whether the trial may proceed or should be placed on clinical hold. Document all information obtained from the sponsor through telephone conversations or faxes. Note this documentation in the Recommendation Section of the Product Review Template, throughout the review document, or as an attachment to the review, as appropriate. Upon completion, sign and date the review and then obtain concurrence from your supervisor.

XI. COMMENTS TO SPONSOR GENERATED BY FDA REVIEWERS

Note to FDA Reviewers: Draft letter comments on unresolved issues as discussed below. Refer to SOPP 8201, "Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications" (Ref. 25), for additional information. After you have obtained supervisory concurrence on your review, forward your comments to the RPM for inclusion in a letter to the sponsor.

A. Clinical Hold

Clinical hold comments are comments that the sponsor must satisfactorily address prior to allowing clinical studies to proceed after FDA has imposed a clinical hold. These comments must meet the criteria listed in 21 CFR 312.42(b).

B. Non-Clinical Hold

Non-clinical hold comments are comments that the sponsor should address as product development progresses. In some cases, a sponsor may need to address specific manufacturing issues by a certain point in clinical development, such as prior to initiation of Phase 3 studies.

XII. REFERENCES

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14. ICH Topic Q3. Impurities.
Guidance for Industry: Q3A Impurities in New Drug Substances, February 2003, http://www.fda.gov/cber/gdlns/ichq3a.pdf.
Guidance for Industry: Q3B(R2) Impurities in New Drug Products, July 2006, http://www.fda.gov/cber/gdlns/ichq3br.pdf.
Guidance for Industry: Q3C Impurities: Residual Solvents, December 1997, http://www.fda.gov/cber/gdlns/q3cresolvent.pdf.

15. Guideline on Validation of the Limulus Amebocyte Lysate test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices, 1987, http://www.fda.gov/cber/gdlns/lal.pdf.

16. Revisions to the General Safety Requirements for Biological Products, 68 FR 10157, March 4, 2003.

17. Guideline for Industry: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, July 1996 (ICH Q5C), http://www.fda.gov/cder/guidance/ichq5c.pdf.

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APPENDIX A – PRODUCT REVIEW TEMPLATE (GENE THERAPY)

PRODUCT REVIEW (GENE CELL)
Supervisor Concurrence/Date

IND:	XXXX	Sponsor's Submission Date:	Month DD, YYYY
		30 Day Review Due Date:	Month DD, YYYY
		STATUS:	Pending

DATE: Month DD, YYYY

REVIEWER: Your Name
Your Title, OCTGT/DCGT/Your Branch

THROUGH: Branch Chief Name
Branch Chief, OCTGT/DCGT/Branch

SPONSOR: Name:
Address:
Title:
Phone:
Fax:

SPONSOR POINT OF CONTACT:
Name:
Address:
Title:
Phone:
Fax:

TITLE OF IND:

PROPOSED USE:

REVIEW TEAM: Clinical:
Pharm-Tox:
RPM:
Consults:

PRODUCT DESCRIPTION:

PHASE OF STUDY:

CROSS-REFERENCED INDS, IDES, MFS:

KEY WORDS:

INTRODUCTION / RATIONALE:

STUDY OBJECTIVES:

PRODUCT MANUFACTURING AND CHARACTERIZATION:

Product Manufacturing - Components

Cells

Allogeneic or Autologous Cell Components

Cell Source:

Method of Collection:

Donor Screening:
Description

Tabulation of Testing

Cell Bank System - If Applicable

Master Cell Bank (MCB)
Description

Tabulation of Testing

Working Cell Bank (WCB)
Description

Tabulation of Testing

Reagents

Tabulation of Reagents Used in Manufacture

Reagent/Excipient	Concentration at use	Source	Grade	Vendor	COA

Qualification Program

Determination of Removal of Reagents from Final Product

Combination Products - If Applicable

Drug or Device Components - If Applicable

Consult Review Issues:

Areas of Concern for Components:

Product Manufacturing - Procedures

Preparation of Autologous or Allogeneic Cells

Method of Cell Collection/Processing/Culture Conditions

Irradiation - If Applicable

Process Timing & Intermediate Storage

Final Harvest

Timing/Methods/Wash Procedure

Final Formulation

Formulation/Infusion Buffer

Excipients

Cell Density/Concentration in the Final Product
Storage Method Prior to Use

Areas of Concern for Manufacturing

PRODUCT TESTING

In-Process Testing and Criteria

Tabulation of Tests, Manufacturing Step, Test Methods, Criteria, and Test Sensitivity & Specificity

Test	Manufacturing Step Where Performed	Method	Criteria	Sensitivity	Specificity
Sterility					
Mycoplasma					
Purity (endotoxin)					
Purity (other contaminants)					
Identity					
Potency					
Others (cell dose)					
Others (cell viability)					

Description of Test Methods

FINAL PRODUCT RELEASE CRITERIA/SPECIFICATIONS

Tabulation of Final Product Release Criteria Tests, Test Methods, Criteria, Test Sensitivity & Specificity

Test	Method	Criteria	Sensitivity	Specificity	Results Available Prior to Release

Description of Test Methods

PRODUCT STABILITY

In-Process Stability Testing

Cryopreserved Cells

Other Intermediate Holding Steps

Final Product Stability Testing

Product Formulation to Patient Infusion

Shipping Conditions

OTHER ISSUES

Product Tracking

Labeling and Containers
In-Process Labeling

Final Product Labeling

Container Closure & Integrity

Environmental Impact

Validation and Qualification of the Manufacturing Process

QA/QC Program

Manufacturing Process Validation

Biostatistics

PRECLINICAL STUDIES

CLINICAL STUDIES

Protocol Title

Subject Population

Route of Administration

Dose

Frequency

Genetic, Biochemical, and Immunological Testing

Informed Consent

RECOMMENDATION

COMMENTS TO SPONSOR

Clinical Hold
Non-Clinical Hold

Signature Date:_____
Reviewer Name

APPENDIX B – CONSIDERATIONS FOR DEVELOPMENT OF FINAL PRODUCT RELEASE CRITERIA SPECIFICATIONS AND STABILITY PROTOCOLS

Specifications are the quality standards (i.e., tests, analytical procedures, and acceptance criteria) that confirm the quality of products and other materials used in the production of a product. Acceptance criteria are the numerical limits, ranges, or other criteria for the tests described. For additional information, see ICH Guideline Q6B: "Test Procedures and Acceptance Criteria for Biotechnological/Biological Products".[4] We believe that certain release specifications, such as those related to product safety, should be in place prior to initiating Phase 1 clinical studies. As product development proceeds, additional specifications for product quality and manufacturing consistency are developed and implemented. For additional discussion of manufacturing quality control, see "Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products"[5] and "Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information".[6]

A. Development of Release Acceptance Criteria

We recommend that proposed release acceptance criteria for the final product be based on scientific data and manufacturing experience obtained during development of the product as described below:

- Phase 1 – Based on data from lots used in preclinical studies.
- Phase 2 – Refine and tighten based on data generated during Phase 1.
- Phase 3 – Based on information collected during product development.
- Licensure – Based on information collected during product development using validated assays.

B. Development of Acceptance Criteria Analytical Procedures

We recommend that proposed analytical procedures be based on scientific data and manufacturing experience as described below:

- Phase 1-3 – Usually based on Code of Federal Regulation (CFR) methods or alternative methods, if appropriate.
- Phase 2 – If an alternative to the CFR method is used, we recommend that the sponsor initiate validation of the alternative by Phase 3.
- Licensure – The product specification should be in place and established under a validated assay.

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[4] Guidance for Industry: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, August 1999, http://www.fda.gov/cder/guidance/Q6Bfnl.pdf.

[5] Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products (Human and Animal), dated March 1991, reprinted November 1992, http://www.fda.gov/cder/guidance/old042fn.pdf.

[6] Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information, May 2001, http://www.fda.gov/cber/gdlns/ind052501.htm

C. Development of Stability Protocols

In order to develop adequate stability data for timely submission in a license application, we recommend that a sponsor implement and expand the stability program as described below:

- Phase 1 - 3 – Preliminary data on product stability must indicate whether the product or components are likely to remain stable for the duration of the clinical trial. Note: the regulations require that the IND contain these data at each stage of the clinical trial (21 CFR 312.23(a)(7)(ii)).
- Phase 2 – We recommend that the sponsor initiate a stability protocol to accumulate additional data.
- Phase 3 – We recommend that the sponsor begin to establish the dating period, storage conditions, and shipping conditions based on data derived from the stability protocol.

Guidance for Industry

Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissues, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2006

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Guidance for Industry

Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides to you, sponsors of gene therapy studies, recommendations regarding the design of studies to include the collection of data on delayed adverse events in subjects who have been exposed to investigational gene therapy products. We, FDA, are providing: (1) recommended methods to assess the risk of gene therapy-related delayed adverse events following exposure to investigational gene therapy products, (2) recommended methods to determine the likelihood that long-term follow-up observations on study subjects will provide scientifically meaningful information, and (3) specific advice regarding the duration and design of long-term follow-up observations.[1] When a gene therapy clinical trial presents long-term risks to human subjects, a gene therapy clinical trial must provide for long-term follow-up observations in order to mitigate those risks. Without such long-term follow-up observations,

[1] This guidance does not cover the following topics:

- Inadvertent germline gene transfer. (The term "germline" is used to designate genetic material destined to be transferred to gametes). For a discussion of risks associated with inadvertent germline gene transfer for gene therapy products, we refer you to the following meeting transcripts:
  - December 15-16, 1997, Recombinant DNA Advisory Committee (RAC) meeting (http://www4.od.nih.gov/oba/rac/minutes/12151697.htm),
  - March 11-12, 1999, RAC meeting (http://www4.od.nih.gov/oba/rac/minutes/3-99RAC.htm), and
  - November 16-17, 2000, Biological Response Modifiers Advisory Committee (BRMAC) meeting (http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm. November 17, 2000, 3664t2_b.pdf).
- Vaccines used to prevent infectious diseases even if you use products analogous to those used for gene therapy (consult the Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER)).
- Post-marketing or licensure requirements for performing long-term follow-up studies of subjects. The specific information needed for a licensure or post-marketing study will vary, and therefore, will be addressed with individual sponsors.
- Replication-competent non-transgene-containing viruses used as agents to mediate oncolysis. Due to the diversity of the viral agents employed, we recommend that you discuss with the Office of Cellular, Tissues, and Gene Therapies (OCTGT, CBER) the potential for risks of delayed adverse events.
- Risks due to shedding of vector to close contacts, the public, or the environment. The specifics of how and whether to address these risks in your clinical trial design should be discussed with OCTGT, CBER. For general information, see "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, Revision 1" dated July 1998 (http://www.fda.gov/cber/gdlns/environ.pdf).

the study would expose the subjects to an unreasonable and significant risk of illness or injury (21 Code of Federal Regulations (CFR) 312.42(b)(1)(i) and (b)(2)(i)).

Exposure to gene transfer technology means any exposure to gene therapy products or to cells or tissue that has been transduced with gene therapy products ex vivo by any route of administration. Except as noted below, this guidance applies to all subjects in clinical studies using gene transfer technology. The recommendations in this guidance are limited to the performance of long-term observations for evidence of delayed adverse events, i.e., adverse events that occur more than one year after exposure to the investigational gene therapy product.

This guidance finalizes the draft guidance entitled "Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events" dated August 2005. This guidance also supplements the recommendations for study subject long-term follow-up in the "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" (Retroviral Vector guidance), dated November 2006 (Ref. 1).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Potential Risks of Delayed Adverse Events Following Exposure to Gene Transfer Technology

Study subjects exposed to gene transfer technology may be at risk of delayed adverse events as a consequence of persistent biological activity of the genetic material or other components of the products used to carry the genetic material. The persistent biological activity may be necessary for the product to provide a continuing clinical benefit. However, persistent biological activity could have adverse effects upon normal cell function, placing subjects at risk for development of adverse events, some of which may be delayed by months or years.

Factors likely to increase the risk of delayed adverse events following exposure to gene transfer technology include persistence of the viral vector, integration of genetic material into the host genome, prolonged expression of the transgene, and altered expression of the host's genes. Persistence of the viral vector, sometimes associated with latency, could permit continued expression of the gene or delayed effects of viral infection. Integration of genetic material from a viral vector into the host cell genomic DNA raises the risk of malignant transformation (see Section V.F for a discussion of risks of malignancy associated with retroviral vectors). Prolonged expression of the transgene

may also be associated with long-term risks resulting from unregulated cell growth and malignant transformation, autoimmune-like reaction to self antigens, and unpredictable adverse events. Altered expression of the host genes could also result in unpredictable and undesirable biologic events.

B. Previous FDA Recommendations

We previously issued a guidance related to retroviral vector-mediated gene therapy (Ref. 1). We considered retroviruses to carry the highest known risk because of a reported case of new malignancy associated with a preclinical gene therapy study following exposure to cells transduced by a retroviral vector (Ref. 2), and therefore included in that guidance specific recommendations on performing long-term observations of subjects in trials of retroviral-mediated gene therapies.

We then sought additional information regarding gene-therapy related delayed adverse events following exposure to other gene-therapy products. We convened three separate meetings of our Biological Response Modifiers Advisory Committee (BRMAC) to solicit advice about long-term risks to subjects in gene therapy clinical trials exposed to other gene therapy products. The BRMAC meetings were held on November 17, 2000; April 6, 2001; and October 24, 2001.[2] Since 2001, and after reviewing BRMAC's recommendations, we have advised sponsors of studies involving gene transfer technology to submit to us their plans for long-term follow-up observations. We typically advised sponsors to observe subjects for potential gene therapy-related delayed adverse events for a 15 year period, and to include a minimum of five years of annual examinations, followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

C. Concerns Raised by the Gene Therapy Community

Members of the gene therapy community asked that the issue of long-term follow-up following exposure to gene transfer technology be discussed in a public forum. Accordingly, in June 2004 a public workshop was held in association with the annual meeting of the American Society of Gene Therapy (ASGT). The workshop was entitled "Long-Term Follow-Up of Participants in Human Gene Transfer Research" and was co-sponsored by the ASGT, Biotechnology Industry Organization (BIO), CBER, the NIH Office of Biotechnology Activities (OBA), and Pharmaceutical Research and Manufacturers of America (PhRMA). The workshop included a forum in which invited speakers discussed the challenges associated with long-term follow-up of subjects in gene therapy clinical studies. The workshop organizers published a summary of the discussion (Ref. 3).

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[2] If you desire background information regarding prior recommendations from the BRMAC about gene therapy trials and long-term follow-up observations, we refer you to the transcripts for the November 17, 2000; April 6, 2001; and October 24, 2001, BRMAC meetings. The references can be located at http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm by searching under the year of the meeting.

Key issues identified by workshop participants include the following:

- Not all gene therapy products present the same risks of delayed adverse events. Uniform recommendations for long-term follow-up for all gene therapy products did not take product characteristics into account.
- Some study subjects appear unsuitable for meaningful long-term follow-up observations because of high short-term mortality, poor general health, or exposure to mutagenic agents.
- Our recommendations regarding the duration and design of long-term follow-up have not been sufficiently specific.

These issues are addressed in Sections IV and V of this guidance.

III. DEFINITIONS AND ABBREVIATIONS

The following definitions apply to this guidance:

Gene therapy products:
All products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient.

Gene transfer:
The transfer of genetic material into a cell.

Gene transfer system:
The combination of the vector, regulating elements, vector formulation, and the route and method of vector delivery.

Gene transfer technology:
The use of genetic material either alone or in a suitable transfer medium, such as lipids, viruses, or other microorganisms, to mediate an effect by transcription, translation, or integration into the host genome or any combination of these processes. Exposure to gene transfer technology may result from direct administration of the product to a study subject or through use of cells or tissues exposed to such products ex vivo prior to administration to a study subject.

IND:
Investigational New Drug Application, as described in 21 CFR Part 312.

Integration (of DNA):
The process whereby exogenous DNA sequences become incorporated into a genome.

Latency (of a viral infection):
A period of time during which a virus is present in the host without producing overt clinical symptoms.

Long-term follow-up observations:
Long-term follow-up observations are extended assessments that continue some of the scheduled observations of a customary clinical trial. Long-term follow-up observations are an integral portion of the study of investigational products, such as gene therapy, that are considered to present a high risk of producing delayed adverse events.

Maximum feasible dose (MFD) (in preclinical studies):
The highest dose that can be administered to a non-human animal. Limitations may be due to animal size, administration site, or product characteristics. The MFD may not be equivalent to the clinically relevant dose.

Persistence:
With respect to transferred genetic material, the continued presence of genetic sequences in the host after acute exposure to a transfecting agent, whether due to integration of the genetic sequence into the host genome or to latent infection with the viral vector bearing the genetic sequence.

Preclinical Study:
An investigational study performed in non-human animals or in isolated cells or tissue from humans or other animals. Preclinical studies may be performed prior to or during clinical studies.

Reactivation (of a viral infection):
The re-emergence of a symptomatic or asymptomatic viral infection following a period of latency.

Transgene:
An exogenous gene that is introduced into a host cell.

Vector Sequences:
Refers to specific sequences of nucleotides, either DNA or RNA, that have been introduced into a gene therapy vector. The sequence includes all components of the gene therapy vector, the vector backbone, transgene(s), and regulatory elements.

Viral Vector:
A virus that has been modified to transfer genetic material.

IV. PRECLINICAL DATA USED FOR ASSESSMENT OF DELAYED RISKS IN GENE THERAPY CLINICAL TRIALS

A. Criteria to Assess Potential Delayed Risks of Gene Therapy

We generally will not require long-term follow-up observations following exposure to gene transfer technology when the risk of delayed adverse events is low. To assess the risk related to your product, we recommend that you use available preclinical and clinical evidence. To assess the risks of delayed adverse events, you may use current information about your product and similar products based on studies that you and others have performed. As more data accumulates, it is important to reassess the risk to your subjects and, if appropriate, revise your protocol as it relates to long-term follow-up observations.

We consider the assessment of risks to be a continuous process. New information may support the need for long-term follow-up observations or the revision of an existing study. For example, if recently reported evidence suggests a newly identified risk associated with your product or similar products, long-term follow-up observations may be necessary to mitigate long-term risks to subjects receiving these vectors. Similarly, if sufficient data accumulate to suggest that your product is not associated with delayed risks, it may be appropriate to reduce or eliminate provisions for long-term follow-up observations.

Pertinent previous preclinical and clinical experience with your product or similar products is highly relevant in the assessment of delayed adverse events. Experience with products in the same vector class, administered by a similar route, and given for the same clinical indication may contribute helpful information.

We recommend you refer to the series of questions in Figure 1, "Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events" to help you assess the level of risk. When the risk of delayed adverse events is low based on your answers to these questions, a plan for long-term follow-up observations may not be necessary to mitigate risks to subjects. Evidence from preclinical studies will help you answer questions 1 – 3. Include all of the primary data relevant to the assessment of the risk of delayed events when you submit your IND to FDA (see 21 CFR 312.23(a)(8), (10)(iv), (11)).

We suggest you use the framework in Figure 1 by answering the questions in sequence as follows:

- **Question 1:** "Is your gene therapy product used only for ex vivo modification of cells?"

  If the answer is "no," go to Question 2. If the answer is "yes," go to Questions 3 and 4.

- **Question 2:** "Do preclinical study results show persistence of vector sequences?" If the answer is "no," the risk of gene therapy-related delayed adverse events is low, and long-term follow-up observations may not be needed. If the answer is "yes," go to questions 3 and 4.

  If it is unknown whether your vector persists, for the purpose of assessing risk, we recommend that you either assume that it does persist, or perform a preclinical study to assay for vector persistence in a relevant animal species. Please refer to Section IV.B, "Considerations for Preclinical Study Design to Assess Vector Biodistribution and Persistence," for help with preclinical trial design and details on the use and expected sensitivity of polymerase chain reaction (PCR) assay for biodistribution studies. In assays performed after the final administration of vector, persistence is indicated by detectable levels of vector sequences above the threshold level in the PCR assay and absence of an apparent downward trend over several time points. In contrast, persistence is unlikely if you cannot detect vector sequences with a sensitive PCR assay or if the assay for vector sequences demonstrates a downward trend over time. We encourage you to consult with OCTGT, CBER for specific advice about determination of persistence and biodistribution in your test system.

- **Question 3:** "Are vector sequences integrated?"

  If the answer is "no," go to question 4. If the answer is "yes," we would require that clinical protocols with the product include clinical long-term follow-up observations.

- **Question 4:** "Does the vector have potential for latency and reactivation?"

  If the answer is "no," the risk is low that exposure to your gene transfer technology will be followed by gene therapy-related delayed adverse events. Long-term follow-up observations may not be needed. If the answer is "yes," we would require that all your clinical protocols with the product include clinical long-term follow-up observations.

Laboratory and preclinical evidence of the low risk of delayed adverse events following exposure to a similar product may show that long-term follow-up observations are not needed. If you provide data from a similar product, we can assess the relevance to your product if you provide a clear explanation.

We provide the following two examples:

- Your product is a plasmid and the similar product is also a plasmid, but has different coding sequences for the proposed therapeutic gene product. The similar product has been used in preclinical and clinical studies, administered by an identical route and in an identical final formulation to that proposed in the prospective studies. Reference to a published study demonstrating lack of persistence of the vector for the similar