

March 6, 2000 FDA Gene Therapy Letter
Preclinical and Clinical Issues

Background

On September 19, 1999, the first (and only) death attributed directly to the administration of a gene transfer product was reported to FDA and to the NIH/Office of Biotechnology Assessment (OBA). FDA undertook a series of steps intended to further investigate this event and to determine what additional actions might be undertaken to minimize the risks to subjects participating in clinical trials of gene transfer products. The investigation included, but was not limited to,

- review of the gene transfer product characterization (lot release, stability),
- review of the preclinical (animal) toxicology studies which supported the clinical trial,
- review of the clinical protocol and all protocol modifications,
- review of the clinical results obtained in all patients enrolled, with detailed review of the clinical course of the patient who died in the clinical trial,
- and inspection of the clinical study site to assess the conduct of the study and the local oversight of the conduct of the study.

The results of a directed inspection at the clinical study site identified serious deficiencies in the conduct of the trial. Specific violations included failure to submit safety reports within required time frames (21 CFR 312.32 [Attachment A]), failure of both the clinical investigator and the sponsor to fulfill their obligations under 21 CFR 312.50-60 (Attachment B). Based on the findings at this site, FDA determined that a more systematic review of the procedures in place to ensure adherence to Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP) and to conduct a series of inspections at randomly selected sites. The purpose of this systematic review was to determine the scope of the problem (failure to adhere to GMPs or GCPs) and to identify whether there were particular patterns of non-compliance or specific barriers to compliance.

A letter was issued on March 6, 2000 (attachment C), requesting information on current manufacturing and clinical study practices, and specific data supporting the adequacy of the manufacturing program. The March 6, 2000 letter to Gene Therapy IND or Master File sponsors was sent to individuals who were the sponsor of one or more INDs or Master Files, requesting a response within 3 months (June 6, 2000). A follow-up letter was issued to individuals who did not respond by June 26, 2000. Those not responding to the second mailing by July 27, 2000 were placed on clinical hold.

This report summarizes FDA's review and assessment of the responses to items 6 and 7 of the letter. The requests for information posed in these two items were as follows:

6. *For each clinical trial contained in your IND, please submit a 2-3 page summary of the procedures you have in place to ensure:*
 - a. *there is adequate monitoring of the clinical investigations to demonstrate the trial(s) are conducted in accordance with regulatory requirements and Good Clinical Practices (GCPs), and the protocol; that the rights and well-being of human subjects are protected; and that data reporting, including safety reporting to you (the sponsor), the IRB, and NIH is accurate and complete; and*

- b. *you, as the sponsor, have adequate oversight over the clinical investigation, as outlined in 21 CFR 312, Subpart D. Please include with your summary an organizational chart identifying each individual responsible for oversight of clinical studies and his or her duties. If you have transferred some or all of these obligations to a Contract Research Organization (CRO), please so indicate, verify that these obligations are being appropriately met, and provide a summary of the CRO's oversight procedures.*

For further guidance regarding sponsors' responsibilities in a clinical trial, including monitoring, please refer to the ICH document on GCPs, which can be found on the Internet at <http://www.ifpma.org/pdfifpma/e6.pdf>. (Attachment D)

7. *Please confirm that all animal safety information has been submitted as described in 21 CFR 312.32-33. For any such information not previously submitted, please provide the required information. Please note that results from animal studies that suggest significant clinical risk must be reported, in writing, to this Office and to all investigators within fifteen calendar days after initial receipt of this information and that IND annual reports are to include a summary of major preclinical findings.*

The intent of 6.a. was to confirm compliance with current regulations and obtain information regarding the manner in which sponsors met their obligations under 21 CFR 312.50-55. The regulations are supplemented by the information contained in Good Clinical Practice guidance in the ICH E6 document (Attachment D). The intent of question 6.b. was to obtain information on aspects of the clinical monitoring staff and on the relationship (degree of independence) between the sponsor and the clinical monitoring staff. There is no FDA guidance on the organizational structure or minimum qualifications for clinical monitoring staff. The intent of question 7.a. was to confirm compliance or to bring sponsors into compliance with current regulations for reporting of pre-clinical animal safety studies.

Categorization of Responses to the Item 6 of the March 6, 2000 letter and Administrative Actions

The March 6, 2000, letter was sent to approximately 150 sponsors holding 276 active INDs or Master Files. Responses to the March 6, 2000, letter, were submitted to 200 INDs as of March 8, 2001. In order to capture systematically the information received, a form for collection of the responses (Attachment F) was generated and the information entered into a database. In addition, review staff were encouraged to add comments, which were also captured in the FDA database. Since the information for the clinical monitoring program is protocol-specific, separate information on the monitoring program for each protocol within an IND was recorded.

The status of the assessment of the clinical programs for each protocol within these INDs is as follows:

- There are 26 INDs, containing 64 protocols, in which the description of the clinical monitoring program is complete and adequate; 24 of these INDs are active and 2 INDs were recently inactivated (contain no active studies and no patients continuing on treatment).
- There are 139 INDs containing 212 protocols for which the description of the clinical monitoring program is incomplete. Of these:
 - 6 INDs were withdrawn or inactive prior to the March 6th letter.
 - 27 INDs have been withdrawn or inactivated in response to the March 6, 2000 letter.

- 106 INDs are active; 10 are currently on clinical hold. For these 106 INDs, the sponsors have been contacted by telephone and/or written correspondence and have been asked to provide additional information.
- There are 35 INDs for which the initial response to the March 6th letter is under review and/or being entered into the database.

In addition, 32 INDs for gene therapy products which have been submitted between March 6, 2000 and March 8, 2001. All of these INDs have been evaluated for description and adequacy of the clinical monitoring program. The current status of these INDs follows:

- 5 INDs were withdrawn prior to initiation
- 16 INDs are active and responses contained some information regarding the monitoring program. For 2 INDs, all information is complete and acceptable. Additional information has been requested for the remaining 14 INDs however the deficiencies in the description of the program were not sufficient to place the IND on hold.
- 11 INDs were placed on clinical hold, generally for multiple reasons, including failure to provide or attempt to provide the information requested in the March 6, 2000 letter.

FDA Assessment of Responses and Identification of Deficiencies to Item 6

The information received in response to the March 6, 2000, letter was variable but consisted generally of two types of responses:

- 1) an attempt to describe the clinical monitoring program for those INDs with active studies

For the majority of INDs that remain active, the initial responses generally failed to provide information on either monitoring or auditing of clinical trials as outlined in the ICH E6 document. Instead, the responses often consisted of the steps surrounding protocol initiation, such as confirmation that the protocol and informed consent document were reviewed by the IRB and generation of an eligibility checklist. Based on apparent misunderstanding of what FDA intended or requested, the majority of respondents were contacted by phone and also sent an additional letter, specifying in greater detail the type of information requested (example letter in Attachment E).

- 2) a request to withdraw or inactive the IND with no attempt to describe the clinical monitoring program.

FDA did not request information regarding the clinical monitoring programs for INDs where the sponsor stated that all clinical development of the product had concluded, no further studies were planned, and the response consisted of a request to inactivate or withdraw the IND. Sponsors were asked to identify each protocol, by title, conducted under the IND and to confirm that no patients were continuing to receive drug or active follow-up. For INDs investigating retroviral vectors, where life-long monitoring is currently required, the sponsor was allowed to inactivate but not withdraw the IND. The request for inactivation was acknowledged along with the reminder to submit long-term monitoring information annually and, in the event of a request for re-activation, to provide all the information requested in the March 6, 2000 letter.

FDA Assessment of the responses regarding clinical monitoring procedures

Monitoring and auditing are fundamental aspects of GCP. Although their purposes are similar (to assure appropriate trial conduct and data validity), the approaches differ. As stated in the ICH GCP document, monitoring is "the act of overseeing the progress of the clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements." Medical monitors, usually employees of the sponsor, perform on site (and, if indicated, off site) evaluations of trial-related activities. The extent and frequency of monitoring should be appropriate for the length, complexity, and other particulars of the trial. Among the functions of the monitor is identification of deviations in protocol conduct and taking appropriate corrective steps, e.g., retraining investigators, closing out certain sites, etc.

Auditing is defined in the ICH CGP document as "the systematic and independent examination of trial-related activities and documents." The sponsor may conduct an audit at any time during the course of the trial, particularly if there is cause to suspect problems with certain sites/data. However, the study audit is usually at the conclusion of the trial. The sponsor is responsible for hiring the auditors, and auditors are required to document findings in a written report to the sponsor. FDA field inspectors also conduct independent study audits. Traditionally, the purpose of the FDA audits has been to verify the data submitted to FDA in support of a marketing application. FDA and the sponsor may conduct "for cause" audits at any stage of clinical investigation if there is reason to suspect a problem with trial conduct or data integrity.

Clinical Monitoring and Auditing Procedures

While larger commercial (industry) sponsors generally provided an adequate response to the initial letter, many smaller firms and academic sponsors misunderstood the intent of the letter, and provided a description of implementation or initiation of the study, but did not describe evaluation during or after the conduct of the study. In telephone conversations requesting further information of the monitoring program, comments such as "Isn't this the responsibility of the FDA?" or "Monitoring is performed by the IRB." resulted in the generation of more detailed letter more clearly identifying our requests.

After receipt of telephone calls and/or letters from FDA specifying our request in greater detail, the majority of the sponsors submitted expanded responses. FDA's review of these supplemental responses indicates that the monitoring program generally contain procedures to evaluate the conduct of the protocol and adherence to reporting requirements. The description of the auditing procedures was also generally acceptable and included the elements described in the ICH E6 document. There were, however, a small number of responses in which deficiencies in the standard operating procedures for the clinical monitoring and/or auditing programs were noted. This primarily included the absence of a specific procedure to ensure the following:

- No procedure in place to ensure that modifications to a protocol were submitted to FDA
- No procedure described for audit (verification of study information against source documents) for final study reports or for maintenance of study records
- No individual identified as responsible for receipt and tracking of investigational drug and/or procedures not established for receipt and tracking of investigational drug
- No procedure in place to ensure that safety reports are filed to the IND in a timely fashion.

FDA comment: Some sponsors believe that the IRB forwards adverse event reports to FDA, others believe reports are sent to the Medwatch system for post-marketing reports, and others simply failed to identify FDA as one of the recipients of safety reports.

- No procedure in place for corrective action in the event that an investigator fails to adhere to the clinical protocol or fulfill his/her regulatory requirements.

Extent and Frequency of Monitoring and Auditing

With regard to the description of the extent and frequency of monitoring and auditing, the responses were highly variable in both the extent and frequency of either monitoring or auditing. In addition, sometimes only the extent or frequency was specified. For example, the description for some programs specified the proportion of subjects for whom records were reviewed (e.g., 10%, 100%, or “at least 50%”) and in other programs, the intervals of assessment, from weekly to annual, was specified. There were instances described in which not all studies were continuously monitored but were subject to “spot checking” on a selected basis. The selection of a given study for monitoring in such programs most commonly occurred as a random selection among a proportion of active studies. In this situation, a portion of all the studies being conducted at the institution were considered in the pool for selection rather than a selected assessment of active patients within each study. This type of program raises the concern that any individual investigator study might not be monitored at all for a period of up to several years.

With regard to verification of data, in those programs where all patient information was not verified against source documents, the procedure for selection of records to be reviewed varied. The most common schemes were random selection or a combination of random selection plus review of records for patients in whom significant adverse events had been observed. Generally when a small number of patients were enrolled (e.g., 10 patients) at one site, auditing of all or part of each patients records was planned. However, some programs failed to clearly state if there were a minimum absolute number of patient records to be assessed. For example, the criteria that data from “at least 10% of patients” would be audited against source documents might be inadequate for a small, phase 1 study enrolling only 14 patients.

The extent of the records reviewed ranged from portions of clinical site patient charts to all records at the clinical study site plus all copies of outside physician notes and laboratory information.

Organizational structure; training and qualifications of staff

Even upon resubmission, the response to this portion of the March 6, 2000, letter was frequently not addressed. With regard to the description of the clinical monitoring staff, the following arrangements were noted:

- The clinical investigator (PI) and study nurses review the charts at a regularly scheduled meeting (e.g., weekly or monthly). The PI remains the final authority on conduct of the study and veracity of the study data.
- The institution where the study is performed maintains a “quality-assurance” staff, who operate under the direction of the IRB or to the administration. The QA staff generally review selected medical records for some portion of the studies conducted at that institution. The QA staff also provide a report to the clinical investigator of their findings.
- Contract research organization (CRO)- this option was most common with smaller biotech firms. The firm remains responsible for final verification of data. Institution of

corrective actions to address deficiencies in the conduct of the trial may still remain with the IND sponsor.

- Split of responsibilities in which certain functions are retained by the IND sponsor (typically drug shipment and accountability, at minimum) and other aspects transferred to CRO. This arrangement seemed to be used by many of the larger commercial sponsors but was also noted in some academic sponsor-investigator INDs.

The basis for qualifications of the monitoring staff under most INDs was not provided, however the staff generally consisted of individuals with degrees in health-related fields. Contract research organizations provided the greatest detail regarding specific training for monitoring staff, which occurred over weeks to three months.

In the review of the description of the clinical monitoring staff, three specific areas of concern were identified.

- 1) There are sponsors who transferred the obligations of their clinical monitoring program to a CRO and did not have a copy of the procedures that the CRO used. The sponsor believed it was acceptable simply to acknowledge the transfer of obligations, however FDA felt that the sponsor needed to have reviewed the program and to have determined its adequacy prior to transferring their obligations to another party.
- 2) For sponsor-investigators, the monitoring staff may be directly under the control of the investigator. The lack of independence raises concerns that monitors cannot take corrective action when deficiencies are found.
- 3) Commercial sponsors may acquire clinical studies from other companies and/or individual investigators. In some instances, serious deficiencies in the conduct of the study were uncovered. Sponsors were unclear as to their obligations to investigate and report such deficiencies.

Categorization of Responses to the Item 7 of the March 6, 2000 letter and Administrative Actions

Responses to the March 6, 2000 letter have been submitted to 200 INDs and Master Files. In order to capture systematically the information received, a form for collection of the responses (Attachment F) was generated and the information entered into a database. In addition, review staff were encouraged to add comments, which were also captured in the FDA database. The responses for animal safety study were not considered to be protocol specific and responses are considered for the entire IND file.

The status of the assessment of the animal safety information submitted to each IND is as follows:

- Responses from 137 INDs or Master Files (MFs) to item 7 were adequate
 - For 119 INDs or MFs, the sponsor indicated that all safety information had already been submitted as described in 21 CFR 312.32-33.
 - For 14 INDs or MFs, the sponsor supplied additional information and confirmed that all safety information is now submitted. In some instances, this consisted only of a copy of the publication of a study, where the raw data had been submitted previously to the IND. In other instances, this consisted of entirely new information.
 - For 2 INDs, the sponsor identified additional required information but did not provide the information in its entirety. For these two INDs (held by the same sponsor), a summary report of animal safety studies was submitted and the sponsor confirmed that they will provide the final study report or primary data to the IND in a timely manner.

- There are 39 INDs or Master Files where the response did not address the question or contained an unclear response (e.g., “not applicable” or “animal safety studies not required”). These sponsors have been contacted by telephone and/or letter and asked to provide clarification of their response.
- There are 16 INDs or Master Files where the response is under review/not yet entered in the database

FDA Assessment of Responses and Identification of Deficiencies to Item 6

The review of response to item 7 indicates that most sponsor are in compliance with the requirements to the extent they are capable. However a limited number of sponsors are unclear about the role of animal safety studies and appeared unaware of, or failed to recall, animal safety studies which existed in cross-referenced INDs or MFs in support of their clinical studies. There were also a few sponsors who stated that they had provided all required information but failed to note that they were currently on hold for failure to provide certain types of pre-clinical animal safety data requested by FDA.

The major concerns raised by the FDA staff reviewing these submissions was in regard to animal safety information that was contained in cross-referenced INDs and MFs held by a different sponsor. The first issue concerned sponsors who believed that animal safety data in a cross-referenced IND was being used to support their clinical studies. In a few cases, the IND/MF was known only to contain product and manufacturing information, whereas in others, the letter authorizing cross-reference did not indicate that animal safety studies were included in the scope of the cross-reference letter. FDA contacted such sponsors to obtain additional clarification on the location of animal safety studies or clarification of the correct cross-reference. In a larger number of INDs, sponsors asserted that all animal safety studies had been submitted to a cross-referenced file, however reviewers raised questions as to how sponsors could verify this, as they generally do not have access to the contents of cross-reference file. The FDA staff considered whether sponsors seeking cross-references to information contained in other files should obtain a commitment from the cross-referenced IND or MF-holders that all required animal and product data will be submitted per 21 CFR 312.32 and 33.