Cellular and Gene Therapy Products - CBER Update

Well Characterized Biological Products
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Cellular and Gene Therapies and Related Products (1)

- Stem cells and stem cell-derived products
  - (hematopoietic, mesenchymal, embryonic, umbilical cord blood, etc)
- Cancer Vaccines and immunotherapies
  - Dendritic cells, activated T lymphocytes (TIL, LAK), B cells, monocytes, cancer cells chemically modified or unmodified
  - Peptides, recombinant proteins
- Somatic cells
  - Allogeneic pancreatic islets, Chondrocytes, myoblasts, keratinocytes, hepatocytes
- Cell lysates and extracts
- Cells plus scaffold/matrix
  - Encapsulated cells
  - Tissue engineering construct
Cellular and Gene Therapies and Related Products (2)

- Plasmids
- Viral vectors
  - Adenoviruses
  - Adeno-associated Virus (AAV)
  - Retroviruses
  - Herpes Simplex Virus
  - Pox Viruses (Vaccinia, Fowlpox, Canary pox)
- Bacterial Vectors (*Listeria, Salmonella*, etc)
- Oncolytic viruses
- Gene modified cells
Total Active Files in OCTGT (IND, IDE, MF) FY 2003-2008
New IND Applications
FY 2003-2008

Cell Therapy
Gene Therapy
New IND Applications – Commercial or Research Sponsors
Trends in Cell Therapy

- Sources of adult stem cells
  - Placental and amniotic membrane, adipose
- Cell Products designed to induce immune tolerance
- Xenotransplantation
- Cells encapsulated in a biomaterial
- Tissue engineering
Trends in Gene Therapy

- AAV Vectors
  - Increased use of serotypes other than AAV-2
    - AAV-1, AAV-8, AAV-1/2, potential use of AAV-5, AAV-6
  - Self–complementary vectors (SC-AAV)
- Use of AD-5/35 vectors
- Increased use of HSV Vectors
- Replicating vectors
  - Oncolytic viruses
  - Bacterial vectors
Active Gene Therapy INDs as of May 2008

- Plasmids
- Adenovirus
- Retrovirus
- Poxvirus
- AAV
- RNA
Challenges

- Small lot size/limited sample volume
- Limited shelf life (due to cell viability)
- Patient to patient variability and cellular heterogeneity
- No terminal sterilization
- Ancillary materials- limited sources, quality
- Lack of reference standards
- Complex manufacturing schemes
- Multiple potential mechanisms of action
- Control of cell differentiation
- Storage/shipping conditions
- Biocompatibility with biomaterials or delivery device
Regulatory challenges

- Most regulations not written with cell and gene therapy in mind
- Limited “success stories” (i.e. licensed products) to learn from or use as examples
- Experience with other biologics such as blood, vaccines or therapeutic proteins and antibodies may not be directly applicable
Common Areas of Need

- Starting cells or cell banks, ancillary materials
  - Safe, consistent quality and activity
  - Availability
- Bioprocessing
  - Manufacturing that is transferable to commercial operation and scale
- Assays
  - Product Release and characterization, stability and comparability protocols
    - capacity to detect product degradation
    - capacity to detect and assess effects of changes
- Reference Standards
Outreach to Cell and Gene Therapy Stakeholders

- Advisory Committees
- Regulations
- Guidance Documents
- Workshops
- Liaison Meetings
- International Harmonization
Safety of Cell Therapies Derived from Human Embryonic Stem Cells
CTGT Advisory Committee
April 10, 2008

- Safety Concerns
- Product Characterization
- Trial Design
CTGTAC April 10, 2008

Safety Concerns

- Stem cells and inappropriate differentiation
  - Teratoma
  - Ectopic tissue
  - Currently concerns restrict direct use of hESC
- Persistence of Undifferentiated Cells
  - Likely to be present in ESC-derived products
  - Proliferation, migration
- Anatomic location and constraints
  - Enclosed space (eg IC vs. IV administration)
Product Characterization

- Establish sensitive analytical methods to detect cells with undesired characteristics
  - Minimize undifferentiated stem cells
- Identify characteristics capable of reliably predicting safety and anticipating clinical effectiveness
  - In-process and lot release testing
- Ensure that products are as safe as possible
  - Current limitations in scientific knowledge
CTGTAC April 10, 2008

Major Considerations

- Stronger than usual proof of concept evidence may be required
- The dose of cells administered to humans should be below the minimum number of cells observed to form tumors in animal models
- First in man clinical applications should be picked carefully due to inherent risks
- Long term follow up recommended due to perceived risk
Regulations/Guidance

- Guidance for Industry: CGMP for Phase 1 Investigational Drugs 7/15/2008
- Current Good Manufacturing Practice and investigations New Drugs Intended for Use in Clinical Trials; Final Rule 7/15/2008
Guidance


- Provides manufacturers of cellular and gene therapy (CGT) products, with recommendations for developing tests to measure potency
- For IND and BLA stages
- Does not make recommendations regarding specific types of potency assays, nor does it propose criteria for product release.

http://www.fda.gov/cber/gdIns/testcellgene.htm
Meetings/Workshops

- FDA/NIST Sponsored Workshop—In Vitro Analyses of Cell Scaffold Products December 6-7, 2007
- FDA Public Workshop: Processing of Orthopedic, Cardiovascular, and Skin Allografts October 11-12, 2007

http://www.fda.gov/cber/minutes/workshop-min.htm
http://www.fda.gov/cber/scireg.htm
International Harmonization Activities

- ICH Gene Therapy
  - ICH Considerations
    - General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors, published 10/2006
    - Oncolytic Viruses, published 11/2008
    - Viral/Vector Shedding, target completion 6/2009
  - ICH Guidance
    - Proposing to further develop Viral/Vector shedding considerations to formal guidance
    - Input from US stakeholders

- FDA-EMEA Cluster on Advanced Therapy Medicinal Products
Contact Information

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General CBER Issues
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CBER Regulatory and Guidance Documents:
http://www.fda.gov/cber/guidelines.htm