FDA Requirements for Nonclinical Safety Testing of Cell Therapy Products

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Focus of Talk

• Nonclinical development of cell and tissue therapy products
• FDA regulation of cell and tissue products
• Pharmacology and toxicology studies
• FDA expectations for nonclinical animal safety studies
• Discussing your nonclinical program with FDA
Cell, Tissue and Gene Therapies
Classes of Products

- Somatic cell therapy (non-stem cells)
- Adult stem cells
- Placental/umbilical cord blood stem cells
- Mesenchymal stem cells
- Tissue engineered products and/or organs
- Bioartificial Organs
- Plasmid DNA vectors
- Viral or Bacterial Vectors
Unique Properties of Cell Therapy Products Drives their Regulation and Development

- Naturally derived, not synthesized
- Cannot be terminally sterilized
- Unlike Drugs, cells are living products.
- Usually species-specific
- Variable immunogenicity
- Long-term persistence
- Assess distribution, rather than pharmacokinetics
- Potential to secrete or express new/foreign proteins
Other Unique Concerns and Issues with Cell Therapy Products

- Potential long-term or “lifetime” effects
- Significant concern over potential contaminants
- Challenge to define dose response
- Often intended for single dose or limited multiple dose administration
- Overall class heterogeneity “case-by-case” assessment of safety for each product
FDA Regulation of Cell and Gene Therapy Products

- Traditional development programs for drugs do not apply to these products
- A “tiered” or risk-based approach taken by FDA on regulation of these products
- Level of regulation and requirements increases proportionately with perceived risk
- Products regulated by FDA Center for Biologics (CBER) in the Office of Cell, Tissue and Gene Therapy Products (OCTGT)
FDA Organization and Regulation of Biological Products

FDA

CDER
Drugs

CBER
Biologics

CDRH
Devices

Center for Food Safety

Center for Veterinary Medicine
FDA Regulation of C/GT Products (Continued)

- Regulation contingent on “Degree of manipulation”
- Organ transplants – No FDA regulation
- “361 HCT/Ps”: Tissue transplants (e.g. corneas, reproductive cells) or other “minimally manipulated” products intended for homologous use in donor/patient or close blood relative. Regulated under Section 361 of PHS Act – No IND or regulatory submission required
FDA Regulation of Cell Therapy Products

- “351 HCT/Ps” Products: More typical “cell therapy” products are regulated under Section 351 of the PHS Code....IND filing required!

- INDs and marketing application (BLA) required or IND/PMA if regulated as device

- Examples: Cell therapies from allogeneic or xenogeneic donors, cultured or expanded cells that are more than minimally manipulated, genetically altered or combined with a foreign substance or scaffold (tissue engineering)
FDA Guidance on Cell Therapy Products

- Presently, FDA guidance on C/GT Products is still relatively dated (1994, 1998, 2003). (Guidances are also provided toward end of presentation)

- **1997**: Proposed Approach to Regulation of Cellular and Tissue-Based Products


- **2003**: Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (Final Guidance)
FDA Expectations for Nonclinical Testing of Cell Therapy Products

- OK...regulations are all well and good, but.......WHAT DOES FDA ACTUALLY EXPECT to see nonclinically for Cell Therapy Products?

- “Tiered” or risk-based approach to regulation contingent on:
  - Source of cells (Autologous, Allogeneic, Xenogeneic)
  - Degree of manipulation of cells
  - Inclusion of exogenous DNA (Gene Therapy)
  - Intended use of cells (homologous or heterologus)
‘Tiered’ or Risk-Based Approach to Regulation of Cell and Gene Therapy Products

<table>
<thead>
<tr>
<th>Level of Regulation</th>
<th>Complexity of System/Difference from Host (Degree of Risk)</th>
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</thead>
<tbody>
<tr>
<td>Phs 351  Hct/P cell</td>
<td>Unmodified Autologous Cells grown in culture intended for novel function</td>
</tr>
<tr>
<td>Phs 361  Hct/P product regs</td>
<td>Autologous or Allogeneic Cells</td>
</tr>
<tr>
<td>phs 361  hct/p</td>
<td>Gene Therapy or Xenogeneic (Animal) cell Therapy</td>
</tr>
<tr>
<td>phs 361  hct/p</td>
<td>Genetically modified Allogeneic or Xenogeneic cells combined with implantable or extracorporeal device</td>
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Cell and Gene Therapy and Device Regulations and/or Xenogeneic Product Regulations
Expectations for Nonclinical Studies

- FDA Nonclinical Review Division in OCTGT expects sponsors to determine:
  - Safe starting dose and dose escalation scheme
  - Potential target organs and key adverse effects
  - Parameters to monitor in nonclinical and clinical studies
  - Populations that may be at risk
General Considerations for Nonclinical Studies of Cell Therapy Products

- Product to be administered (Cell type)
- Intended clinical route of administration
- Site of administration/implantation
- Relevance of animal species and physiological state for safety and efficacy studies
- Animal dose and dose scaling
- Treatment regimen
- Follow-up parameters
Product-Specific Considerations for Nonclinical Studies

- **Gene Therapy**: (1) Gene sequence similarity between human and animal species. (2) Vector tropism (3) Vector pathogenicity (4) Distribution and persistence

- **Cell Therapy**: (1) Immunogenicity in animal model (2) Distribution and persistence (3) Tumorigenicity

- **Tissue Therapy**: (1) Species relevance (2) Immunogenicity (3) Biocompatibility
What Does FDA REALLY Want to Know About Your Product...?

- What is the product’s function in vivo? (Efficacy)
- Is the product SAFE in vivo? (Toxicity)
- Does the product distribute where it shouldn’t and does it persist? (Biodistribution)
- Does the product cause or form tumors in vivo? (Tumorigenicity)
- Does the product secrete or regulate any proteins or other factors?
Translating FDA Expectations into Tangible Nonclinical Study Designs

Part 1: Efficacy Studies

• Demonstrate that the vector or cells produce the desired pharmacological response in animals
• Utilize and refine animal model of disease
• Define active dose and dose limits
• Establish optimal dose route and regimen
• Obtain basic safety and distribution information
• Define markers for follow-up
Translating FDA Expectations into Tangible Nonclinical Study Designs

Part 2: Safety Studies

• Use a relevant animal model, establish safety of product delivered by the intended clinical route, with a sufficient dosing regimen and dose levels

• Studies often single or limited multiple dose, include multiple dose levels and all standard toxicology endpoints

• Most relevant animal model must be used, whether rodents, nonhuman primates or immune compromised animals (SCID, athymic animals)

• Studies must run sufficiently long to look for chronic toxicity and/or biodistribution.

• Studies often performed in animal disease model
Safety (Toxicology) Studies for Cell Therapy Products

- Use intended clinical product if possible
- Generally both sexes must be used, unless only one is justified based on indication and population
- Group sizes: 10/sex/timepoint for rodents, 3/sex for large animals (2/sex for recovery), dogs, monkeys, etc.
- Endpoints: Clinical signs, food consumption, BW, pathology, blood chemistry and hematology
- Studies usually run 1, 3 or up to 6 months following even a single dose (or limited multiple doses)
- Studies should be conducted in accordance with GLPs whenever possible
Part 3: Biodistribution Studies

- Persistence and biodistribution must be established using the intended clinical route of administration.
- Relevant species and dose level
- Sensitive method (PCR or Immunohistochemistry)
- Studies should run sufficiently long (up to 3-4 or possibly even 6 months)
- Use clinical product if possible
Part 4: Tumorigenicity

• For cell therapy products, potential tumorigenicity must be assessed, not often required for gene or tissue therapy

• Usually studied in immunocompromised rodents

• Assessments may often be incorporated into safety studies

• Studies often run out 3-6 months, based on safety design or incorporated into safety study endpoints.

• Limited number of dose levels necessary
New Twists to Nonclinical Study Designs

- Safety endpoints in animal models of efficacy
- Tumorigenicity and biodistribution by intended clinical route of administration
- “Hybrid” study designs combining safety, tumorigenicity and biodistribution into single study
Pre PRE-IND (ppIND) Meetings with FDA

- FDA now encourages early stage (very early) discussions with sponsors to assess design of preclinical studies.
- Prior to formal Pre-IND meeting, ppIND meetings are informal and not minuted. Recommendations are not binding.
- Brief data package of available efficacy and/or early stage toxicology data provided to FDA with proposed clinical plan and basic product information.
- An informal teleconference is held with FDA representatives of OCTGT (usually 60 minutes).
- Sponsor should provide detailed safety study designs for FDA review and comment BEFORE initiating GLP studies.
Pre-IND Meetings

- More formalized meetings with CBER OCTGT preclinical, CMC and clinical review team
- Formally scheduled with FDA project manager
- Multiple copies of briefing package provided for FDA review
- Comments are minuted and binding
- 60-90 minute teleconference or face-to-face
- Briefing package due 30 days before scheduled meeting
- Hold meeting 2-3 months before IND filing or earlier if questions persist, allow time to modify program based on FDA comment
Summary and Take-Home Points

- Consider function and biology of product
- Programs must be tailored individually for product
- Studies must address safety, biodistribution, persistence and tumorigenicity
- Use sufficient numbers of animals
- Run studies out adequately long
- Obtain safety data in early nonclinical studies
- Hold early stage discussions with FDA OCTGT regarding nonclinical program BEFORE initiating studies
- Follow up with Pre-IND meeting with CMC and clinical Information
References


- Full Listing of FDA Guidance Documents may be found at: http://www.fda.gov/cber/genetherapy/gtpubs.htm
Questions or Comments

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