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Cell and Gene Therapy:
From Preclinical Program To IND

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Introduction

The evolution of drug development from small molecules and proteins to the next generation of cell and gene therapy (CGT) provide tremendous promise for patients. CGT products involve complex and diverse chemistry and biological mechanisms aided by rapidly evolving scientific research. The intrinsic material composition and putative MOA(s) of CGT products differ from conventional drugs. Therefore, the traditional, standardized approaches for a preclinical program may not be appropriate for evaluating the safety of CGT products. This position paper is intended to briefly introduce the current thinking of FDA on the preclinical program development of CGT products, and to provide Aleon's position on the path from preclinical program to IND application for CGT products.

Uniqueness of CGT preclinical development

The Office of Tissues and Advanced Therapies (OTAT; previously Office of Cellular, Tissue and Gene Therapies / OCTGT), under the Center for Biologics Evaluation and Research (CBER), regulates products including gene therapy, tumor vaccines, xenotransplantation, stem cells, human tissue for transplantation, combination products, bioengineered tissues, and certain medical devices.[1]

CGT products involve diverse biology, clinical indications, and the rapid state of evolving scientific research, which pose unique scientific challenges in terms of regulatory review. The intrinsic material composition and putative MOA(s) of CGT products differ from small molecular drugs, macromolecular biologic drugs, and medical devices. Therefore, the traditional, standardized approaches for preclinical toxicity testing, which were developed for drug development and device testing, may not be appropriate for evaluating the safety of CGT products. In addition, specific terms in pharmacokinetics, such as absorption, metabolism, and excretion, may not apply in the same manner as they do for non-CGT products.[2]

As a result, the regulatory review process for the evaluation of investigational CGT products requires a careful risk-benefit analysis based on the particular clinical indication. OTAT uses a flexible, science-driven review process to address safety issues in a context that considers both the biology (and biomechanics, if applicable) of the product and the intended clinical indication. Although flexible, such an approach incorporates the basic toxicological principles that underlie more traditional, standardized preclinical testing.[2]

Even though some elements of ICH safety guidance do not specifically address or recognize the unique properties and characteristics of CGT products, the basic testing principles in the ICH S6 and its addendum may be useful.[3, 4]

GCT-specific considerations in preclinical program for IND

- **Types of Preclinical Studies**

A primary objective of proof-of-concept (POC) studies is to help validate the utility of an investigational CGT product in the targeted patient population. POC studies also help to establish

the beneficial side to a risk-benefit assessment of the CGT product and provide some safety data if design appropriately. Data from POC studies contribute significantly to animal species selection for safety/toxicology studies. Data derived from *in vitro* and *in vivo* POC testing can guide the design of toxicology studies and early-phase clinical trials and help define the reasonable risks of the investigational CGT product in the intended patient population.[2]

Regarding the general toxicology studies, preclinical assessment of the safety of an investigational CGT product contributes to the determination of an acceptable risk-benefit ratio for a proposed clinical trial. The safety assessment should be sufficiently comprehensive to permit identification, characterization, and quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed), the possibility for resolution of any toxicities, and the effect of product dose level on toxicity findings.[2] The characterization of the vector tissue biodistribution profile following *in vivo* administration is an important component of the preclinical development program for GT products. A new ICH S12 Guideline on "Nonclinical Biodistribution Considerations for Gene Therapy Products" is under development.[9]

The potential for reproductive/developmental toxicity may need to be addressed, depending on the product type or target patient population. In general, such studies should be conducted prior to Phase 3 clinical trials or not until licensure.[5] The IND-enabling preclinical studies would establish a platform for conducting future reproductive/developmental toxicity studies.[2]

Due to the biological attributes of the CGT products, conducting studies to assess the carcinogenicity/tumorigenicity potential generally occurs during the early stages of product development.[2]

According to 21 CFR Part 58, all preclinical toxicology studies are to be conducted in compliance with GLP. However, it is recognized that some toxicology assessments may not fully comply with the GLP regulations. A brief statement of the reason for the noncompliance must be submitted in the final study report. Compliance of *in vitro* and *in vivo* pharmacology/POC studies with GLP is not required.[2, 6]

- **Investigational Products used in preclinical studies**

Similarities and differences between product lots intended for preclinical use and lots intended for clinical use should be highlighted and discussed in the IND submission. In certain cases, due to the species-specific nature of the clinical product, testing the CGT product intended for clinical administration in animals may not be informative; therefore, testing of an analogous product may be a suitable alternative.[2]

- **Animal Species and Disease Models Selection**

The animal species selected for assessment of bioactivity and safety should demonstrate a biological response to the investigational CGT product similar to that expected in humans. Prior to initiation of the pivotal preclinical studies for the IND, it is recommended to conduct *in vitro* studies and *in vivo* pilot studies to establish the biological relevance of a specific animal species to the investigational product(s). A summary of the more detailed assessment regarding the

relevancy of each animal species used in support of each potential clinical trial should be submitted as part of the preclinical section of the IND.[2]

Due to the features of CGT products, animal models of disease/injury may be preferable to healthy animals when assessing activity and safety. The IND submission should include information supporting the usefulness/ability of the selected animal model(s) to mimic the target disease population and to permit assessment of the safety of the investigational CGT product.[2]

Product Delivery Considerations

The IND sponsor is responsible for providing sufficient data to allow FDA to determine the safety of the delivery device system. The IND submission should state whether a device master file (MAF) has been submitted to the Center for Devices and Radiological Health (CDRH) for the delivery device. If a MAF exists, the IND submission should include a letter of authorization from the MAF holder granting permission for FDA to cross-reference specific information in the MAF.[2] The safety/toxicology study should use the clinical route as intended for the clinic, and if using a delivery device it should be the same on as the clinic unless a scientific justification is provided.

From Preclinical Development to IND: What Do We Do?

Communication with OTAT Pharmacology/Toxicology Staff

To allow for seamless product development, FDA recommends communication with OTAT Pharmacology/Toxicology staff early in the investigational CGT product development program to ensure that the timing and design of preclinical studies are adequate.[2] Aleon will plan strategically and provide effective guidance throughout the process to establish a strong relationship between FDA and your team; and more importantly, to ensure that regulatory expectations related to safety, demonstration of nonclinical biological activity, and understanding of likely MOA(s) are addressed.

The pre-IND meeting can be very valuable in planning a drug development program, especially if the sponsors' questions are not fully answered by guidances and other information published by FDA. Especially for CGT products, a pre-IND meeting would provide sponsors with valuable information for the preparation of a complete IND application.[7] Aleon possesses extensive experience in various types of formal meetings with FDA and NMPA, especially in pre-IND meetings. We will support you in developing both the best quality meeting request and meeting information package, always in a timely manner. For more details please see Aleon's position paper on pre-IND meetings.

Preclinical Consultation and IND Preparation

Aleon has access to leading preclinical experts, including former FDA senior reviewers/directors, as well as an experienced on-site team providing deep understanding and insight about FDA guidelines. We will provide nonclinical studies gap assessments for the CGT products by utilizing our strategic regulatory expertise.

Aleon has gained valuable experience through over 80 successful IND submissions, which we will share. Our regulatory expertise will ensure high quality and timely CGT product IND preparation and submission. For more details on IND preparation, please see Aleon's position paper on INDs.

Conclusion

CGT as next generation medicine is a rapidly expanding field that has the promise to treat serious conditions. FDA has innovative approval pathways for these products, including the regenerative medicine advanced therapy (RMAT) designation, established in 2019.[8] CGT products involve diverse biology and rapidly evolving scientific research, and the intrinsic material composition and putative MOA(s) of CGT products differ from conventional drugs, which warrants unique regulatory review. As a dedicated team with professional expertise, Aleon will work closely with the sponsor to facilitate your investigational CGT product from the stage of preclinical development to a successful IND.

References

1. FDA Website - OTAT Learn: https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otat-learn
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3. ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (July 1997)
4. ICH S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (May 2012)
5. ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010)
6. 21 CFR Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies.
7. FDA Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017)
8. FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (February 2019)
9. Concept Paper: ICH S12: Nonclinical Biodistribution Considerations for Gene Therapy Products