Regulatory considerations for Global Haplobank

Jacqueline Barry
### Good Practice

**Cell & Tissue Procurement**
- Donor consent
- Cell procurement
  - Screening
  - Testing
- Traceability
- HLA typing

**MCB production**
- Active substance
- Reprogramming
- QC/Standards
- Methodology
- Characterisation
- Stability
- Sterility

**Manufacture to clinical product**
- Multiple products
- QC/Standards
- Methodology
- Characterisation
- Stability
- Sterility

**Testing**
- Preclinical safety assessment
- Clinical Trial
- Post-marketing Surveillance

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**GTP**

**GMP**

**GLP, GCP, GVP**
**Cell & Tissue Procurement**
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- HLA typing

**REGULATORY DOCUMENTATION**
- International Guidelines
  - WHO
  - ISBT
- International and Local Accreditation
  - JACIE/FACT/Netcord etc
- Local Legislation and Guidelines
  - e.g. EUTCD, 21 CFR 1271
## Cell and Tissue Procurement

<table>
<thead>
<tr>
<th>Country</th>
<th>Guidelines/Acts</th>
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</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>The guide for Good Manufacturing and Laboratory Practice from the Act 119/2012</td>
</tr>
<tr>
<td>Australia</td>
<td>Australian Regulatory Guidelines for Biologicals</td>
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<tr>
<td>Brazil</td>
<td>In draft</td>
</tr>
<tr>
<td>Canada</td>
<td>Schedule D of the Food and Drugs Act</td>
</tr>
<tr>
<td>EU</td>
<td>EUTCD/EUBD&lt;br&gt;Translated differently in each MS</td>
</tr>
<tr>
<td>Korea</td>
<td>Human Tissue Safety and Control Act</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>In draft</td>
</tr>
<tr>
<td>India</td>
<td>National Guidelines for Stem cell Research</td>
</tr>
<tr>
<td>US</td>
<td>361 of the PHS Act &amp; 21CFR 1271&lt;br&gt;HTC/P guidelines and cGLP guidelines for procurement</td>
</tr>
</tbody>
</table>
Good Practice

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MCB production
- Manufacture to clinical product

Testing

ISSUES
- Autologous/Allogeneic
- Variable starting material
- Raw materials
- Future test results
- Viral/TSE safety - Unknown transmissible agent
- Malignancy
- Consent issues
- Ethical concerns

REGULATORY
- Mandatory testing requirements
- Traceability requirements e.g. 30y EU & Japan; 15y US
- Testing using territory approved kits
- Vigilance
- Licensure of collection organisations
- Accreditation (JACIE/FACT ETC)
- Inspection report sharing
- Source material
CELL BANKING AND DOWNSTREAM MANUFACTURE

Cell Banking – GTP/ GMP
REGULATORY DOCUMENTATION

- International Guidelines for manufacture and testing at GMP
  - WHO
  - ICH
  - PIC/S
- Local Legislation and Guidelines
- Local Competent Authority Inspections (MRA)
ICH Guidelines

- Q2(R1): Validation of Analytical Procedures
- Q4: Pharmacopoeias
- Q5A(R1): Viral Safety Evaluation of Biotechnology Products
- Q5C: Stability Testing of Biotechnological/Biological Products
- Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotech/Biological Products
- **Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process**
- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- Q8(R2): Pharmaceutical Development
- Q9: Quality Risk Management
- Q10: Pharmaceutical Quality System
- Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
- Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
EU guidance (selection)

- Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (CHMP/CPWP)
- Guideline on human cell-based medicinal products (EMEA/CHMP/410896/06)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008)
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/05)
- Guideline on safety and efficacy follow-up - risk management of ATMPs (EMEA/149995/08)
- Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/08; 2010)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/08; 2012)
- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)
- Points to Consider on xenogeneic cell therapy (CHMP/1199/02) - revised
- Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing ATMPs (EMA/CAT/418458/08; 2010)
- Reflection paper on stem cell-based medicinal products (CAT/571134/09)
- Xenogeneic cell-based medicinal products (CHMP/CPWP/83508/09)
**GENERAL ISSUES**
- Aseptic processing – prevention of (cross) contamination
- Reprogramming method
- Different culture methods; Media, Passaging
- Control of proliferation/differentiation
- Testing; identity, purity, characterisation
- Standardisation
- Stability testing
- Labelling
- Documentation
- Traceability

**REGULATORY ISSUES**
- GTP or GMP - definition of GMP
- If GTP derived – testing requirements for MCB as a starting point
- Mandatory testing requirements
- Testing using territory approved kits
- Inspection report sharing
**GENERAL ISSUES**
- Aseptic processing – prevention of (cross) contamination
- Testing; identity, purity, characterisation
- Standardisation
- Stability testing
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**REGULATORY ISSUES**
- Mandatory testing requirements
- Testing using territory approved kits
- Adventitious agents
- Characterisation, potency, identity
- Inspection report sharing
TESTING

Preclinical
Clinical
Stability
GENERAL ISSUES
- Traceability
- Stability testing and re assigning of shelf-life
- Different registration procedures

REGULATORY ISSUES
- Different donors different lots/batches?
- Preclinical and clinical requirements differ in different territories
- Preclinical testing – suitable animal model
- Clinical testing
iPSC Bank
Defined Specification

Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
Donor 6

iPSC line 1
iPSC line 2
iPSC line 3
iPSC line 4
iPSC line 5
iPSC line 6

Product 1
Product 2
Product 3
Product 4
Product 5
Product 6
Next steps

- QC standardisation
- Common Specification
- Resource databank
- Engagement with regulatory bodies