Preclinical Considerations for Cell and Gene Therapy Products, an FDA Perspective

Ying Huang, Ph.D.
Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)

FDA Oncology Therapy Development Workshop
Pivotal Steps and Avoiding Pitfalls for Startups
March 30-31,2020
Virtual Meeting

Presentation Overview

- Diversity of OTAT regulated products in oncology
- Preclinical testing program
- Animal species/model(s) considerations
- Safety assessment considerations for cell and gene therapy (CGT) products
- Early communication with CBER / OTAT
- Selected FDA Guidance

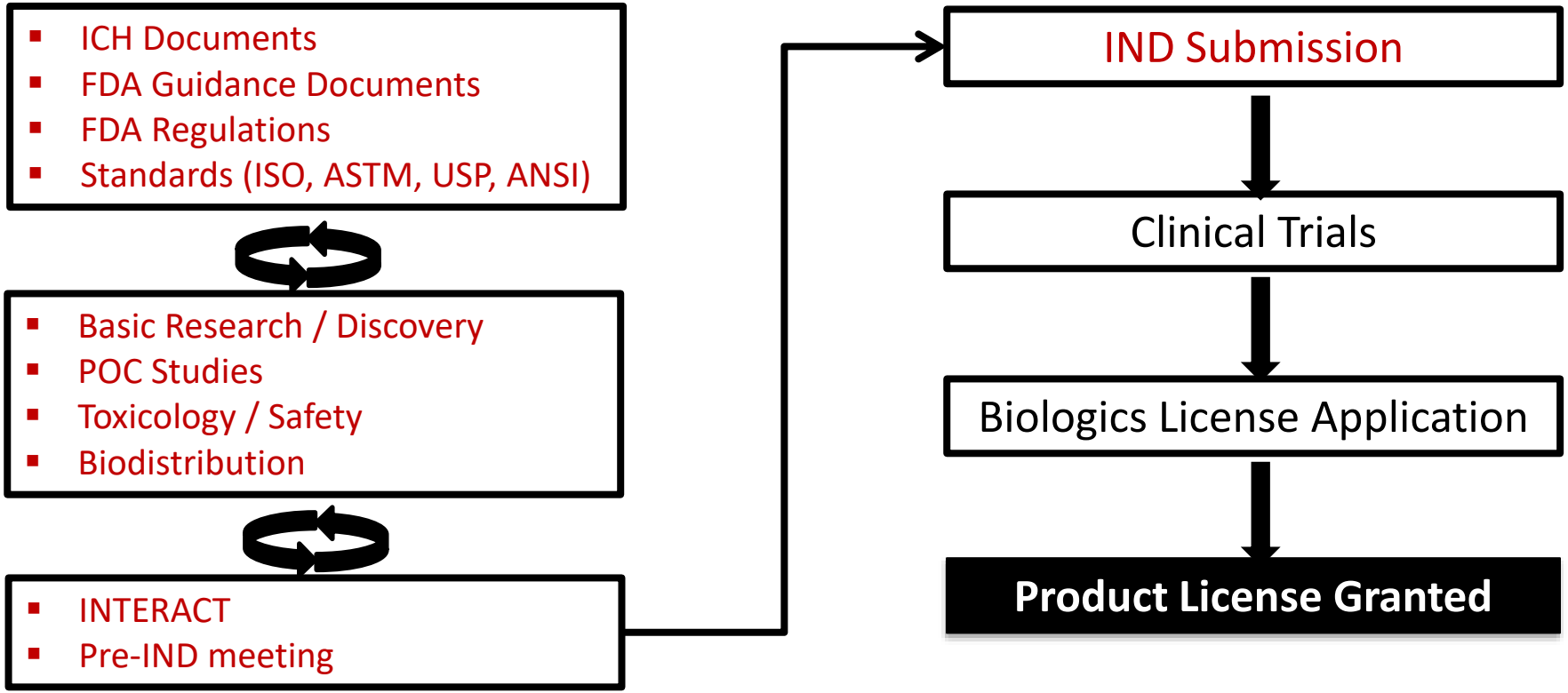
Diversity of OTAT Regulated Products in Oncology

- Ex vivo genetically modified cells (e.g., CAR T-cells)
- Non-viral vectors (e.g., plasmids)
- Replication-deficient viral vectors (e.g., adenovirus)
- Replication-competent viral vectors (e.g., adenovirus, vaccinia, herpes)
- Microbial vectors (e.g., Listeria, Salmonella)
- Genome editing products
- Tumor vaccines
- Cell-based immunotherapy products

Cell-based Immunotherapy Products: Examples

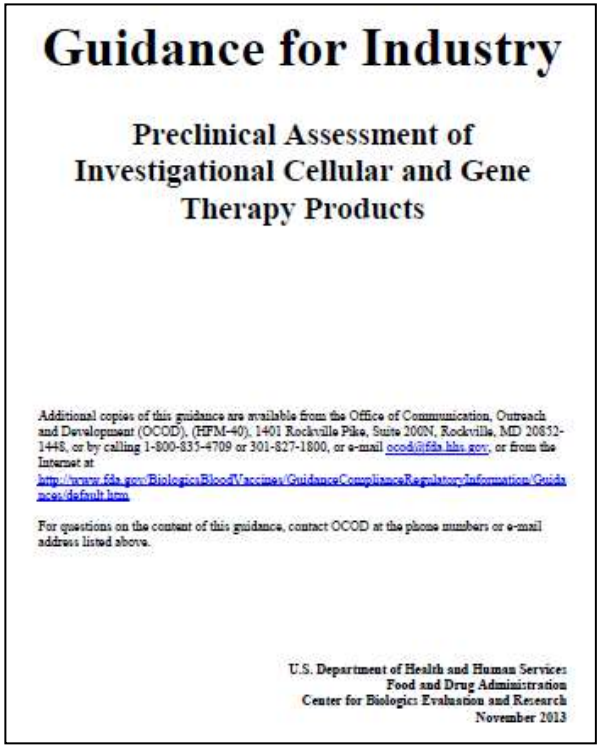
- Chimeric Antigen Receptor (CAR) T-cells
- TCR transgenic (Tg) T-cells
- Non-T-cell CARs (B-cell, NK cell, etc.)
- Stem cell / iPSCs-derived
- Cell-based therapeutic vaccines (e.g., dendritic cells, irradiated tumor cells, etc.)

CGT Product Development: *Focus on Preclinical Phase*



Preclinical Testing Program

- Preclinical study considerations
  - Objectives
  - General program design
- Recommendations for assessment of cell therapy, gene therapy, and therapeutic vaccines
- Incorporation of the 3R's of animal testing
  - **R**educe, **R**efine, **R**eplace



Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

Preclinical Program Objectives

- Support the rationale for the first-in-human clinical trial / proof-of-concept (POC)
  - Bioactivity of the intended product
  - Pharmacologically effective dose range
- Demonstrate the safety for administration to humans
  - Toxicology testing
  - Biodistribution (BD) assessment
  - Tumorigenicity, immune-related risk, neurotoxicity, cardiotoxicity, and/or other tests, as applicable

Preclinical Program Objectives

- Inform the clinical trial design
  - Dose (e.g., initial safe starting dose level, dose-escalation scheme, dosing schedule)
  - Risks to subject population
  - Clinical route of administration
  - Clinical monitoring (e.g., safety, activity, duration of follow-up)

- Support the assessment of benefit : risk profile for subjects

Animal Species / Model(s) Considerations

- Use of relevant species / model(s)
  - Healthy rodents and / or non-rodents
  - Tumor-bearing models, syngeneic vs human xenograft
  - Immunocompetent or immunodeficient animals
  - Transgenic animals
  - Companion animals

- Permissiveness to vector / virus transduction / replication
- Immune tolerance to cell-based products
- Animal model availability; technical feasibility

Sources of Data to Support an IND

- GLP-compliant toxicology assessment conducted by a certified testing facility
- Well-controlled studies conducted in house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted files to FDA
- Detailed clinical data from clinical trials

Potential Safety Concerns for Cellular Products

- Potential inflammatory / immune response to the administered cellular product
- Inappropriate cell proliferation (i.e., tumor formation)
- Inappropriate cell differentiation (i.e., ectopic tissue formation)
- Cell migration to non-target areas / tissues
- For allogeneic cells: GvHD

Safety Concerns for Genetically Modified Cellular Products

- Toxicity related to gene modification
  - On-target / off-tumor and off-target toxicities for engineered TCR or CAR-T cell products
- Undesired immune activation - cytokine release syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- Vector related genotoxicity, tumorigenicity

Preclinical Data Used to Assess a CAR T-Cell Product, an example

- On target activation
  - Cytokine release assays (e.g., IFN-γ)
  - Cytolysis of target tumor cells
- Targeting specificity
  - Antigen dependent T-cell proliferation
  - Protein arrays to screen for reactive epitopes

Preclinical Data Used to Assess a CAR T-Cell Product, an example, cont'd

- Expression profile of target in human tissues
- Off-target testing against cells from various tissue sources
- Tissue cross-reactivity using test articles with the same scFv, as appropriate
- Assessment of risks related to novel integrating vectors

Preclinical Data Used to Assess a CAR T-Cell Product, an example, cont'd

- POC / Tox studies in appropriate animal models
  - Anti-tumor activity and survival benefit
  - Safety parameters, including in-life and terminal analyses, any additional product- and indication- specific analyses
  - Cell expansion and persistence
- Studies using analogous T-cell product in animal models, as applicable
  - Uses a surrogate product similar to clinical T-cell product for the assessment of anti-tumor activity, on-target activity and off-target risks

Additional Supporting Data for a CAR T-Cell Product

- Any previous clinical experience with similar T-cell products (e.g., same CAR scFv)
- Any previous experience with investigational or approved monoclonal antibody with identical specificity
- Any published experience with the same target

Current Genome Editing (GE) Technologies

- Four families of engineered site specific nucleases:
  - Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR / Cas systems)
  - Mega nucleases
  - Transcription Activator-Like Effector Nucleases (TALENs)
  - Zinc Finger Nucleases (ZFNs)

Current GE Technologies, cont'd

- Delivery methods include use of viral vectors, plasmid DNA, mRNA, protein, ribonucleotide protein (RNP) complexes
  - Genome modification of cells *ex vivo* (e.g., CAR T-cells)
  - Direct administration *in vivo*

Unique Aspects of Incorporating GE

- Process by which DNA is inserted, deleted, or replaced in the genome using engineered site-specific nucleases
- Nucleases create site-specific double strand breaks (DSBs) at specific locations in the genome
- Induced DSBs are repaired through non-homologous end-joining (NHEJ) or homology directed repair (HDR)
- GE process introduces risks of nuclease-cleavage related on- and off-target effects, genotoxicity, chromosome translocation, tumorigenicity

Preclinical Considerations for a Genome Edited Cell-based Product

- Characterization of nuclease-mediated on-target site editing using sequencing-based methods
- Characterization of off-target sites occurring in the genome using orthogonal approaches
  - *In silico* prediction and deep sequencing of the predicted cleavage events
  - Biochemical approaches (non-cell based)
  - Cellular approaches (cell-based)
  - Whole genome sequencing

Preclinical Considerations for a Genome Edited Cell-based Product, cont'd

- Assessment of risks associated with off-target and undesired on-target effects
  - Coding genes and functional non-coding sequences
  - Chromosomal integrity
  - Cellular physiology
  - Cell transformation

Potential Safety Concerns for GT / OV / MV Products

- Type of vector / virus
- Vector / virus BD and persistence in non-target tissues and biofluids
- Level of viral replication in the body

GT: Gene Therapy; **OV**: Oncolytic Virus; **MV**: Microbial Vector

Potential Safety Concerns for GT/ OV / MV Products, cont'd

- Inappropriate immune activation by the vector, virus, transgene(s)
- Vector insertional mutagenesis and oncogenicity
- Risks of the delivery procedure

GT: Gene Therapy; **OV**: Oncolytic Virus; **MV**: Microbial Vector

Preclinical Testing Considerations

- Assess POC, to determine product bioactivity using *in vitro* and *in vivo* systems (i.e., animal model)
- Assess POC / BD to determine target and non-target tissues in animal model
- Assess safety / toxicology (T) / BD in healthy animals
- Assess pharmacology-toxicology in animal model(s) i.e. POC + T + BD – incorporate activity & safety endpoints

Safety Study Design Considerations

- Nonbiased design
- Mimic the planned clinical scenario as closely as possible
- Administration of clinical vehicle formulation and multiple dose levels of the investigational product
- Use of the clinical product or its surrogate with justification

Safety Study Design Considerations, cont'd

- Include adequate numbers of animals per group
- Multiple sacrifice time points and sufficient study duration
- Comprehensive safety assessments
  - Mortality, clinical observations, body weights, clinical pathology, immunogenicity, macroscopic analysis, histopathology, etc.
  - Other specific non-terminal/terminal assessments (e.g. imaging)

BD Assessment Considerations

- Evaluate pharmacokinetic aspects of GT / OV / MV
- Determine BD profile (distribution, persistence, clearance) in biofluids and tissues (target / non-target)
- Determine levels of transgene and its product (e.g., proteins), where possible
- BD can be assessed as a separate study or as a component of a pharmacology or toxicology study

International Pharmaceutical Regulators Programme: Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products. 12 April 2018

BD Assessment Considerations, cont'd

- BD should be assessed in a vehicle control group and a group of animals that receive the maximum dose level in the toxicology study
- Assessment should include several sacrifice intervals
- Sample collection includes blood and a core list of tissues (injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen)

Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020)

BD Assessment Considerations, cont'd

- Consider other tissues for assessment, depending on the product type and tropism, transgene(s), and the route of administration (e.g., draining lymph nodes, bladder, urine)
- Sample collection should avoid the potential for cross contamination among different tissue samples
- BD assay method is to be sensitive and quantitative to detect product sequences (e.g., qPCR)

Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020)

Additional Testing Considerations

- Product-specific testing for concerns related to:
  - Neurotoxicity
  - Cardiotoxicity
  - Genotoxicity
  - Tumorigenicity
  - Other studies, as applicable

- Testing may be incorporated in the definitive safety study as appropriate

Conduct of Safety Studies

- Each toxicology study submitted should be performed in compliance with Good Laboratory Practice (GLP) per 21 CFR Part 58.

- For non-GLP studies conducted in-house, oversight of the conduct of the study and the resulting final study report by an independent QA unit / person (per 21 CFR Part 58.35) is recommended.

Early Communication at CBER

INTERACT - INitial Targeted Engagement for Regulatory Advice on CBER producTs

- Previously known as pre-pre-IND interactions
- You initiate the contact when you have generated preliminary data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies
- You provide a concise briefing package (approximately 50 pages), with key issues for consideration clearly identified

INTERACT
Briefing Package P/T Content

- Comprehensive summary of all completed *in vitro* and *in vivo* preclinical studies
  - POC studies, pilot safety studies, relevant cited references
- Description of the preclinical development plan
  - Completed and planned studies intended to support the rationale and safety of product administration in humans
- Specific questions you would like to discuss regarding your submission

The designs for the definitive safety studies are discussed in detail in the pre-IND meeting

Early Communication at CBER

Pre-IND meeting

- To communicate the initial development plan
  - Product characterization issues
  - Preclinical testing program
  - The scope and design of the planned clinical trial
- To facilitate an eventual IND submission

Summary

- Comprehensive product characterization is key to understanding product risk
- The preclinical testing program may need to be adapted to the specific CGT product and level of perceived risk
- New *in vitro* and *in vivo* test models should be considered as the science and technology advances
- The 3Rs should be applied to preclinical testing programs
- Communication with FDA at early stages of product development may be beneficial

Selected FDA Guidances

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
  https://www.fda.gov/media/87564/download
- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
  https://www.fda.gov/media/106369/download
- Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017)
  https://www.fda.gov/media/109951/download
- Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020)
  https://www.fda.gov/media/113768/download

Contact Information

- **Ying Huang, Ph.D.**

  Ying.huang@fda.hhs.gov

- **Regulatory Questions:**

  OTAT Main Line – 240-402-8190

  OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

FDA Headquarters
Federal Research Center at White Oak
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov

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