

Gene Therapy Patient Tracking System

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Gene Therapy Patient Tracking System

1. Introduction / Objectives / Overview

1.1. Rationale for a Gene Therapy Patient Tracking System (GTPTS)

FDA has a variety of patient safety programs and procedures in place for assessing and promoting the safety of investigational and approved new drugs and biological agents. For investigational products, FDA requires sponsors to report serious and unexpected adverse events associated with use of a product as soon as possible and within 15 calendar days. Sponsors must report any unexpected fatal or life-threatening experience associated with the use of the product as soon as possible, and within seven days. Prompt reporting allows the agency to analyze reports and take immediate action as indicated. Sponsors summarize other events in annual reports and information amendments that facilitate our periodic comprehensive overview of the effects of a product, including safety. FDA review teams either review related products or meet periodically to share information and discern trends.

Through experience in the review and regulation of gene therapy products, FDA has identified several concerns and issues raised by gene therapy products that differ from those typically raised by more traditional products. Because of the specific issues raised by gene therapy and because continuing and expanding research in gene therapy is creating new demands on oversight systems, FDA has pursued the development of a comprehensive Gene Therapy Patient Tracking System (GTPTS) to help ensure the appropriate oversight and safe development of these therapies.

1.2. Objectives

The objectives of the GTPTS are to supplement or replace current systems for assessing and promoting the safety of gene therapy so that the oversight system will be optimized for dealing with relatively specific gene therapy issues. We have identified five areas in which the GTPTS can improve upon pre-existing FDA systems for assessing and promoting product safety.

1. To facilitate collection and analysis of types of information unique to gene therapy, particularly information regarding long-term safety outcome.

Many of the potential adverse effects of concern in gene therapy patients are the same as those of concern for other therapies; however, gene therapy raises some concerns that are relatively unique. Perhaps the greatest area of concern is that of late-occurring toxicities. By permanently altering the genetic makeup of the recipient cells, some forms of gene therapy may cause toxicities that do not

manifest themselves until years later. Additionally, some gene therapies use viral vectors with the potential to form latent infections that may emerge clinically years later. Thus, an important objective of the GTPTS is to provide a better system for collection and analysis of such information.

2. To facilitate analysis of safety trends across multiple, related products.

In large part, FDA safety systems are organized around individual products. Most traditional drugs and biologics are either unique or have a small number of closely related products of the same class that are likely to have related safety profiles.

In contrast, large numbers of gene therapy products under development by different sponsors share common features that may affect safety. For example, otherwise unrelated therapies may have closely related vectors, genetic inserts, or concomitant cellular therapies. As the field grows, databases that facilitate safety analyses across products that are related in different ways will lead to enhanced safety assessments.

3. To allow correlation of events by patient.

In current premarketing systems, annual reports and study reports frequently provide the numbers of patients having noteworthy outcomes, whether favorable or adverse. There may be no simple way for the Agency to determine whether or not, for example, one of the four patients experiencing event A was also the patient who experienced event B previously. For standard therapies, most adverse reactions occur over a relatively limited period of time and the need to follow outcomes by patient over time is small. In contrast, many gene therapies are intended to affect the physiology and to persist in the patient for extended periods. Linking early events to later events in the same patient may provide useful insight into the unintended biologic and physiologic properties of the agent.

4. To facilitate preparation of periodic summaries of gene therapy safety information.

Periodic review of aggregate gene transfer clinical trial data could help identify trends indicating potential areas of concern. Public discussion of summary safety information would promote awareness among gene therapy study sponsors, research investigators, and the general public of emerging issues in the medical, scientific, and ethical aspects of clinical gene therapy research.

5. To bridge the gap from pre-market to post-market.

Typically, the goals of safety oversight differ from the premarket to the postmarket situation and FDA uses different systems. At the time of marketing approval, FDA performs a comprehensive assessment of the premarket safety profile and the sponsor commits to address outstanding issues in post-market

studies. Post-marketing surveillance is then designed to capture unanticipated events that may result with more widespread, less controlled use. With gene therapy products, there is a greater potential for delayed serious adverse events, and a need to conduct safety assessment across related products, including investigational and approved products. These factors support a patient tracking system that would coordinate the current premarket and postmarket surveillance systems.

1.3. What is the GTPTS?

The GTPTS is a system for the collection and analysis of information pertinent to the safety of gene therapy recipients. Far more than an adverse event database, it represents a comprehensive, integrated collection of procedures, policies, programs, databases and report structures pertinent to the conduct of studies; the collection of short-term and long-term outcome information; the transmission of information to FDA; the storage of information in electronic databases in an accessible and analyzable format; and the analysis and use of the information to make informed regulatory decisions and to increase the understanding of researchers, subjects, and the public. Critical to development of this system is an evaluation of the specific needs of gene therapy oversight with regard to what information should be collected; how best to collect that information; and how best to store, analyze, report, and use the data. One component of the GTPTS involves information technology and the need for adequate databases. No existing database satisfies the needs of the GTPTS. The National Institutes of Health (NIH) and FDA are developing a database application, the Genetic Modification Clinical Research Information System (GeMCRIS), to facilitate the evaluation and analysis of human gene therapy clinical information. GeMCRIS will be one of the databases used in support of the GTPTS.

FDA has made substantial progress in the development of the GTPTS. To date, FDA has identified data elements regarding product, animal, toxicology, and clinical studies necessary for a patient tracking system database to support the analyses necessary to help ensure safety. We have developed an FDA standardized approach to product characterization and classification. We have initiated efforts to standardize product-testing requirements using appropriate contemporary methods. We have defined clinical outcome information pertinent to a safety assessment of gene therapy products. FDA and NIH have worked together to harmonize adverse event reporting practices. We have identified relevant long-term clinical patient follow-up data information and are developing strategies to collect, abstract, store, analyze, and report the results of these analyses. FDA has redirected educational and training resources to educate sponsors, investigators, and the public about gene therapy safety and product development advances. Abstraction into a temporary archival database of historical IND information from clinical trials has been initiated. FDA is implementing and evaluating procedures and enforcement tools to ensure compliance with data-reporting requirements. Plans are under development for periodic analyses and public discussion of gene therapy information.

This document outlines the GTPTS discussions and activities that have taken place to date including an evaluation of the relevant issues that the Center for Biologics Evaluation and Research (CBER) has identified through internal, interagency, and public discussions (e.g., discussion with the gene therapy industry, FDA advisory committees, NIH/Office of Biotechnology Activities (NIH/OBA), professional societies, and at numerous other public forums). This evaluation provides the basis for current and future development efforts described in the later sections that will help achieve the GTPTS objectives.

2. What information should be part of a patient tracking system

A fundamental step in designing and developing a GTPTS is determining what information should be collected.

2.1. Product issues

One of the objectives of the GTPTS is to support analyses of trends occurring across many types of related gene therapy product classes; therefore, it is critically important to include all of the relevant products and product information to allow meaningful analyses.

2.1.1. Determining how to characterize/classify products

Paramount to the success of the GTPTS is a standardized approach to the classification and characterization of gene therapy products. Such standardization is required if correlative analyses between adverse events occurring over time and across product classes or product component classes is desired.

Gene therapy products are complex biologics composed of multiple structural and functional components. Likely classes for analysis may be defined by the type of vector used (e.g., virus type or plasmid), product gene components (e.g. therapeutic gene, regulatory elements), mode of gene therapy product administration (e.g. ex vivo or in vivo), and the type of cellular products, if any, that are used. Any of these elements may impact the adverse event profile of a specific product, and information about each of the product components is necessary.

The vector can be of any variety of viral types or can be non-viral, such as a plasmid. The therapeutic gene or genetic material contained within the vector can be protein coding, protein non-coding, and regulatory elements. Protein coding genetic sequences would refer to any protein produced by the therapeutic gene. Non-coding genetic sequences are expressed elements that may function as a marking sequence. By themselves, non-coding genetic sequences do not convey any specific therapeutic effect. Another type of genetic element contained in a gene therapy vector is the regulatory element. Regulatory

elements are nucleic acid sequences that function to enhance or promote the expression of the therapeutic gene.

Additionally, gene therapy products can also be characterized as either “in vivo” or “ex vivo” products depending upon whether they are directly administered to the patient (in vivo) or introduced outside the patient, for example, into a cell that is then administered to the subject (ex vivo). To date, the majority of gene therapy products under development are considered *ex vivo* products. *Ex vivo* products can also be further divided into two different classes; the first originating from the subject’s own cells (autologous) and the second being derived from another donor or cell line (allogeneic). The source and testing of allogeneic cells is an important factor to be considered when tracking gene therapy products. This source of *ex vivo* gene therapy product can introduce a number of adventitious viral agents not present in the treated subject population and therefore would need to be adequately tracked in the event that subjects present with adverse events of viral nature.

The GTPTS will therefore be designed to categorize and analyze the gene therapy product in regards to vector class and genetic material, as well as the types of cells co-administered, if any. In addition, this system also will have the ability to track the mode of administration, an important factor, since direct in vivo administration of vector may lead to adverse events resulting from the systemic dissemination and expression of vector protein and/or gene insert. The patient tracking system will enable the FDA to collect and analyze information pertaining to specific gene therapy products and their components and delineate adverse events that could occur after administration of specific agent based on the vector class, therapeutic gene insert, other vector components, source of product, and mode of gene transfer.

Discussion generated during the October 2001 Biological Response Modifiers Advisory Committee (BRMAC) meeting¹ has played an important role in guiding the FDA’s decision to include product information and related data fields in the GTPTS. In order to be able to classify gene therapy products using this type of product information, it is essential that there be a standardized nomenclature for use in the GTPTS. Consequently, in collaboration with NIH/OBA, FDA has undertaken an effort to standardize the nomenclature for gene therapy products.

2.1.2. Updating critical product characterization and testing data

The technologies involved in manufacture and testing of gene therapy products are evolving rapidly, as are applicable standards. In reviewing the status of safety related testing of gene therapy products (e.g., testing for purity from

¹ The Biological Response Modifiers Advisory Committee meeting minutes are available at [http://www.fda.gov/ohrms/dockets/ac/cber01.htm#Biological Response](http://www.fda.gov/ohrms/dockets/ac/cber01.htm#Biological%20Response)

replication competent vectors) as part of efforts related to the GTPTS development, FDA found that the Agency had not reliably received updated product information for products under older INDs. If the GTPTS is to contain information about the nature and testing of the product for use in assessing product class-related adverse events, it is critically important that it contain up-to-date information about critical changes.

To address this concern and others, the Agency sent a letter on March 6, 2000 to all gene therapy sponsors asking for updated information on product testing and characterization, test methods, specifications, other products produced in the facility, and quality control procedures.² In addition to ensuring that we have up-to-date information, the goals of this request included:

- (1) To ensure that all gene therapy products currently used in clinical trials are adequately tested by relevant appropriate contemporary standards;
- (2) To determine industry testing and technology standards;
- (3) To determine where testing requirements need to be increased and/or decreased;
- (4) To ensure that updated information is sent on a yearly basis so that potential lapses in product safety testing do not occur;
- (5) To gain information concerning product characterization and manufacturing processes and arrangements in order to move these products forward toward licensure;
- (6) To gather information concerning what additional guidance should be developed;
- (7) To determine appropriate use of training resources; and,
- (8) To re-establish public confidence in the oversight of gene therapy products and clinical trials.

FDA received much helpful information in response to the March 6 letter request. The internal analyses of this information, and subsequent public review and discussions, have greatly facilitated achieving the goals listed above. FDA was able to facilitate practical scientific, medical, and ethical discussions to promote the development of improved gene therapy products. We did this by redirecting educational resources to those areas where gene therapy product manufacturing

² Dear Gene Therapy IND or Master File Sponsor Letter - 3/6/2000

and testing problems were noted and focusing FDA advisory committees to address the issues.

To date, FDA has held advisory committee meetings on sequencing, product testing of vectors made from plasmids, and replication competent adenoviral (RCA) level based on safety data and patient population. In addition, we are working with industry to develop a reference material for use in standardizing the test methods for RCA. We are also in the process of working with sponsors to standardize and improve their product testing and characterization. Keeping up-to-date information about product characterization and testing will facilitate conducting such efforts in the future.

After analyzing the data, the Agency addressed the question of what aspects of the information submitted would be appropriate for inclusion in a GTPTS to facilitate product class safety analyses. Some categories of information, e.g., testing methods and some specifications, can be very dependent upon the manufacturing process and the particular product, and thus are not particularly suitable for use in classifying products for safety analysis in the GTPTS. Other types of product information collected could help link patient adverse event with product class or characteristic, using a database appropriately constructed to allow tracking of the information and to facilitate the analyses. Furthermore, if the Agency is to periodically review the adequacy of current policies pertaining to good manufacturing practice and testing of gene therapy products, a systematic collection, storage, analysis, and interpretation of product specific information (including lot release information) is critical. Therefore, the GTPTS is being designed to capture detailed product information.

2.2. Clinical data issues

2.2.1. Types of clinical data to collect

Many types of outcome and health status data were considered for collection in the GTPTS database. Determination of which data to include requires careful consideration of several factors. The GTPTS should focus on capturing data that are important to safety assessment and that can be collected with an adequate degree of reliability and completeness. Collection of unnecessary data not only may be costly, but also can make it harder to recognize critical findings. Collection of unreliable or substantially incomplete data would impair the validity of the analyses.

The adverse events that have the most significant impact on patients meet the definition of serious adverse events (see 21CFR312.32(a)). Furthermore, serious adverse events, when unexpected and associated with use of the therapy (21CFR312.32(c)) must be reported to the FDA as soon as possible in IND safety reports (fifteen and seven day expedited reports) with detail and format suitable for a database. Consideration was given to limiting the database to such reports; however, two major drawbacks were identified. First, a limitation

to unexpected serious adverse events would necessarily exclude serious adverse events that are expected (i.e., those that have occurred previously with the gene therapy in question and are described in the investigator's brochure, see 21CFR312.32(a)). Such expected events are still critical to consider in safety assessments. Collection of such events helps determine trends and rates, and helps determine which events are more likely to be treatment related. Furthermore, non-serious adverse events, while less likely to lead to important conclusions than are serious events, often provide the background against which serious events and toxicities can be understood. For example, reports of sudden death and of syncopal (fainting) episodes can be better understood and attributed when one can also examine reports of cardiac arrhythmias resulting from the same therapy.

Data regarding adverse events that the sponsor and investigator believe have no reasonable possibility of having resulted from the therapy would not be included in the database. Most gene therapy patients have serious underlying diseases and receive a variety of therapies, drug and otherwise, in addition to the gene therapy. Each patient typically experiences many adverse events as a result of his or her disease, other therapies, and concomitant illnesses. The collection of all such events, while creating a tremendous burden on patients, sponsors, and investigators, would create a huge amount of irrelevant data potentially obscuring important information. Any reporting system depends ultimately on the appropriate judgment of expert investigators in deciding what meets standards for reporting. Of course, education and oversight efforts (Institutional Review Board (IRB), sponsor, NIH, FDA) should attempt to minimize misclassification of potentially treatment-related events. Of note, current regulations as well as internationally harmonized guidelines do not support the collection of data regarding events deemed not to have a reasonable possibility of having been associated with the treatment. For these reasons, it was decided that the GTPTS would only include adverse events associated with treatment, whether or not serious or unexpected.³

For each patient there is a vast amount of health status data that comes from medical history, physical exam, laboratory testing, medical imaging, etc. When not rising to the level of an adverse event, such data (e.g., normal laboratory findings, symptoms related to a disease not under therapy) can only be interpreted in the context of the medical evaluation of the individual patient and

³ The determination that an event is "associated with treatment" requires a relatively low level of suspicion regarding causality. If there is a reasonable possibility that the product caused or contributed to an adverse event, that event is considered to be "associated with the use of the product." If the event is also serious and unexpected, the adverse event must be reported to the FDA in either a fifteen or seven-day report.

would add little or no value to the GTPTS. This type of clinical information will not be included in the GTPTS.

Death reports typically contain important information and can be obtained reliably and will be included in the GTPTS along with other appropriate data.

Outcome information pertinent to the efficacy of the intervention is very important to the assessment of gene therapy. Efficacy related outcomes are tracked at the individual IND level. Each IND is unique and typically involves a different product, given at a different dose and regimen, with different concomitant therapies, in a different disease and/or patient population and measuring different efficacy outcome measures than other INDs. Each of these factors may profoundly impact efficacy. Broadly different gene therapy products, e.g., an adenovirus containing a gene to correct cystic fibrosis and an adenovirus containing a gene to kill cancer cells, may have related toxicities but pooling or cross study analysis of efficacy would be of limited value. The GTPTS may contain some outcome data regarding efficacy but is being designed to focus on safety outcome. The FDA will continue to rely on the studies of a particular product in a particular disease for assessments of efficacy.

2.2.2. What long-term clinical data to collect

Long-term clinical data collection is an important and relatively unique aspect of gene therapy assessment. Storage and facilitation of analysis of such data is a critical function of the gene therapy databases.

FDA did substantial background work investigating the types of long-term concerns, the classes of gene therapy products to which they apply, and the feasibility of various approaches to collecting such data. In these efforts, we gave careful consideration and deliberation not only to the safety issues that need to be addressed, but also to the practical difficulties in reliably collecting such data. As will be discussed in the subsections of section 3.1.2, these practical issues dictate that, in order to succeed, long-term data collection efforts must be focused on obtaining the most important information.

2.2.2.1. Current long-term follow-up published guidance

In current guidance documents, FDA's long-term testing and subject-monitoring recommendations focus on those subjects treated with retroviral vectors.⁴ FDA currently has published no specific recommendations for long-term follow-up of subjects treated with any other classes of gene transfer

⁴ October 18, 2000 Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors <http://www.fda.gov/cber/gdlns/retrogt1000.htm>

vector. One rationale for recommending long-term follow-up⁵ in subjects participating in gene transfer clinical trials using retroviral vectors is based on the fact that these vectors are known to integrate into the genome. The consequences of life-long exposure to the gene product or to the introduced genetic sequences can only be assessed through the long-term follow-up of these patients.

Another reason for long-term follow-up efforts in studies using retroviral vectors is that use of retroviral vectors carries the potential for exposure of patients to replication competent retroviruses (RCR). Retroviral infection, including HIV infection, in many species can result in latent infection with disease appearing years later. In 1993, a report of lymphoma in 3 out of 10 immunosuppressed non-human primates that received retrovirally transduced bone marrow cells with high titer RCR (Donahue, R. E. et al. 1992. Helper virus induced T cell lymphoma in nonhuman primates after retroviral mediated gene transfer. *J. Exp. Med.* 176:1125-1135) led to recommendations for patient testing for evidence of RCR infection in a 1993 guidance. Those recommendations have recently been refined (in the above mentioned guidance document) as follows:

...Analysis of patient samples at the following time points: pretreatment, at 3, 6, 9 months, 1 year after treatment, and yearly thereafter. If all post treatment samples for the first year are negative, remaining samples can be archived... At time of collection of yearly samples, a brief clinical history should be obtained and targeted towards determination of clinical outcome suggestive of retroviral disease, such as cancer, neurologic disorders, or hematologic disorders... If patients die or develop neoplasms during a gene therapy trial, every effort should be made to assay for RCR in a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue. At any time, additional testing and patient follow-up is required if it is clinically indicated and/or any laboratory sampling is positive for RCR.

⁵ For the purpose of this document, "long-term follow-up" (LTFU) is defined as the follow-up of study participants that occurs beyond the first year after final treatment on protocol. Clinical concerns restricted to an individualized or specific vector or study reagent and arising before, or during the first year after treatment, would be addressed in the study protocol and would not be material to any guidance on "long-term follow-up".

2.2.2.2. Impact of vector characteristics on the approaches to long term follow-up

Current medical and regulatory systems are not well designed to track individual gene therapy study subjects over long periods to identify very late treatment related toxicities (i.e., years later) and to examine causal association with the gene therapy.

Prior to consulting an advisory committee and considering new policy in this area, FDA did substantial background work investigating the types of long-term concerns, the classes of gene therapy products to which they apply, and the feasibility of various approaches to collecting such data.⁶ In these efforts, we gave careful consideration and deliberation not only to the safety issues that need to be addressed but also to the practical difficulties in reliably collecting such data (see section 3.1.2.1).

To detect latent or long-term effects, clinical follow-up for extended periods of time is important. FDA convened the BRMAC on November 16-17, 2000, April 5-6, 2001, and October 24, 2001, to discuss issues pertaining to the long-term follow-up of gene transfer study participants. Deliberations of the committee largely focused on three areas: what types of vectors raised concerns warranting long-term follow-up (briefly summarized in this section), what types of clinical information should be obtained in long-term follow-up (next section), and how such information should be obtained (section 3).

In addition to reviewing the adequacy of current recommendations for studies that use retroviral vectors, BRMAC was asked to consider the appropriate long-term follow-up in conjunction with the growing use of other non-retroviral, RNA- and DNA-based delivery mechanisms (vectors) for which there is no FDA guidance. Briefing materials for BRMAC members included information on vector design, product characterization, preclinical models, known and hypothetical risks associated with vector class and vector properties, procedures for reporting adverse events, the value of centralized database, limitations or barriers to effective data collection and reporting, and types and time courses of late adverse events associated with other types of therapies and infections.⁷

The BRMAC deliberated on the risks associated with RNA- and DNA-based vectors and the various factors that contributed to those risks. They noted

⁶ FDA scientists did extensive background work and prepared briefing materials assessing the various types of long-term toxicities potentially associated with use of various classes of gene therapy vectors, their associated risk factors, mechanisms, and time courses. Time courses for late toxicities of other modalities of therapy were also assessed as models. The briefing document is available at <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3794b1.htm>.

⁷ Briefing material for the November 16-17, 2000, April 5-6, 2001, and October 24, 2001 BRMAC meetings are found at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>

that all gene therapy vector systems carry sufficient concerns about long-term side effects to warrant some level of long-term follow-up, but certain categories of gene transfer vectors warranted more attention. BRMAC pointed out vector classes of particular concern included: 1) vectors with the potential to integrate; 2) vectors with the potential to replicate; 3) vectors with altered tropisms; and, 4) vectors with long latency. Some additional vector characteristics were thought to have significant impact on the degree of long-term risk. For example, integrating vectors have the potential to initiate neoplastic processes depending upon the site of integration or presence of strong promoter/enhancer elements present in the gene transfer vector. Host characteristics such as the immune status of recipient, the route of administration (intra-venous, intra-arterial, subcutaneous, etc.), and the type of cell targeted for transformation (ex-vivo transformation of stem cell, cells capable of division and lasting life cycle vs. irradiated cells, etc) were also discussed and felt to be influential factors.

Recognizing the large number of factors that could influence the nature and degree of long-term risks in any given study, the BRMAC was reluctant to endorse a specific global approach to long-term follow-up based on vector characteristics. Instead, BRMAC recommended that FDA scientists apply scientific principles and judgment to determining appropriate follow-up.

2.2.2.3. Type of clinical outcome on which to focus long-term follow-up

Based on practical experience and early discussions with BRMAC (see section 3.1.2.1), FDA recognized the importance of focusing long-term data collection on those areas of particular concern regarding potential toxicities.

Considering several disease models illustrating pathogenic mechanisms potentially applicable to existing and evolving gene transfer strategies, BRMAC concluded that the most significant risks associated with gene transfer studies include treatment-related cancers, hematologic, neurologic, and autoimmune disorders. In most cases, BRMAC estimated that these conditions would be expected to develop months or a few years after initial administration of gene transfer product; however, potential risks of second cancers and some other treatment-related toxicities could occur 10 years or more after initial therapy. BRMAC recommended that sponsors of gene transfer trials collect specific but very limited clinical information on all subjects for at least 15 years.⁸ FDA is considering issuing guidance to

⁸ In general BRMAC recommended that all gene therapy study sponsors have a long-term clinical monitoring protocol in effect for all new studies under IND. Long-term follow-up should focus on the collection of clinical information pertaining to de novo cancer, neurologic, autoimmune, and hematologic disorders. In addition, unexpected medical problems including information on hospitalizations and

address this issue further. As FDA reviews gene transfer INDs, we assess whether the studies adequately address LTFU, taking BRMAC's recommendations into consideration.

3. How should information be collected

One factor critical to the success of the GTPTS will be the methods for getting information to the FDA and the methods for getting information into the database. Substantial efforts have gone into addressing this issue.

3.1. Getting information from the patient to the FDA.

3.1.1. Roles of sponsor and investigator

The GTPTS would allow a comprehensive evaluation of information pertinent to the safety of recipients of gene therapy. The collection of data from gene therapy recipients and the transmission of those data to the FDA depend on all individuals or responsible organizations or institutions involved in the research subject's care.

FDA regulations require that investigators report adverse events to the sponsor but do not require investigator or patient reporting to the FDA. As described in existing FDA regulations, the sponsor of an IND is responsible for collecting and submitting relevant gene therapy information to the FDA. FDA's oversight of drug development relies upon the sponsor's role as the primary conduit of information to the FDA. FDA rarely receives information directly from patients and receives information directly from investigators only under limited circumstances (e.g., at site inspections).

3.1.2. Collection of long-term follow-up data

3.1.2.1. Assessment of current problems

As described above, published FDA recommendations have, for several years, addressed long-term follow-up for patients receiving gene therapy employing retroviral vectors. To date, sponsor-supplied data on RCR testing of subjects have been negative for evidence of RCR infection. After the first year of monitoring, some of the sponsors have expressed difficulty following the published recommendations, citing a variety of reasons.

From October through November 2000, CBER spoke by telephone with 66% of retroviral gene transfer clinical trial sponsors representing 74% of active protocols under IND. CBER confirmed that 89 percent of these sponsors'

medications should be collected. The long-term follow-up clinical information should be included in annual reports to the FDA.

INDs had an established lifelong monitoring protocol for their studies. Almost all of the sponsors, however, noted difficulty meeting all of the suggestions in the guidance document.

The following feasibility and practical issues were commonly provided as reasons for poor success in collecting long-term safety data:

1. Study participants can move away and be lost to follow-up, or they may simply refuse to return for follow-up testing or refuse testing of their progeny.
2. Tracking study participants is resource intensive and small companies, academic institutions, or sponsor/investigators may not have available resources or the necessary infrastructure to complete long-term follow-up. Clinical research at academic centers is frequently funded by grants whose funding period is commonly limited to 5 years or less. Thus clinical research may be funded without funding for associated long-term follow-up. Cost estimates to complete long-term follow-up ranged from \$1,500 to \$5,000 per patient per year.
3. Companies that funded the initial studies may go out of business or academic sponsor/investigators may move on to another institution or career, without contingency plans for who is responsible for continuing long-term follow-up.
4. Clinical follow-up by the investigating physician is not always practical. For instance, almost all sponsors reported that they were unable to obtain autopsies because most subjects do not die at the research centers under the care of the investigator. Rather, they die at home or under the care of a hospice service or under the care of a treating physician. When the patient dies or is near death, it is unusual that the sponsor or investigator will be notified in time, and often, an opportunity to request an autopsy is lost.
5. The value of long-term follow-up is not always obvious to investigators and once a patient has completed the central part of the study, there is often little motivation for the investigator to keep track of each subject.

Sponsors also may lose interest in long-term follow-up once the central part of a study is completed, particularly if the product is no longer under development. This issue was highlighted, when in response to the March 6, letter to all gene therapy sponsors, in which FDA asked for information about trial monitoring and oversight of the clinical investigations, some sponsors who had completed all studies asked to withdraw their INDs without volunteering any approach regarding collection of long-term data.

3.1.2.2. Questionnaire development

On November 11, 2000 and April 6, 2001, BRMAC discussed practical means to obtain long-term clinical information from gene transfer study subjects. The discussions were focused on existing models and organizations with successful histories for doing long-term follow-up studies. The United Network for Organ Sharing (UNOS) and International Bone Marrow Transplant Registry (IBMTR) databases were discussed as examples of successful models for long-term follow-up of subjects.

On April 6, 2001, representatives from UNOS summarized their experience collecting and analyzing information from their database and provided valuable insights used as a basis for discussing instruments to obtain gene therapy registration and long-term follow-up clinical information. UNOS maintains the entire U.S. list of patients waiting for organ transplant (over 67,000 people), matches every donor organ to every transplant recipient, and maintains data on every organ donor and transplant event (over 340,000) since 1986.

The Scientific Registry portion of the UNOS database stores post-transplant information pertaining to organ recipients. Data are collected on organ-specific Transplant Recipient Registration Forms and Transplant Recipient Follow-Up Forms. After a transplant has been performed and the feedback process is complete, the organ-specific Transplant Recipient Registration Form and hospital discharge Transplant Recipient Follow-Up Forms are generated. Additional follow-up data are collected at six months and 1 year post-transplant and annually thereafter. Based on review of the UNOS and IBMTR experiences and the expertise of BRMAC members and consultants, BRMAC emphasized the need for a simple instrument (e.g., a single-page questionnaire) to obtain relevant long-term follow up information. They advised that attempting to get more detailed information through extensive questionnaires was likely to substantially diminish compliance and thereby diminish the utility of the data obtained.

Additionally, BRMAC noted that some gene therapy recipients might be more difficult to follow long-term than are transplant recipients, many of whom remain under lifelong care by transplant specialists. The committee recommended that long-term follow-up efforts focus largely on information that might be obtained by mail or telephone rather than on information requiring long-term visits to the investigating physician.

BRMAC advised that a questionnaire should provide information on development of de novo solid tumors or lymphoproliferative disorders, hematologic disorders, neurologic disorders, and autoimmune disease. The committee agreed that as with other clinical data, long-term information collection would be the responsibility of the study sponsor but could be done by investigators. The study sponsor would transmit the information obtained

in the questionnaire for all study subjects to the FDA in the form of annual reports.

3.1.3. Assessing compliance with FDA GT safety data reporting requirements

Critical to the success of the GTPTS is ensuring that the appropriate information is indeed reported to the FDA. Over the past few years, FDA learned of inadequate safety data reporting to the Agency in a small number of well-publicized gene therapy trials. Concerns arose that, due to some factors common in gene therapy research (e.g., sponsors and investigators inexperienced in drug development), reporting problems might be more likely in gene therapy research. Assessment of the adequacy of IND safety reporting by gene therapy sponsors to the FDA was a critical step in determining what actions to take to improve compliance and thereby, not only to improve oversight and safety directly, but also to allow creation of a useful GTPTS.

CBER assessed the extent of problems and compliance with safety reporting at sites where “for-cause” inspections have been conducted. CBER also conducted surveillance inspections to evaluate the extent of the problems with safety reporting and compliance with requirements. These requirements are sometimes referred to as Good Clinical Practice (GCP).⁹ The results of these inspections are briefly summarized below.

3.1.3.1. For-cause inspections

FDA field office investigators, in conjunction with medical and clinical toxicology reviewers and compliance officers from CBER, conducted directed inspections at two clinical sites: The Institute for Human Gene Therapy (IHGT) in Philadelphia and St. Elizabeth’s Medical Center in Boston. Specific problems were observed and Warning Letters issued. FDA placed the INDs on clinical hold until the sponsors could assure the Agency they had appropriate procedures in place, including assurance of appropriate safety data reporting. Problems with patient safety reporting were observed at both sites, and at IHGT lack of compliance with reporting requirements for animal safety data were also noted.

⁹Good Clinical Practice (GCP) is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. Following GCP assures that the data and reported results are credible and accurate and that the rights, safety, and well being of trial subjects are protected. Responsibilities of sponsors and investigators are outlined in 21 CFR 312 subpart D (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html) and further delineated in the International Conference on Harmonisation (ICH) E6 consolidated guideline on Good Clinical Practice (<http://www.ich.org/ich5e.html#GCP>). FDA has established a focal point within the agency for Good Clinical Practice issues arising in human research trials regulated by FDA. An FDA website was established and is found at <http://www.fda.gov/oc/gcp/default.htm>

3.1.3.2. Surveillance Inspections

As noted, FDA also initiated surveillance inspections of randomly selected gene therapy clinical sites. The purpose of these inspections was to assess whether the types of problems observed in the for-cause inspections were widespread throughout gene therapy research. In addition, a program of random inspections would help ensure that all gene therapy investigators and sponsors paid careful attention to GCP and incorporated GCP into their studies.

Specific questions regarding the product background information and the clinical study were developed by the inspection team, and focused on the conduct of the protocol; the reporting of adverse events; blinding of study medication where applicable; and whether the clinical endpoints were met. FDA's field investigators conducted a series of gene therapy surveillance inspections for CBER between April and August 2000.

In general, these inspections found that most sponsors, both commercial and academic, as well as clinical investigators, were in substantial compliance with the regulations. The inspectional findings were typical of those observed for clinical trials submitted to support new drug and biologic approvals.

Of the seventy sites inspected, eleven had no current, active clinical trials or had never initiated their proposed studies. Of the remaining 59 sites, twenty-three (39%) required no further action from FDA. Thirty-six sites (61%) had deviations identified by the inspection team; however, in thirty-three cases (56%), the nature and extent of these deficiencies were deemed to be relatively minor. No official regulatory action was indicated and only voluntary action to correct the deficiencies was called for. Three sites (5%) were identified where official regulatory action (*i.e.*, a warning letter) was required. Common deficiencies included: 1) failure to follow the protocol; 2) an inadequate consent form; 3) lack of supporting data for case report form entries and/or discrepancies between the source documents and the case report forms; 4) inadequate drug accountability records; and, 5) the failure to notify the IRB(s) of protocol changes, adverse events, or deaths.

Thus, about 40% of the inspections were classified as "no action indicated," slightly over half as "voluntary action indicated," and 5% as "official action indicated." This outcome distribution is quite similar to that observed in FDA inspections of other types of clinical trials, typically those trials from which data are submitted to support new drug and biologic approvals.

Inadequate reporting of adverse events to the FDA was not a prominent finding of these inspections. Reliability of adverse event reporting was found sufficient to support development of a useful GTPTS. The FDA continues to perform inspections of clinical, preclinical, and/or manufacturing sites involved in gene transfer research on a "for cause" basis as well as routine basis, as

part of our role in protecting the safety of patients enrolled in these trials and helping ensure the quality of the data received therefrom. Substantial efforts are taking place to improve GCP in gene therapy research in particular (see section 3.1.4) and in clinical research in general.

3.1.4. Monitoring programs and GCP

3.1.4.1. Review of monitoring plans

In addition to requests for information on manufacturing practices (see section 2.1.2), the March 6 letter also asked sponsors to provide a summary of the monitoring program for each clinical study conducted under their IND and documentation of their oversight function. Monitoring is a tool used by sponsors to ensure investigators are conducting the study appropriately and are reporting information accurately and completely. FDA regulations require that sponsors monitor clinical trials to ensure they are conducted in a manner that protects the rights and welfare of subjects and ensures quality of the data.

As hoped, in response to FDA's request to review monitoring plans, many sponsors developed more extensive and better-documented plans for monitoring. FDA review of the descriptions of the clinical monitoring programs found that the monitoring programs in general incorporated many of the activities and procedures in accordance with the International Conference on Harmonization (ICH) GCP guidance and the requirements listed 21 CFR 312 Subpart D. However some areas of deficiencies were noted, including but not limited to lack of procedures to ensure reporting of protocol modifications to FDA and to ensure safety reports are filed to the IND in a timely fashion. FDA worked with sponsors to address those deficiencies thereby improving protection of human subjects and ensuring a higher quality of data reporting to support the GTPTS.

3.1.4.2. Other efforts

To improve compliance, CBER is routinely involved in educational and training activities aimed at sponsors and investigators who are involved in gene transfer research. However, following the death of a patient in the ornithine transcarbamylase (OTC) deficiency study, the Agency recognized a need for additional efforts to inform potential sponsors of not only the issues specific to the conduct of gene transfer studies, but also on the issues involved in the design of a clinical program and the elements of GCP. Education sessions have taken place at various venues, including the Drug Information Association (DIA) annual meetings and a special satellite broadcast co-sponsored by DIA and the FDA, the annual meetings of the Society of Toxicology, the American College of Toxicology, the International Society for Genetic Anticancer Agents, meetings of the Pharmaceutical Research and Manufacturer's Association, meetings of the RAC, the annual

American Society of Gene Therapy meetings (ASGT), and the FDA advisory committee meetings (e.g., BRMAC).

In the March 6, letter to all gene therapy sponsors, FDA reminded sponsors of their obligation to submit as expedited safety reports certain findings in laboratory animals. Sponsors specifically were asked either to verify that such animal data, if relevant, had already been submitted as required under regulation, or, to promptly submit the data to the IND or master file. In general, most sponsors indicated they were already in compliance with reporting requirements for such data.

3.1.5. Reporting of findings of Data Monitoring Committees

The safety and efficacy of experimental therapies is most commonly and powerfully demonstrated in blinded, randomized clinical trials. Such trials are expected to be an important source of safety information regarding gene therapy and the timely reporting of such data will be important to the success of the GTPTS.

Real time assessment of some adverse events in blinded trials can be hampered by the fact that the sponsor and investigators are blinded to what treatment is received. Data Monitoring Committees (DMCs), committees of experts not otherwise involved in the trial, are often used, among other things, to examine the unblinded data during a trial and determine whether there are safety concerns that should be brought to light and acted on.

FDA has recognized and addressed a need to provide guidance to promote optimal usage of such DMCs. FDA has developed draft guidance in consultation with other experts and has published it for public comment.¹⁰ Of particular relevance to the issue of timely data collection for a GTPTS, this guidance addresses the sponsors' responsibilities, under current regulations, for notifying FDA of safety concerns identified and reported by the DMC to the sponsor.

3.1.6. Standards for IND and post marketing reports for GTPTS data entry

Collection of safety data should occur for as long as deemed important for patient safety both pre and post licensure. The collection and reporting of safety data are critical elements of ensuring that a study or licensed product poses no significant and unreasonable risk. Therefore, the GTPTS will contain specific information collected periodically. FDA intends to work toward a standardized format for data entry.

¹⁰ Draft Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees - 11/15/2001 - <http://www.fda.gov/cber/gdlns/clindatmon.htm>

Currently, there is considerable lack of specificity regarding the format for reporting safety and trial specific information. For example, we have observed that annual report information and some other critical information come in a broad variety of formats and may not contain the appropriate information for database entry and analysis. This lack of standardization significantly complicated FDA's recent effort to analyze historical safety information across clinical trials involving adenoviral vectors. Consequently, the FDA is currently reviewing existing reporting requirements and intends to provide necessary guidance on submissions for the GTPTS to facilitate the submission of information in a format suitable for analysis. This effort will seek to standardize reporting formats for both IND and post marketing data including but not limited to (1) clinical trial protocol(s) information updates including changes to procedures for clinical trial monitoring; (2) product manufacturing information updates; (3) product lot release and testing information; (4) preclinical, animal and toxicology study results; (5) clinical trial(s) accrual summary updates; (6) product safety and efficacy updates; (7) per-patient adverse event reporting; (8) per-patient long-term clinical follow-up updates; (9) relevant per-patient laboratory study results; and, (10) per patient disposition information including post-mortem examination reports.

Although no gene therapy product is currently approved for marketing, it is anticipated that some will be during the lifetime of a GTPTS. When appropriate, FDA will consider the collection and reporting of safety data after approval to ensure patient safety.

3.2. Getting information from the FDA IND submissions into the tracking system

3.2.1. Extracting old data – needs assessments and contracts

CBER has already obtained substantial information in over 300-gene therapy INDs over the past 10 years. Of these 300 INDs, 188 are currently active. FDA recognizes the importance of reviewing the information from these INDs and entering it into the new database able to support comprehensive safety analyses across multiple INDs for related gene therapies. This process is particularly intensive in that the information in IND files that predates existence of the GTPTS generally lacks the format and details important to facilitate GTPTS entry and analysis.

3.2.2. Entering new data

With the implementation of the GTPTS, there will be a substantial increase in the information in an IND that is entered into an FDA database. Furthermore, new recommended content and formats for submitting expedited adverse event and annual reports (see section 3.1.6) will likely result in more complete reporting to FDA of gene therapy product and patient specific information, adverse event information, and more complete long-term clinical follow-up of subjects.

4. Data storage/ analysis system

4.1. Biologics Investigational New Drug Application Management System (BIMS) enhancements

The BIMS is a CBER database system to manage investigational new drug applications (INDs). Enhancements to CBER's current data storage system, the BIMS, that have been implemented over the last two years allow for repository of additional data elements and for improved search capabilities. FDA expects that the GTPTS will greatly expand existing capabilities and include an interface with BIMS.

- Previously, our ability to track expedited reports was limited to a tabular listing of all IND amendments coded as 15-day reports, without an ability to differentiate the nature of the event, nor an ability to differentiate between an amendment that was a follow up to a prior 15-day report from a new 15-day report. Enhancements of adverse event data fields can now differentiate deaths from all other serious adverse events, and follow up reports from initial reports.
- A clinical trials module designed to capture detailed trial information such as protocol title, eligibility criteria, indication, study phase, subject gender, age, race, and other information, is currently under development, but not yet operational. This module will supplement the current system with the addition of a screen to capture more detailed information regarding each clinical trial protocol. Once established, FDA will be able to perform specific searches by title and other study attributes, thereby enabling the Agency to perform more efficient safety analyses.
- An investigator/site module is also under development. This module is intended to capture details on all investigators and sites associated with the IND, and to link them to specific amendments and protocols. To facilitate data entry, the module is being designed in the same format as the FDA Form 1572. This module will contain basic search capabilities and complement the clinical trials module described above.

4.2. Assessment of other systems

During FY 2000, the Agency considered various existing computer system options for establishing the gene therapy patient tracking database and integrating the database into the adverse event reporting system. Because any new system development is resource intensive in both time and money, it was important for FDA to first examine the capabilities of existing related systems to determine whether they already met the needs for the gene therapy patient tracking database or if they could feasibly be modified. This has been accomplished. The systems considered were the CBER's BIMS, FDA's post-approval Adverse Event Reporting System (AERS), the National Xenotransplantation Database (NXD), and the National Cancer Institute's Adverse Event Expedited Reporting System (AdEERS).

4.2.1. BIMS

The BIMS system only contains premarket information. The BIMS tracks applications, but not the human subjects involved in the clinical trials. The BIMS is capable of linking adverse event reports and clinical protocol amendments. One potential advantage of using the BIMS as a gene therapy database is that it could be handled within CBER and there would not be a need to forward information for coding and data entry into the gene therapy database. The main disadvantage of utilizing the BIMS is that BIMS was not designed for systematic coding of adverse event information in a standardized format. BIMS was not designed to capture specific details of adverse events but only to identify those submissions, which contained adverse event information. Using the system would require additional permanent, highly trained, technical personnel to enter data using standardized codes and also the purchase of Medical Dictionary of Drug Regulatory Affairs (MedDRA) autocoding software with regular updates. The BIMS will undergo a major upgrade, which could disrupt or be disrupted by modifications to accommodate the gene therapy patient tracking requirements.

4.2.2. AERS

The AERS is primarily a system to collect adverse event reports on products after approval. The AERS has an infrastructure for coding adverse events in a standardized format. The FDA MedWatch Form is used for reporting adverse events to AERS and is designed to collect patient information such as patient identifier, age, gender, dose, route of administration, date(s) of administration, adverse event description and outcome. The system is not designed to collect long term patient information on a per-study and per-IND basis. The AERS was not designed to integrate with BIMS, CBER's IND submission tracking system. AERS captures information from many sources (i.e., patients, physicians, manufacturers) whereas the information contained in an IND must come from the IND sponsor. Use of AERS as the primary GTPTS database element would require that expedited safety reports which are submitted to the IND be forwarded by CBER staff to the AERS for data entry and coding and that the encoded data be maintained in a separate (premarket) database from the AERS information. Logistically, this would create the potential for delays in data entry and loss of data accuracy through additional processing.

4.2.3. NXD

The NXD, originally based on the design of the Gene Therapy Information Network (GTIN), was developed to track adverse events relating to infectious complications occurring during INDs using xenotransplantation products. The system is designed to integrate with CBER's current premarket database, BIMS. The NXD uses MedDRA codes for adverse events and will utilize an auto-coding system with the capability for automated updates as MedDRA is upgraded. The NXD is currently designed for a different, complicated product class. Unlike gene therapy, safety concerns in xenotransplantation are primarily focused on transmission of infectious diseases. Additionally, the database focuses on

supporting the ability to analyze events in donor animals and to connect events in humans with donor animals. Also, the number of current and projected gene therapy applications is vastly larger than those for xenotransplantation. Thus, while some lessons learned in its development are relevant, the NXD does not provide an optimal base upon which to build a gene therapy database.

4.2.4. AdEERS

The NCI's AdEERS is already developed and is presently in the field-testing phase for phase 1 clinical trials conducted by investigators under NCI funded projects. The AdEERS was fully implemented as the premarket adverse event reporting system for all NCI cooperative group studies during January 2001. The AdEERS is an Oracle-based format, Internet accessible by investigators conducting clinical oncology trials, and investigators can submit data electronically directly. Like AERS, the AdEERS does not gather information about patients until an adverse event has occurred.

4.3. General architecture/ work with NIH

FDA and NIH/OBA have information needs related to gene therapy clinical protocols, with each agency having overlapping, but distinct uses for the information. FDA and NIH have devised a strategy to pool efforts on database development where feasible, and to maintain a core set of data that would address both FDA and NIH needs. FDA and NIH have determined through working groups a core set of data information fields that contain common information basic to the needs of each agency. This includes basic administrative information on the clinical protocol, adverse event data and product information.

FDA and NIH decided to use the AdEERS as one of the models for the gene therapy database. However, to be effective the AdEERS-model must be modified to satisfy the needs of both agencies. By using gene therapy databases based on AdEERS, FDA and NIH will efficiently and effectively coordinate their reporting requirements. The agencies will work together to develop and disseminate guidance to sponsors and investigators concerning information requirements, standardized and control vocabulary terms, and format. The FDA will develop additional modules to accommodate long-term patient tracking capability and inclusion of additional gene therapy-related products that are not tracked by NIH.

As noted, FDA and NIH have already agreed on a core set of data fields. There are a number of technical and logistical issues that are being addressed in a systematic fashion. Such issues include determining the basic platform for the database and the medical dictionary for encoding adverse events.

4.3.1. Harmonizing FDA and NIH on AE reporting requirements

NIH has had differing adverse event reporting requirements for gene therapy investigators from FDA. Over the past two years, FDA, NIH, and the RAC have worked to harmonize requirements as described below.

IND sponsors are required by federal regulations to report safety information to FDA and all principal investigators who receive NIH funding for recombinant DNA research or who conduct such research at institutions that receive federal funding are required to report safety information to NIH.¹¹ The types of safety data that previously rose to the level of an expedited report to NIH were adverse events that were 1) serious, regardless of whether expected or unexpected, and 2) adverse events that were unexpected, regardless of whether serious or not. Differences between FDA and NIH standards for expedited reporting resulted in dissimilar databases, time-consuming efforts to reconcile the differences, and some confusion amongst sponsors and investigators. After input from an outside body convened to address this issue among other areas of concern in gene therapy trials, public discussions at the NIH RAC, and input from organizations such as ASGT, NIH is taking action to enable sponsors to submit the same data to both agencies, in the same format at the same time.¹²

While the IND sponsor is the individual or organization responsible for providing information to FDA, including safety data, it is the principal investigator who is responsible for communicating with NIH/OBA. In cases where the sponsor is also the investigator (termed the sponsor/Investigator), the lines of communication to FDA and to NIH/OBA will be the same. Recognizing the potential for differential interpretation of and categorization of safety information as well as the timing of reporting to FDA and the NIH when the sponsor and the investigator are distinct entities, FDA and NIH are continuing to work together to minimize this problem.

4.4. Specific field content

4.4.1. Designing product fields (see also 2.2.1)

A multi-tiered system for data storage and analysis will define a given gene therapy product and the major components that are an integral part of the product. The first tier describes vector type. All gene therapy products contain

¹¹ Appendix M in the NIH Guidelines: Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>

¹² Federal Register: November 19, 2001 (Volume 66, Number 223): Office of Biotechnology Activities; Recombinant DNA Research: Notice of actions under the NIH Guidelines for research involving recombinant DNA molecules (NIH Guidelines) and request for comment on the information collection provisions under the Paperwork Reduction Act of 1995.

genes and genetic elements, which have a defined biological function. The data fields describing the gene or genetic material contained in a specific vector are further broken down into protein coding, non-protein coding, and regulatory elements. As stated above, a protein coding sequence represents the protein expressed by the therapeutic gene, whereas the non-coding sequences and regulatory elements represent either sequences used as marking genes to follow the presence of the gene therapy product or nucleic acid sequences that are not expressed, but in some manner effect the expression of the therapeutic gene.

The next level or field in the database describes the cell system used to produce the vector. This data field would include packaging cell lines or transient production cell lines. These cell lines provide proteins necessary for the vector to infect the host cell. Since the majority of viral vectors used in gene therapy clinical trials are defective, meaning they cannot infect a cell by themselves, these producer cell lines provide the proteins necessary for one cycle of viral replication. The last field in the current database defines how the vector is administered to the subject. Vectors are administered one of two ways, either directly to the subject or first introduced into a cell outside of the body and then administered to the subject. The first scenario would be classified as an “*in vivo*” product and the latter as an “*ex vivo*” gene therapy product. The “*ex vivo*” field is further delineated into autologous, meaning patient derived, or allogeneic, which can be from another donor or from a cell line.

4.4.2. Designing clinical fields

There were multiple meetings held with the OBA contractor, representatives of FDA and NCI. These meetings resulted in the development of agreed upon fields of clinical information for use by the FDA and NIH.

5. GTPTS - data analysis, reports, utilization

The GTPTS will provide the necessary database infrastructure and ad hoc reporting and query tools to longitudinally track all gene transfer study participants within each trial of all INDs. Such information is critical to performing relevant safety analyses and epidemiologic studies to detect rare or delayed adverse events related to the investigational therapy. In addition, because the GTPTS will integrate several regulatory database modules, the tracking system will also serve to enhance available databases to help with FDA’s regulatory functions. As such, the extent of information that will be required is significantly different from what the Agency is accustomed to receive. Reporting format in both annual and expedited reports will need to be standardized according to the GTPTS and GeMCRIS databases requirements and specific data elements.

5.1. Periodic reports

As our understanding of human gene therapy progresses, FDA will use the GTPTS to help support the best scientific, clinical, and regulatory decisions possible. FDA intends to use the GTPTS on a continuing basis to inform its review and decision making process. In addition, FDA will utilize the GTPTS in preparation of periodic gene therapy safety reports intended both to disseminate information and to advance scientific understanding. As development of the new gene therapy database proceeds, while awaiting functionality of the system, in a near-term transitional project, FDA will utilize a temporary Access database in conjunction with other existing FDA databases to facilitate its ongoing analyses of data relevant to gene therapy. Full implementation of the GTPTS will enable more informative analyses.

5.1.1. Reports planning

Data analysis will initially concentrate on the assessment of acute toxicity, while subsequent efforts will focus on long-term safety concerns and, possibly, efficacy analyses.

A short-term project to develop a database with the capability to conduct analyses of serious and non-serious adverse events in expedited safety reports (deaths and serious adverse events), annual reports and safety updates is under development. Using this database, analyses will be conducted within an individual or limited number of selected INDs to assess product-specific toxicities. Analyses may also be conducted across the entire database or a major subset to assess adverse event trends, for example in major product classes or among patients with specific underlying diseases. Trend analyses may be further assessed by evaluation of dose, route of administration, and severity, and type of event. The system will be capable of providing output for individual adverse events in which all the data contained in the database for that event are displayed.

1. Report of adverse events across database according to product

- Adverse events by product class (vector type)
 - Reports refined by functional gene insert, regulatory promoter, direct product administration vs. ex vivo transduction of cells, and lot number
- Adverse events by product class & dose/schedule
 - Reports refined by dose, route of administration, site of administration

2. Reports of specific types of adverse events

- Adverse events according to high-level categories (e.g., neurologic disorder)
 - Reports refined by product class, dose, route of administration, underlying disease, co-morbid disease, concomitant medications, and/or severity (expedited vs. other)
- Adverse events by preferred terms
 - Reports refined by product class, dose, route of administration, underlying disease, co-morbid disease, concomitant medications, and/or severity (expedited vs. other)
- Serious adverse events by outcome (death, hospitalization/extension of hospitalization, congenital anomaly)
 - Reports refined by product class, underlying disease, co-morbid disease, concomitant medications

3. Reports of all adverse events within individual INDs

- Summary listing of all AEs within an individual IND or multiple INDs for the same product
 - Reports refined by protocol, dose, co-morbid disease, concomitant medications, and/or severity (expedited vs. other)

Long-range plans are that the database will capture additional elements to permit for assessment of adverse events in progeny, delayed onset adverse events, infectious complications, immunologic response to and to allow for analyses of persistence and biodistribution of integrating vectors. Functional capability of the tracking system could include:

- Analyses of long-term safety or delayed safety data, e.g., malignancy/second malignancy, incidence and types of birth defects in progeny
- Assessment for incidence of treatment-related infectious complications, e.g., reactivation of latent virus
- Analyses of the type of immunologic response to vectors and the impact of anti-vector immune response on safety, vector persistence, and efficacy
- Analyses of activity or efficacy across clinical trials as a means of evaluating potential for benefit in a broader dataset.

5.1.2. Gene Transfer Safety Assessment Board (GTSAB) planning with NIH

CBER and NIH/OBA staffs have begun developing procedures for quarterly assessments of a common safety database to develop reports to provide to GTSAB and for public presentations to RAC.

FDA will use the GTPTS to make the best scientific, clinical, and regulatory decisions possible and to foster public discussion to identify and appropriately address specific scientific, clinical, and ethical concerns. To accomplish these goals, FDA and the NIH/OBA have established a working group, the GTSAB, within the auspices of the NIH RAC. Periodically, GTSAB will review the analysis of safety information in gene transfer research studies, including those of the GTPTS. The GTSAB's specific functions are to involve: (1) reviewing in closed session relevant safety information and analyses; (2) identifying significant trends or single events; (3) reporting aggregated data and assessment to the RAC; and, (4) facilitating the dissemination of safety information among gene therapy investigators and participants. This Board is expected to enhance overview of gene therapy safety and improve public understanding and awareness of the safety of human gene transfer research studies as well as inform the decision making of potential trial participants. NIH proposed the establishment of the GTSAB in a December 12, 2000 *Federal Register* notice¹³.

¹³ Federal Register: December 12, 2000: Volume 65, Number 239, pages 77655-77659. Office of Biotechnology Activities; Recombinant DNA Research notice of proposed actions under the NIH Guidelines for research involving recombinant DNA molecules

Appendix – Relevant Publications

Federal Register:

1. Office of Biotechnology Activities; Recombinant DNA Research: Notice of actions under the NIH Guidelines for research involving recombinant DNA molecules (NIH Guidelines) and request for comment on the information collection provisions under the Paperwork Reduction Act of 1995 – **11/19/01**
2. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule - **1/19/2001**
3. Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation; Proposed Rule - **1/18/2001**
4. Office of Biotechnology Activities; Recombinant DNA Research notice of proposed actions under the NIH Guidelines for research involving recombinant DNA molecules; Proposed Rule – **12/12/00**
5. Expedited Safety Reporting Requirements for Human Drug and Biological Products; Final Rule - **10/7/97**

Guidance:

1. Draft Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees - **11/15/2001**
2. Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Postmarketing Expedited Safety Reports - **5/3/2001**
3. Draft Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans - **2/7/2001** FEDERAL REGISTER Notice of Availability - **2/7/2001**
4. Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors - **10/18/2000**
5. Draft Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors - **11/3/1999**
6. Draft Supplemental Guidance Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products - **11/1999**

7. Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors - **10/1999**
8. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy - **3/30/1998**
9. Draft Points to Consider in Human Somatic Cell Therapy and Gene Therapy - **8/27/1991**

Letters to Industry/Healthcare Professionals :

1. New Initiatives to Protect Participants in Gene Trials - **3/7/2000**
2. Dear Gene Therapy IND or Master File Sponsor Letter - **3/6/2000**
3. Disclosure of Information - OTC Gene Therapy - **12/1/99**
4. Dear Gene Therapy IND Sponsor / Principal Investigator Letter - **11/5/1999**
5. Letter to Sponsors of an IND Using a Retroviral Vector - **9/20/1993**

ICH:

1. ICH E6 consolidated guideline on Good Clinical Practice – **5/9/97**
2. M4S: The Common Technical Document - Safety
3. ICH Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin - **9/24/1998**
4. ICH Draft Guideline on Data Elements for Transmission of Individual Case Safety Reports; Notice - **10/1/1996**

NIH Guidelines:

1. Guidelines For Research Involving Recombinant DNA

Advisory Committee Transcripts:

1. FDA Advisory Committees Dockets (Meeting Transcripts, Minutes, Other Documents by Center)