

BRMAC Briefing Document for Day 1 November 16, 2000  
Preclinical Safety and Efficacy Testing of Gene Transfer Vectors

Session II. Preclinical Models

*Introduction*

The recent death of a patient while participating in a clinical trial in gene transfer, as well as the finding that data in Rhesus monkeys using the same class of vectors and route of administration predicted the toxicities observed in this subject have highlighted the importance of preclinical data and the relevance of the animal model in determining a safety profile for these agents. Therefore, CBER is seeking guidance from the committee on two issues related to preclinical testing in support of gene transfer protocols:

1. Selection of appropriate species for preclinical testing
2. The use of animal models of the disease for determination of both efficacy and safety profiles of a gene transfer vector

*Background*

Prior to initial entry of a new drug or biologic agent into humans, the basis for the determination of *in vivo* safety is the preclinical testing performed in animals. Traditional drug development programs evaluating the safety of small molecule or protein therapeutics, typically conduct toxicology testing in normal animals using a well-defined paradigm to establish the acute, sub-chronic, and cumulative toxicities of an agent prior to its first exposure in man. The advantages of this approach include: a wide range of doses may be investigated to give high multiples of the expected human exposure; the metabolism and disposition profiles in the different species may be established as a basis for comparison for the clinical dosing; and the background incidence of any specific, adverse findings may be well-documented in that particular strain of animals being tested. At least two animal species are used for the initial demonstration of safety; typically, testing is done both in rodents (*i.e.* mice, rats, or hamsters), and one non-rodent species (*e.g.* dog, pig, or non-human primate). The use of more than one species in traditional drug evaluation programs is encouraged, to increase the chance of detecting any toxicity to be monitored during the clinical trial.

Traditional toxicology programs, however, frequently are of little value in the determination of safety of biotherapeutic proteins, vaccines, or gene transfer vectors. For many biologics, the issues of species-specificity of the agent under study, as well as limitations in the doses that are feasible to administer and the interaction of the therapeutic with its specific receptor, must be taken into account when designing the safety program. In gene transfer research, demonstration of safety must also take into account toxicities due to expression of the transgene or the ultimate therapeutic protein, as well as any adverse effects associated with the vector, or delivery system (*e.g.* bronchoscopy or aerosol administration to the lung) used to introduce the foreign gene. Additionally, any underlying pathology associated with the disease being investigated may either exacerbate or confound any toxicity related to the gene transfer protocol. These points must be considered in designing a preclinical program to evaluate the safety and efficacy of a gene transfer vector.

### *Current recommendations for preclinical testing of gene transfer vectors*

CBER's current recommendations to sponsors conducting gene transfer trials are to consider the intended clinical use of the vector, any known toxicities associated with the class of vector under investigation, and any toxicities related to expression of the transgene, and then design the preclinical toxicology program to address each of these concerns in the context of the proposed clinical trial<sup>1</sup>. This individualized approach allows for the potential to identify toxicities for each specific vector in each specific indication that may impact on patient safety, and identify parameters to monitor in the clinical trial, with the understanding that no single, toxicology study design may be able to answer all safety questions prior to entry into the clinic.

CBER's recently published "Guidance to Industry: Guidance for Human Somatic Cell and Gene Therapy" document provides a framework for the design of preclinical safety programs in gene therapy. Prior to phase 1, safety information is based upon both the available data from *in vitro* and *in vivo* pharmacology models, as well as preclinical toxicology studies designed to address any specific concerns for the clinical population planned for study<sup>2</sup>. The CBER document follows the scientific principles of the International Congress on Harmonisation S6 document entitled, "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (ICH S6)<sup>3</sup>. Although the ICH guidance does not directly address toxicology study design for gene transfer agents, in general, many of the principles set forth by ICH S6 regarding dose and species selection, route of administration, and study timing can be applied.

CBER's recommendations for selection of species for safety evaluation have generally followed the guidance set forth by the ICH S6 document, taking into account the limitations of the animal model being tested. In summary, safety evaluation and toxicology testing in a single, relevant species, with sufficient, scientific justification provided for the use of that species is permissible to support initial entry into phase 1 clinical trials. A relevant species can be defined by the clinical population and/or intended route of administration or by the species-specificity limitations of the transgene product, or the gene transfer vectors. In some cases, the interaction of the transgene product with its specific receptor occurs only in humans and non-human primates, necessitating toxicology testing in monkeys. For many other gene transfer vectors, however, the toxicities observed are independent of the transgene product (*e.g.* inflammatory reactions in response to adenovirus capsid proteins), and may be tested in rodents, or other small, non-rodent laboratory species. In yet other cases, specific information regarding the safety of a gene transfer approach may only be obtained in an animal model of the disease, in which the underlying disease pathology can contribute significantly to the safety or toxicity of the intervention. Specific cases in which each of these approaches were taken will be presented by the speakers, for discussion by the committee.

*DRAFT Questions to the committee*

1. When is it appropriate to require safety studies of gene transfer agents in non-human primates? In discussing this question, please consider the following:
  - a). phase of clinical trial/product development
  - b). clinical indication
  - c). class of vector
  - d). level of gene transfer observed in preclinical pharmacology models
  - e). the limitations in terms of study design(s), statistical evaluation of the data generated
  
2. When is it appropriate to obtain these data in rodent and/or other small animal models? In discussing this question, please consider the following:
  - a). clinical indication
  - b). class of vector
  - c). what is known about the immunobiology of the vector, as well as the host immune response in the rodent vs. non-human primate models
  
3. Should safety data in efficacy models be required for all new gene transfer protocols, prior to entry in phase 1 clinical trials?

*References*

1. Pilaro, A.M. and M.A. Serabian. 1999. Preclinical development strategies for novel gene therapeutic products. *Toxicol. Pathol.*, **27**:4-7.
2. Food and Drug Administration, Center for Biologics Evaluation and Research. March, 1998. Guidance for industry: Guidance for human somatic cell therapy and gene therapy. Available at <http://www.fda.gov/cber/gdlns>.
3. International Congress on Harmonisation. July, 1997. Guidance for Industry. S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals. Available at <http://www.fda.gov/cber/gdlns>.