

Phase-Specific Control Strategy Considerations for Cell and Gene Therapy Products – a Canadian Perspective

2020 CASSS Cell and Gene Therapy Products

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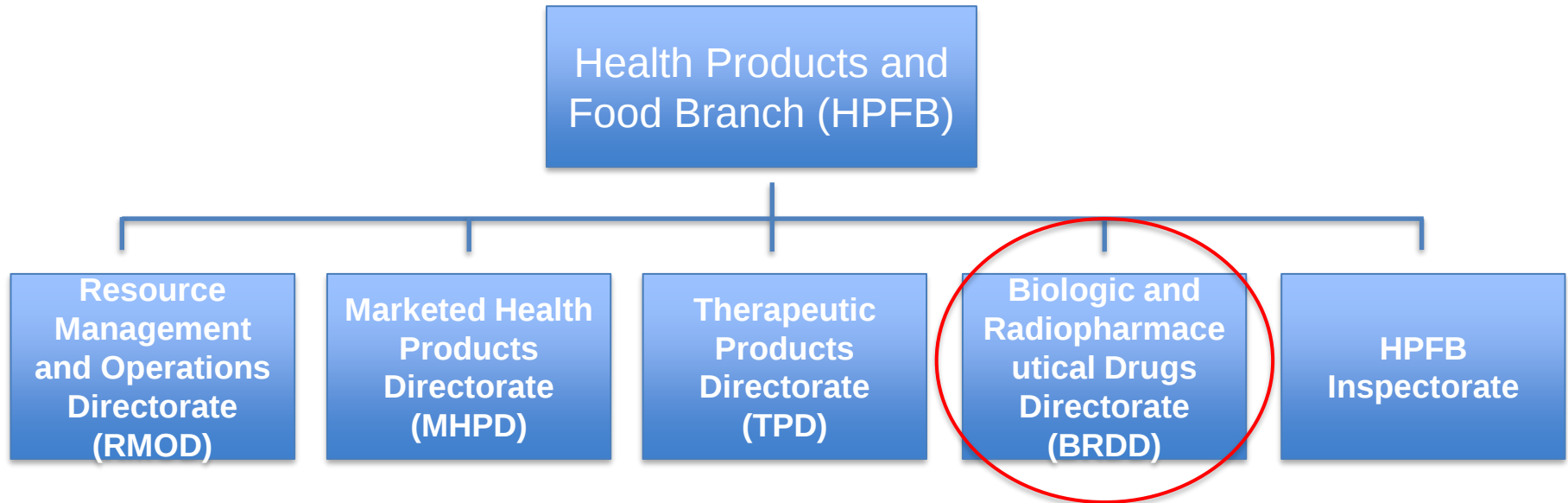
YOUR HEALTH AND SAFETY... OUR PRIORITY.



Outline of talk

- Health Canada Background
- Health Canada experience with Cell and Gene Therapy Products
- Cell and Gene Therapy Product Guidance Documents
- Control Strategy Background
- Phase appropriate expectations for C> products at various points in the control strategy
- Summary

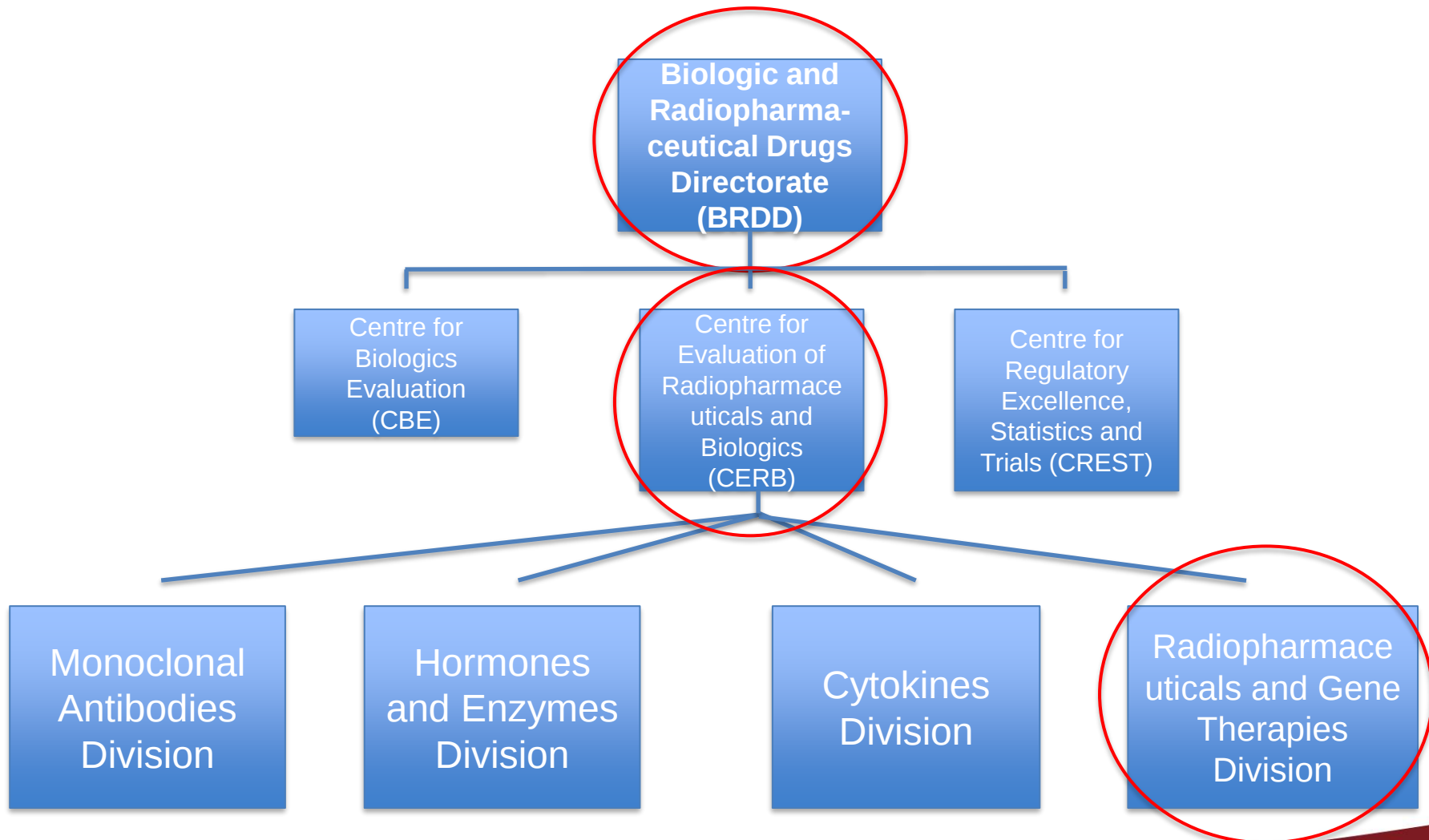
Where does BRDD fit in?



Mission:

BRDD works to maximize the quality, safety and efficacy of biological and radiopharmaceutical products in Canada.

Where do Cell and Gene Therapies go within BRDD (for Quality Review)?



Regulation of Gene and Cell Therapy Products in Canada

- 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 therapy products 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

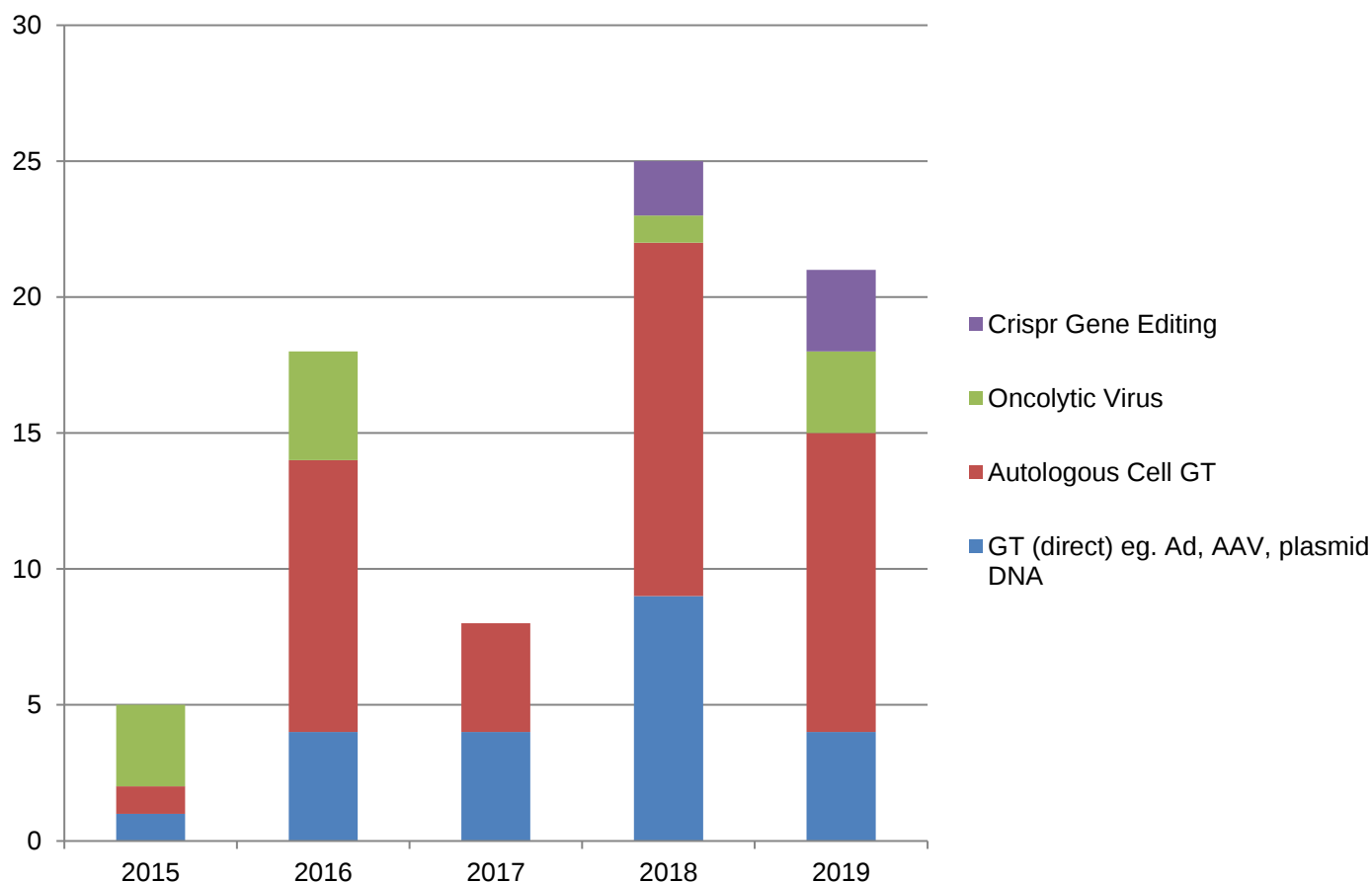
ICH Quality Guidelines

- Although scope may exclude CGT's, many of the principles can and should be applied
 - Eg. viral clearance, stability (Q5A), stability (Q5C), Comparability (Q5E) etc.
- ICH Q8, Q9, Q11
- 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

Other Guidance Documents Considered

- FDA Cell and Gene Therapy Guidance Documents
 - Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) 2020
 - Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up 2020
- EMA Cell and Gene Therapy Guidance Documents
 - EMA/CAT/80183/2014- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
 - EMA/CAT/GTWP/671639/2008 - Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
 - CHMP/BWP/2458/03 - Guideline On Development And Manufacture Of Lentiviral Vectors

Recent Approved Cell and Gene Therapy Submissions to Health Canada – CTAs by Product Type



Approved products in Canada

- Kymriah
- Yescarta
- One AAV gene therapy product NDS under review, one in screening

Control Strategy

What:

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality.

Why:

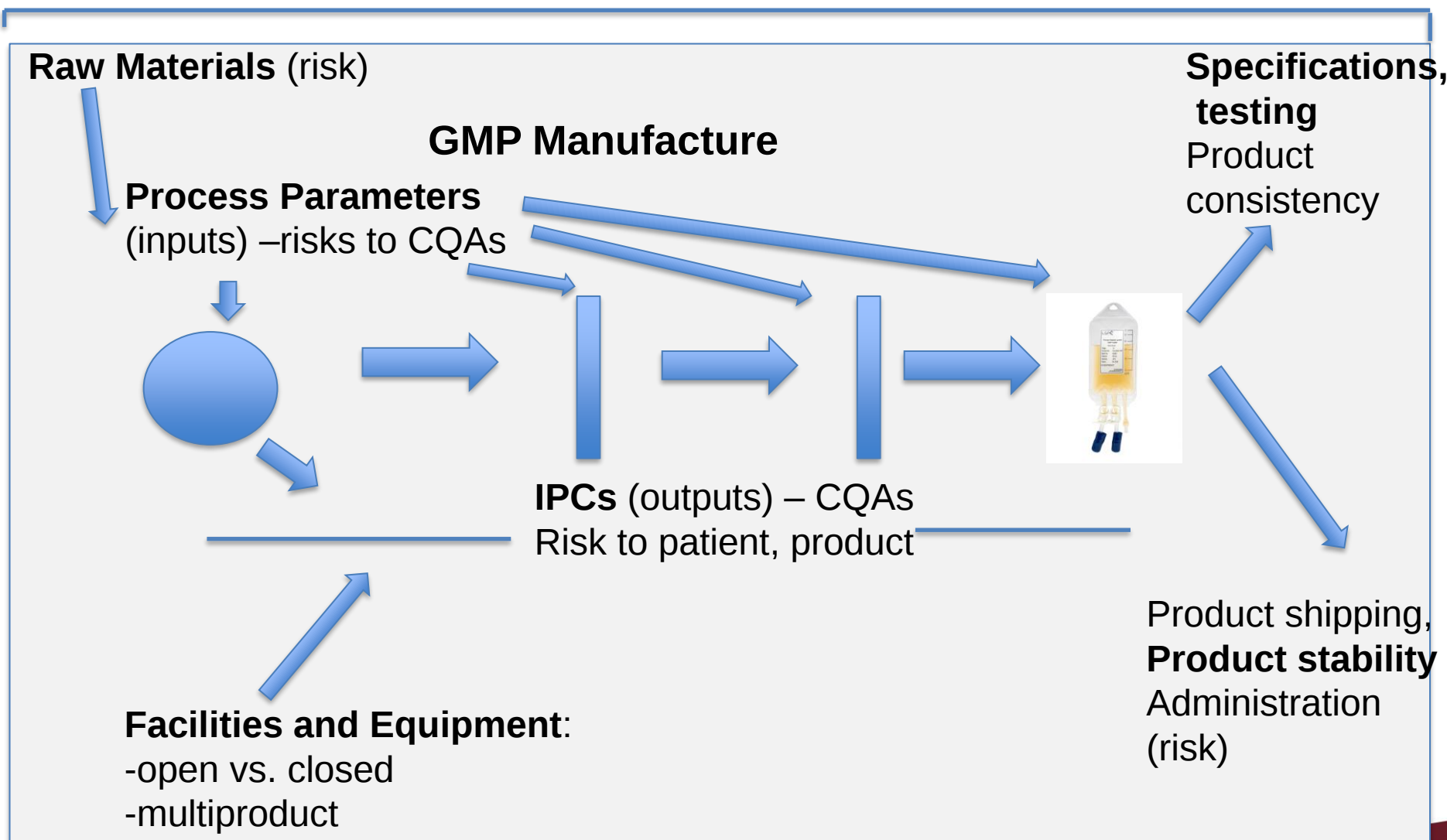
“A control strategy is designed to ensure that a product of required quality will be produced consistently” – ICH Q8, Q10

How:

A holistic approach to defining and achieving product quality through consideration and ranking of all risks potentially impacting product quality:

Control Strategy

Quality Risk Management



Quality Risk Management (ICH-Q9) - Product Quality Risk Assessment

- Backbone of the control strategy
- All possible risks to patient and product safety should be considered
- Details not required for early phase submissions

Control Strategy – developmental approaches

- Control Strategy = Management of Risks
- QTPP, Product Quality Risk Assessment, Assign CQAs based on risk
 - Aids in testing strategy Specification setting/comparability studies, based on process and product understanding
- Enhanced vs. traditional (ICH Q8, Q11)
- QbD – process understanding (ICH Q11)
 - Setting appropriate controls science based and reflects a greater understanding of the process and robustness of the process
- Iterative approach – process understanding and robustness through repetition - PARs
- Hybrid approach

Phase Appropriate Control Strategy Considerations

- Early phases – emphasis predominantly on patient safety
 - Raw materials of biological origin
 - Facilities – multiproduct?
 - Virus safety, sterility, endotoxin, replication competence, genome integration
 - In-use stability
 - Impurity clearance
 - Consideration of next phases – comparability, potency assay (e.g. AAV-GT, oncolytic virus), tightening of specifications
 - Chain of custody (CAR T-cell products)
- Later phases – safety and...
 - Process capability/specifications - focus expands to include more robust evaluation of controls
 - Stability program
 - Manufacturing process development (e.g. comparability)
 - Potency assay
 - Time frame from Early to late stages is often compressed with C> Products
 - Positioning for market authorization

Raw materials

- Area of concern for Biologics, including C> Products
 - Most contaminations arise from raw materials
 - Can be a source of variability
 - Understanding variability (e.g. CAR T-cells – healthy donor vs. patient)
- Materials of biological origin – Safety Concern
 - Human origin (e.g. Human serum or human serum albumin) – monitor for presence of human pathogenic viruses
 - Description of the source (e.g. FDA approved facility)
 - For inclusion in a Canadian product, should be sourced from a Canadian source.
 - Clinical Trials: If not, a note in the informed consent letter indicating excipient or RM is not from a Canadian approved product
 - Marketing: If not, a letter from the supplier indicating the US Product meets the same quality standards as the Canadian product including viral clearance
 - Bovine (e.g. FBS, BSA – country of origin, BSE/TSE safety certificate, bovine virus testing)
 - Porcine (e.g. trypsin) – testing for porcine viruses

Manufacturing parameters

- Based on PQRA, process development studies and resulting understanding of parameter impact on CQAs
- Greater knowledge, tighter control
 - E.g. CAR T-cell: input parameter: MOI utilized for cell transduction
Output: transgene copy number/ percent transduction (CQAs)
 - E.g. AAV mediated gene therapy product – cell density for transfection
- Understanding of process
 - Evolves through development
 - Early phases – parameter ranges less defined
 - Later phases – establishment of MORs, PARs
 - Capability of process to clear impurities (e.g host cell DNA, plasmid DNA)
 - Viral clearance (AAV-gene therapies)
- Manufacturing parameters more closely examined during review of submissions for market authorization

In-process controls

- Safety-related IPCs considered critical for all phases (i.e. bioburden, endotoxin, mycoplasma)
- Other in-process controls can evolve with development and greater understanding
 - E.g. cell viability, cell number for CAR T-cell product, empty:full capsid ratio for AAV-gene therapeutic product
- Early phase: more reliance on release specifications
- Later phase: tighter control of process
- For some products, some key tests are performed in-process (e.g. for some CAR T-products, potency assayed prior to formulation)

Specifications

- Should be reflective of understanding of critical quality attributes (i.e. what is being controlled)
 - Stems from QTPP, PQRA
 - Early Phase: Safety
 - Impurity control – understanding of toxicity, safe levels (e.g. AAV – CsCl, iodixanol, plasmid DNA, empty capsids, transfection reagent, CAR T – NK cells)
 - Specifications reflective of experience with toxicological and engineering batches, evolves with manufacturing and clinical experience
- Early phase: specifications can be wider (and should be justified)
 - limited batches
 - Variability – process, raw materials, parameters
- Later phase: specifications tighter
 - More manufacturing experience
 - Less variability – raw materials more consistent, parameters refined
 - E.g. CAR-T cell product: removal of replication competent retrovirus testing from Drug Product release testing
 - Exception: Orphan drugs

Testing/Methods

- Method validation not required for pre-market submissions
 - must be scientifically sound (capable of detection of analyte (ICH Q2))
 - Suitably controlled
- Establishment of a reference standard
 - Representative batch
- Potency assay
 - Key CQA for Cell and Gene Therapy Products
 - Often complex due to MOA
 - Timing of development – short CMC development time/complexity of assay
 - May be a “matrix” type assay that assesses two or three product characteristics
- E.g. AAV gene therapy/ Oncolytic viruses
 - Early phases titre
 - Later phases capture infection or cell death/expression and functionality of expressed protein

Stability

- ICH Q5C
- Early phase:
 - Real time studies for early batches
 - In-use stability studies covering administration time and conditions important
 - If product frozen, freeze thaw studies
- When used “fresh”, studies should support requested shelf life
- Container closure
 - Should be same MOC as product container closure
- Later Phase:
 - Accelerated/Stress studies – covers excursions, provides understanding product behaviour and degradation pathways
 - Important for comparability studies
- Granting requested shelf life

Facilities and Equipment

- Facility product dedicated?
- Open vs. closed manufacturing
- Qualified equipment
- Trained operators

Summary and Conclusions

- Control strategy for Cell and Gene Therapy Products is built on the foundation of the Product Quality Risk Assessment and built out from Process Development and Process Characterization studies
- Cell and Gene Therapy products are diverse and presents regulatory challenges, however, application of sound risk, science, and knowledge based approaches will help to bridge gaps
- Early Phases: focus on safety risks
- Later Phases: refinements in control strategy, positioning for market authorization
- Early engagement with Health Canada is encouraged

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

Health Canada

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

Office of Regulatory Affairs

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THANK YOU