Fundamental Elements in Gene Vector Development

The information provided below is intended to aid investigators in understanding common elements in the development of gene therapy vectors from preclinical testing to clinical trials.

Preclinical Vector Development and Testing

Laboratory Activities

Produce and characterize vector

Perform functional testing

Perform immunology testing

Perform preliminary pharm/tox testing

Regulatory Activities

Obtain IBC approval for vector use

Obtain IACUC approval of preclinical animal studies

Draft pharmacology/toxicology testing plan

Outline clinical trial plans

Request INTERACT Meeting with FDA (pg. 2)

Vector Development and Pharmacology/Toxicology/Bio-Distribution Studies

Laboratory Activities

Produce GMP-process comparable[#] vector for IND supporting GLP studies

Perform pharmacology testing

Perform toxicology testing

Perform immunology testing

Regulatory Activities

Ensure IBC approval remains current

Submit P/T protocol for IACUC approval

Draft clinical protocol

Request Pre-IND Meeting with FDA (pgs. 2-3)

Preparing for a Clinical Trial

Laboratory Activities

Produce full GMP grade vector

Test vector prep for:

- Adventitious agent
- Sterility
- Potency

Conduct full analysis of vector prep

Regulatory Activities

Finalize Clinical Protocol and Consent Forms

- Submit for IBC review and approval
- Submit to DSMB
- Submit for IRB approval

Assemble IND Application

Submit IND Application to FDA

[#] 'GMP process- comparable' indicates vector prepared using similar cell culture and purification processes as GMP material, but for which some GMP requirements (such as raw materials qualification, manufacturing facility environmental monitoring, and in-process monitoring of process intermediates) are not fully implemented. In addition, characterization and release testing of this material is less extensive than for GMP grade material.

Abbreviations Key:

FDA	United States Food and Drug Administration	IRB	Institutional Review Board
GMP	Good Manufacturing Practices	P/T	Pharmacology/ Toxicology
IACUC	Institutional Animal Care and Use Committee		
IBC	Institutional Biosafety Committee		
DSMB	Data and Safety Monitoring Board		

Investigator's Preparation for Meetings with the FDA Regarding Gene Therapy Products

The INTERACT Meeting

(Formerly known as pre-pre IND)

During the INTERACT meeting the investigator can get initial, non-binding, general advice from FDA regarding chemistry, manufacturing and controls, pharmacology/toxicology, and/or clinical aspects of the development program. This informal meeting can: 1) assist sponsors conducting early product characterization and preclinical proof-of-concept studies; 2) initiate discussion for new delivery devices; 3) inform sponsors about overall early-phase clinical trial design elements; and 4) identify critical issues or deficiencies for sponsors to address in the development of innovative products. This interaction is intended to be a focused, scientific dialogue based upon preliminary work of the investigator. The investigator should consider the advice and questions of CBER staff regarding further development of the gene therapy product.

The investigator should prepare a INTERACT meeting package (no more than 50 pages) that includes:

- A description of the product and disease or condition being treated or prevented.
- A summary of information about the product development to date and future development plans, if appropriate.
- A brief statement summarizing the purpose of the meeting.
- A list of questions for discussion, grouped by topic, with a summary for each question to explain the need or context for the question. Questions regarding combination products should be grouped together.
- A summary of data to support discussion organized by topic and question.

The Pre-IND Meeting

During the formal pre-IND meeting (generally a 1 hour teleconference), the investigator receives non-binding advice from CBER product, preclinical, and clinical reviewers. These meetings are intended to help the investigator prepare for an IND submission. The investigator should consider the advice and questions of CBER staff in the development of the IND.

For guidance regarding requesting a pre-IND meeting/teleconference, please see "Formal Meetings between FDA and Sponsors and Applicants" available at: Formal Meetings Between the FDA and Sponsors or Applicants

As per the Guidance, 60 days prior to the desired date of the teleconference, the investigator should submit a meeting request including the 12 points of information as specified on pages 4 and 5 of the referenced Guidance document to the Branch Chief, Regulatory Project Management Staff, Office of Tissues and Advanced Therapies (OTAT - formerly known as the Office of Cellular, Tissue and Gene Therapies (OCTGT)), 240-402-8190). Of specific note, the meeting request must contain a draft list of specific questions. The Agency must receive the specified number of copies of an information package at least 30 days prior to the pre-IND meeting/teleconference.

The pre-IND meeting package should include:

- Product information including
    - Description of the vector and vector derivations
    - Description of the delivery device, if applicable
- Product manufacturing information including
    - Manufacturing schema
    - Source and grade of critical reagents used during manufacturing
    - Process testing steps and criteria
    - Release testing – microbiology, identity, purity and potency
    - Final formulation buffer
    - The QA/QC system at the manufacturing site(s)
- Product use
    - Product storage requirements
    - The QA/QC system at the clinical site(s)
    - Description of how the product is administered to subjects
- Preclinical information and discussion based on outcome
    - A comprehensive summary (all *in vitro* and *in vivo* studies) and results
    - Rationale for the proposed therapy
    - Recommended initial safe dose and dose escalation scheme(s) in humans
    - Potential target organ(s) of toxicity
    - Patient eligibility criteria
    - The ability of the product to induce the desired pharmacologic/biologic effect
- Discussion of the following:
    - Dose/activity and dose/toxicity relationship
    - The relationship of route of administration and the dosing regimen to activity and toxicity of the product
    - Risks for toxicity
    - How adverse findings observed compare to other disease-induced findings
    - The incidence of toxicity findings in normal animals
- Preclinical studies yet to be performed and intended for inclusion of results in the IND submission
    - Provide detailed outline of study designs
- Proposed clinical study design including
    - Target disease
    - Objective
    - Sample size
    - Study site location(s)
    - Key inclusion and inclusion criteria
    - Dose(s) and route(s) of administration
    - Concomitant Medications
    - Outcome measures
    - Data analysis plan
    - Safety monitoring
    - Termination criteria

To Submit Meeting Packages

Contact:
Food and Drug Administration
Center for Biologics Evaluation
and Research
Office of Tissues and
Advanced Therapies
Document Control Center
10903 New Hampshire
Avenue
WO71, G112
Silver Spring, MD 20993-0002

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