Preclinical Considerations in Cell and Gene Therapy Product Development

SLIDE 1

Pre-clinical studies for cell and gene therapy products are evaluated in the Pharmacology and Toxicology Branch, commonly known as the PharmTox Branch, in the Office of Cellular, Tissue and Gene Therapies, or OCTGT.

This presentation will discuss pre-clinical considerations in cell and gene therapy product development.

SLIDE 2

This presentation will discuss: one, principles that should be applied in the regulatory review of pre-clinical studies; two, a description of some classes of OCTGT regulated products and potential safety concerns for these products; and, three, what one should consider when conducting the pre-clinical evaluation of a cell or gene therapy product, particularly regarding the use of relevant animal species and models as well as the PharmTox study designs.

SLIDE 3

Many of the investigational products regulated by OCTGT originate from basic research projects. Therefore, the transition from a research project to use of a particular product in a clinical trial is reflected in the overall product development program for a particular agent. OCTGT provides regulatory and scientific input on the pre-clinical program for these investigational products, particularly during the pre-pre-IND and pre-IND phases.

In addition, to this direct regulatory input, there are various guidance documents generated by FDA and ICH that contain basic scientific principles, which can also be used in support of the submission of pre-clinical information in the IND that will support the conduct of the initial early-phase clinical trial. As the product development pathway progresses, appropriate PharmTox data should be provided to allow the continuation of subsequent later-phase clinical trials to support the goal of submitting a Biological License Application, and ultimately obtaining a license or marketing authorization.

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Safety at all phases of the clinical investigation of an investigational product is always a primary objective, as stated in the Code of Federal Regulations, or CFR, at 21 CFR Part 312.22a.

SLIDE 5

FDA review is product based. Pre-clinical studies are designed to support use of a specific product to treat a specific clinical indication. Clinical trial design is supported by the manufacturing data and the pre-clinical data. The decisions and conclusions of the reviewers in OCTGT are made based on scientific data of the investigational product, and framed by the regulations.

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One question that is frequently asked is: how are animal studies integrated into the proposed clinical plan? According to 21 CFR Part 312.23, adequate information derived from PharmTox studies is necessary to support the safe use of an investigational product in a clinical investigation. The type of animal study or other pre-clinical tests performed will vary, depending on the scope and the duration of the intended clinical investigation. This point will be elaborated a bit more in this talk.

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This slide provides examples of various cell therapy products, and serves to remind you of the diversity of cell therapy products that are regulated by OCTGT.

SLIDE 8

Potential safety concerns for cell therapy products can include: one, cell survival status following delivery via many routes, and using many different delivery devices, such as a catheter; two, cell migration or trafficking to non-target sites; three, cell differentiation into undesired cell types; four, development of an immune response to the cells; and five, uncontrolled proliferation or tumorigenicity.

You also have to consider the host's physiological and anatomical response to the cell therapy and the safety concerns with the use of immunosuppressants.

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Examples of immunotherapy products include: one, gene-based vectors expressing immunogenic molecules, and two, ex vivo modified cells, such as antigen presenting cells, T cells, B cells, and inactivated tumor cells. This product class also includes therapeutic vaccines, such as those used to treat cancer or Alzheimer's disease.

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Some examples of gene therapy products are listed in this slide. The diversity of gene therapy products comes from the use of many types of replication-deficient viral vectors and non-viral vectors, as well as the various types of transgenes delivered by these vectors.

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Oncolytic viruses, also called viral therapies, add to the diversity of gene therapy products. These viruses can be replication competent or attenuated. They can be

naturally occurring or genetically modified. Oncolytic viruses expressing a transgene are defined as a gene therapy product.

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The potential safety concerns for gene therapy and viral therapy products depend on the type of vector or virus that will be administered, and the route of administration of the investigational product. General concerns can include: one, biodistribution to non-target tissues, and the level and persistence of viral replication in those tissues; two, possible initiation of an inappropriate immune response in the host; and three, the potential for insertional mutagenesis and/or oncogenicity.

In addition, the expressed transgene may have undesired effects.

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The scientific basis and rationale for early phase clinical trials are derived from pharmacology studies. Data from these studies should: one, define a pharmacologically effective dose; two, optimize the route of administration and dosing regimen; and three, provide a rationale for the selection of the animal species and animal model for further preclinical testing.

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Importantly, pre-clinical data that support a potentially safe starting dose level and dose escalation scheme in humans are needed. The data from the pre-clinical studies should also provide information on potential target tissues for toxicity and activity. These pre-clinical data should assist in the selection of various parameters that can be monitored in the clinical trial and in determining patient eligibility criteria.

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Toxicology studies should be conducted in a biologically relevant animal species. These animals can be either healthy, or a disease or injury model. The next several slides will discuss this concept further. Under certain circumstances, a hybrid PharmTox study design may also be used. In these studies, the toxicology end points can be collected in a pharmacological study setting.

For example, a study using tumor-bearing animals can collect both activity and safety information. However, in this case, the life span of a tumor-bearing animal is generally short. Thus, the use of normal animals to obtain long term safety information may be necessary.

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The selection of a relevant animal species in the pre-clinical studies will need to be supported by scientific data. The use of non-human primates and multiple animal species is not an automatic default requirement for every cell and gene therapy product.

An important consideration is to also apply the 3 R's, which are Reduce, Refine, and Replace, to overall animal use in pre-clinical study designs.

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A primary principle in the use of relevant animal species and animal models of disease is the comparability of the animal model to the physiology and pathophysiology of the target human population.

This principle applies to healthy animals, both rodents and non-rodents. Such models can consist of: one, genetically modified animals, such as transgenic animals; two, spontaneous disease models; and three, non-spontaneous disease models, such as chemically induced models of disease or injury. Any of these animal models are acceptable for pre-clinical testing, as long as sufficient information supporting the comparability of disease status or pathogenesis to the intended patient population is provided.

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Toxicology study designs should always include appropriate controls.

In addition, the studies should mimic the clinical scenario as closely as possible, particularly in: one, the administration of the intended clinical product; two, the clinical product formulation; three, the proposed clinical route of administration; and four, the planned clinical dosing regimen. The study design should include reasonable group sizes to allow for adequate analysis or interpretation of the data, and the study should be of sufficient duration to capture the spectrum of any potential toxicities, as well as the recovery of these toxicities.

The study should include multiple dose levels, in order to determine the No-Observed-Adverse-Effect-Level.

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This slide contains a list of standard toxicology end points that are typically used to evaluate potential local and systemic toxicity. Included are: one, mortality; two, clinical observations; three, body weights; four, hematology; five, serum chemistry; and six, gross and microscopic pathology.

In certain circumstances, immunohistochemistry staining might also be included.

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Biodistribution studies for novel gene therapy and viral therapy products should be conducted prior to initiating the clinical trial. For gene therapy vectors similar to those that have been previously used in humans, information from existing databases,or INDs, can potentially be referenced in lieu of conducting biodistribution studies. In such cases, biodistribution studies would then be conducted in parallel with the clinical trials. Biodistribution data for the intended clinical product are needed prior to submission of a BLA.

SLIDE 21

The extrapolation of the dose levels administered in animals to the dose levels that will be administered to the patients involves several sets of information. The proof-of-concept, or pharmacology data, will help to determine the minimally active dose level. This information in combination with the safety data, such as the No Observed Adverse Effect Level, will help determine the dose level selection for the clinical trial.

The extrapolation from the animal to the clinical dose levels can potentially be calculated several ways: one, based on a fixed-dose level, which is the absolute human dose level; two, based on body weight, if the investigational product is delivered systemically or results in systemic exposure; or three, based on the organ mass or volume, if the product is delivered locally, into a target tissue or organ.

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If a device will be used to deliver the investigational product, it is important to determine whether this device is cleared for the proposed use. If the device has not been cleared for delivery of material into the desired anatomical location, and a Master File has been submitted to the Center for Devices and Radiological Health, called CDRH, a letter of cross reference to that Master File must be provided in the IND submission, to allow the IND reviewers access to the contents of this file. If a Master File has not been submitted to CDRH, OCTGT would consult with CDRH to determine the data needed for the IND submission.

It is also important that some of the pre-clinical studies be performed using the intended clinical delivery device, if possible.

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This concludes the presentation, "Preclinical Considerations in Cell and Gene Therapy Product Development".

We would like to acknowledge those who contributed to its development.
Thank you.