporting to a sponsor be complete, self-evident on its face, and patient identifying data dates, entries, etc. be clear and consistent.

b. The patient reports which had been submitted to New England Nuclear were, by their standards, incomplete and contained less information than they or we ultimately would have wanted on each patient. Amending these reports as was done, raised questions of 'after the fact' altering of data. It was again pointed out (and recognized by Dr. Turner) that the data initially submitted to New England Nuclear was clearly preliminary, in some respects almost premature, and not done that way by our choice but per the strong requests of New England Nuclear. Two solutions were suggested for any future such study--to stamp the early reports clearly as "preliminary" or to submit no data until the study is completed.

c. There was confusion with changing case numbers and patient identifier which made it difficult to get either patient count or procedure count or both. They recommended that in such a study a single common study patient identifier be established and be maintained through the life of the study.

d. The reporting format and data reported in each case should be consistent both in content and manner of report even to where on the form a particular item is entered. More than one person's handwriting on the forms should be discouraged.

6. There also was considerable discussion regarding the functions of Human Use Committees in general and here in particular. The FDA is particularly concerned of "stacked" committees, of committee control by vested interests, conflicts of interest, etc. They did recognize that the system which we have clearly provides multiple layers of review and safeguards, making it difficult to impossible to stack a committee. In this particular study, Dr. Triebwasser was both Chairman of the Committee and principal investigator. They recommended that in a future similar situation and in retrospect the Committee minutes should have reflected that Dr. Triebwasser did not vote in the review of the Thallium study. Further, the minutes should have been signed by someone other than Dr. Triebwasser as Acting Chairman. It was also recommended that committee minutes contain a voting record. These items will be considered by Dr. Triebwasser and the committee for local implementation.

7. They will submit a letter report to us which may or may not request a written response. Dr. Turner anticipated that written reply would not be required. Our attention was also called to new FDA regulations published in the Federal Register.

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