Manufacturing Challenges with Cell and Gene Therapy Products: A Health Canada Perspective

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Outline

• Health Canada organization
• Regulation of Gene and Cell Therapy Products
• Types of products- unique regulatory concerns for each – poses challenges to regulators
  – Gene therapies
  – Cell Therapies
  – Oncolytic viruses
• Health Canada expectations
  – Manufacturing development
  – Comparability
• Other Challenges
• Resources available
Mission:
BGTD works to maximize the quality, safety and efficacy of biological and radiopharmaceutical products in Canada.
Where do Cell and Gene Therapies go within BGTD (for Quality Review)?

- Biologics and Genetic Therapies Directorate (BGTD)
  - Centre for Biologics Evaluation (CBE)
  - Centre for Evaluation of Radiopharmaceuticals and Biologics (CERB)

- Virtual Cell and Gene Therapies Group
- Monoclonal Antibodies Division
- Hormones and Enzymes Division
- Cytokines Division
- Radiopharmaceuticals Division
Regulation of Gene and Cell Therapy Products in Canada

- Gene Therapy:
  - Transfer and expression of an exogenous gene compensating for a missing or non-functional endogenous gene including by the following means:
    a) Nucleic acid (DNA or RNA) delivered directly or by viral vector resulting in expression of RNA (mRNA, miRNA or siRNA) and in some cases the translation of protein (directly \textit{in vivo} or via \textit{ex vivo} transduction and re-introduction of cells)
    b) Modification of genes (expression or repair) without transfer of genetic material - Direct treatment of cells \textit{in vivo} or \textit{ex vivo} with regulatory RNA or protein that bind DNA is not considered gene therapy but a therapeutic use of nucleic acids and proteins
    c) Oncolytic viruses for treatment of cancer
Regulation of Gene and Cell Therapy Products in Canada (cont’d)

• Cell and Gene Therapeutic Products
  – Regulated as Biologics, in Schedule D (Biologic Drugs) of the Canadian Food and Drug Regulations
  – Gene therapies are better captured by Schedule D than cell therapies
  – Safety of Human Cells, Tissues, and Organs Regulations for Transplantation Regulations

• Cell therapies meet the definition of a drug as defined by Food and Drugs Act
  – Food and Drugs regulations are widely applicable to Cell Therapies
  – Assisted Human Reproduction Act: embryonic stem cells
Other Applicable Regulations…

• Canadian Environmental Protection Act
• New Substances Notification Regulations (Organisms/microorganisms)
  – An Environmental Assessment is required for new organisms not already on the “Domestic Substances List”
  – Includes viruses (ie. Gene therapy, oncolytic), but not plasmids
  – Sponsors of New Drug Submission (NDS) or Clinical Trial Applications (CTA) for a viral or bacterial vector should notify Environment Canada
  – Review conducted by Health Canada (HECS)
ICH Quality Guidelines

• Although scope may exclude CGT’s, many of the principles can and should be applied
  – Eg. Comparability, stability, viral clearance etc.
• Relevant ICH Consideration Documents:
  – General Principles to Address Virus and Vector Shedding
  – Oncolytic Viruses
  – General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
Health Canada position with Cell and Gene Therapy Products – Manufacturing Considerations

• Early phase Clinical trials
  – Patient safety is main concern

• Later phases
  – More stringent requirements

• Manufacturing
  – Control of raw materials
    • Animal product free
    • Human components appropriately tested
    • Auditing of RM suppliers
    • Cell Therapy – special case
  – Closed manufacturing
    • Reduced risk of contamination
  – Process knowledge
  – Quality system
Cell Therapies
Cell and Gene Therapy Product Manufacture: Autologous Cell Therapy Products

• Batches
  – Usually single batch per patient
• Process Validation
  – Cells obtained from healthy donor
• Comparability
  – Each donor unique
  – Different cell subsets from leukapheresis
  – Different phenotype of purified cells (e.g. IFN-γ production)
  – One approach is to use same donor cells at different sites or using old vs. new manufacturing method
• Safety testing
  – Release prior to final test results
Cell Therapy Product Manufacturing: Other Considerations

- Cell banking system using one or more cryopreserved intermediates
- Cell culture media
  - Use of animal serum
  - Pooled human serum
  - Human platelet isolate/lysate
  - Recombinant growth factors
- Segregation and Tracking of batches
  - Batches may be small and numerous
  - Especially relevant for autologous therapeutic products, directed allogeneic cells
- Closed systems and automation
  - Helps with product segregation and manufacturing consistency
Manufacturing of C&GT Products – Regulatory Concerns

- Inadvertent introduction of adventitious agents
- Inherent variability of manufacturing a product from a living system
  - Variability in PBMCs isolated from patient
    - Huge variability in the number of T-cells
- Precise control of the manufacturing process
  - Purity of product
    - Percentage of T-cells
  - Potency
  - Viability
  - Presence of cells not intended to be in final product
    - NK cells, B-cells
  - Minimizing other impurities
    - Cell Therapies
      - Cytokines, beads
Manufacturing of C&GT Products – Regulatory Concerns (cont’d)

- Viral vector design
  - Integration concerns
  - Replication competence

- Manufacture
  - Multiproduct facilities
    - No contaminating virus from other products

- AAV mediated Gene Therapies – process and product-related impurities
  - Host-cell DNA, plasmid DNA
  - Host Cell Protein
  - Residual CsCl
  - Residual iodixanol
  - Relevance of empty capsids?
    - If they are a part of the mechanism of action this must be demonstrated and (eventually) reflected in potency assay(s)
    - If not, then considered a product-related impurity
    - In both cases, must be controlled
Inadvertent Introduction of Adventitious Agents

- **Raw Materials**
  - From accredited sources
  - Appropriately screened
  - Scale-out
- **Closed manufacturing**
  - Commercially available units
  - Self contained
  - Disposable materials (tubing)
  - Vapour Phase H2O2 sterilization
Management of Inherent Variability

• Raw Materials
  – Autologous Cell Therapies – donor variability
  – Auditing suppliers
• Operators
  – Appropriate training
• Equipment
  – Appropriately qualified
• Process
  – Understanding CQAs early
  – Risk based
    • patient
    • product
Control of Manufacturing Process – QbD concepts

- Generating Process Knowledge
  - Iterative process – collection of process data
  - Data collection through characterization
    - Cell therapies- phenotypic studies based on cell markers (e.g. central memory, effector memory, effector cells, naïve T-cells)
    - Cytokine production profiles
    - AAV-based therapies - plating densities, optimization of transfection reagents, plasmid DNA amount
  - Defining CPPs through Process Characterization/Challenge studies
  - Investment required
- QbD approach or aspects of QbD
- Defines control strategy
Autologous Cell Manufacturing: Transitions to Marketing Applications

• Progression from Clinical Trials to Marketed product
  – Increased automation
  – Advantages
    • Increased product quality and consistency
    • Reduced human/product contact (closed system)
  – Disadvantages
    • Initial costs
    • Numbers of units due to multiple small volume batches
AAV manufacturing: Transitions to Marketing Applications

- Columns/density gradient purification
  - Pro: Can separate empty capsids from viable capsids
  - Con: not scalable, impurity testing
- Column only manufacturing
  - Pro: large scale, purity
  - Con: cannot separate empty capsids, part of the product
Manufacturing - General Considerations

- Mapping and establishing CQAs early
  - Aids in ensuring product understanding - particularly for comparability studies following manufacturing changes
- In process controls
  - Ensures process consistency
- Knowledge of process is essential
  - Understand limitations
- QbD approach?
Emerging Science/Technology

• CAR T-cells
  – Optimal T-cell phenotype?
  – Indication specific limitations
    • Tumour microenvironment
    • Localized immunosuppression
  – Different manufacturing approaches needed (ie. Different T-cell subsets for solid tumours vs. liquid tumours)
  – Expression of transgenes to relieve tumor mediated immune checkpoint inhibition (PD-1)
  – Gene editing to overcome HLA restriction
  – Viral vector – consistent transduction capability

• AAV
  – Directed evolution of different serotypes or strains
  – Applies to Oncolytic viruses also
Comparability Studies

- Challenging even with conventional biologics
- Comparability data required to link clinical trials
  - Process improvements, fewer impurities
  - Manufacturing site change
  - Potency assay or surrogate
- Risk based selection of CQAs for analysis
  - Eg. Cell therapy – yields, viability, fold expansion
- In depth knowledge of the process is helpful
  - Accumulated data – used to calculate equivalence acceptance criteria
  - Expectation approach
- Scale-up – AAV
  - Can force manufacturing change
- Acceptance criteria
  - Linked to historical results
Relevant Guidance Documents

- Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications
- Guidance Document: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans
Harmonization

• Health Canada embraces harmonization of regulations with respect to Cell and Gene Therapeutic Products
• Contributor to international harmonization efforts through ICH
• Welcome discussion if our position differs significantly from other regulatory authorities
Summary and Conclusions

- Cell and Gene Therapy Products are evolving at a rapid pace and Marketing applications will increase
- Autologous Cell Therapy Products pose some regulatory challenges, however, application of sound risk, science, and knowledge based approaches will help to bridge gaps
- Focus on quality and product knowledge at earliest possible stages is encouraged
- Early engagement with Health Canada is encouraged
Health Canada

- We welcome regulatory questions via pre-CTA meetings or pre-NDS meetings in-person or via teleconference
- Contact Office of Regulatory Affairs

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Thank you for your attention!