GMP challenges in cellular therapy products

Gerry McKiernan, Quality Manager
Agenda

Cellular Therapy:

• Landscape
• GMP Challenges
• Future
Winner Nobel Prize in Physiology or Medicine 2012 (iPSCs)
Dr. Berman talks about his research in fat stem cells.

OVERVIEW OF DR. Berman's STEM CELL THERAPY

ADULT (NON EMBRYONIC) MESENCHYMAL STEM CELLS

Most people (doctors included) believe that stem cell therapy is still several years away from being available to the public. However, since 2010, in association with my partner, urologist Elliot Lander, MD, FACS, we have been conducting stem cell deployment as part of an ongoing investigative project collecting data on thousands of treated patients. After several successful outcomes in the orthopedic arena that I obtained in collaboration with orthopedic surgeon, Dr. Tom Grogan, Elliot and I formed the California Stem Cell Treatment Center followed a year later by the Cell Surgical Network – the world's largest network of stem cell physicians utilizing technology we developed with renown Korean plastic surgeon, Dr. Lee Hee Young. We currently teach doctors from the USA and worldwide our techniques using the CSN Time Machine® to effectively harvest and process fat into stromal vascular fraction (SVF) rich in stem cells. Starting with a 10 minute mini-liposuction painlessly done under local anesthesia, this 1 ½ hour process has yielded results that have been successfully recapitulated all over the world. Currently, there are about 100 CSN centers in the US and many more throughout the world, including dozens in China in association with our partners, RE Stem Biotech.
CAR-T Cell Potential

Rapid and sustained response to Chimeric Antigen Receptor T cell therapy in double hit diffuse large B cell lymphoma

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IMAGE 1  (A) Baseline disease status at the time of initiation of lymphodepleting chemotherapy. (B) Disease status 10 days after infusion of CAR T cell therapy. (C) Disease status at day 60 post infusion of CAR T cells
T-Cell Activity 2018

291 CAR-T products in development, 161 in trials
Cell Therapies PTY LTD

- Independent CDMO with PeterMac as shareholder
- In operation for 15 years
- 10 Grade B cleanrooms and associated storage and lab space
- Administered various TGA licences on behalf of clients in the past
- Currently hold generic licences for T-Cell manufacture, clinical trials and commercial supply (1st in Australia)
Located on Level 9, Peter MacCallum Cancer Centre (VCCC)
PeterMac
PeterMac
PeterMac - The Art Gallery
Autologous CAR T-cell therapy process

Day 1 (Starting material)
Apheresis at a hospital
Cryopreservation – hospital or hub?

Clinical site
Cells Collected / Frozen

GMP Manufacturing
Day 2+ Manufacturing
Day 3+ Manufacturing
Day 5+ to 11+ Manufacturing

Clinical site
Infusion
Typical supplier qualification strategy

• Identify reputable supplier
• GMP Accreditation
• History of supply
• Other products on the market
Hospital apheresis units

- GMP Accreditation (exists but rare) ✗
- History of supply ✗
- Supply of other products ✗
Typical starting material strategy

External supplier assessment:
• Technically competency of staff
• Training / GMP training
• Equipment / validation
• Document control / archiving
• QC testing lab
• Facility – structure, waste, cleaning, cross contamination
• QMS systems - Dev., CC., CAPA, Risk Management
• Materials management / status labelling
• Supplier qualification
• Quality independent from production
Typical starting material strategy

Hospital apheresis units:
- Technically competency of staff ✓
- Training / GMP training ✓
- Equipment / validation ✓
- Document control / archiving ✓
- QC testing lab ✓
- Facility – structure, waste, cleaning, cross contamination ✓
- QMS systems - Dev., CC., CAPA, Risk Management ✗
- Materials management / status labelling ✗
- Supplier qualification ✗
- Quality independent from production ✗
Typical starting material strategy

- Hospital apheresis units
- Technically competency of staff ✓
- Training / GMP training ✓
- Equipment / validation ✓
- Document control / archiving ✓
- QC testing lab ✓
- Facility – structure, waste, cleaning, cross contamination ✓
- QMS systems - Dev., CC., CAPA, Risk Management ❌
- Materials management / status labelling ❌
- Supplier qualification ❌
- Quality independent from production ❌

Critical deficiencies to meet GMP requirements
Quality in apheresis hospital units

• Hospitals already run quality systems, however these are solely focussed on the patient
• There is little to no understanding of product quality or GMP within the clinical setting
• Absence of manufacturing process understanding
Clinical vs Manufacturing Quality focus

• Clinical priority:
  • Patient safety is paramount
  • Maximum patient access
  • Wide product specification to allow for patient factors

• Manufacturing priority:
  • Low process variability
  • Tight product specification
  • Quality oversight
Why is quality overlay so important in apheresis?

• Most critical but difficult to control starting material
• A cited cause of manufacturing failure
Apheresis variability & manufacturing drives product variability

- **What manufacturing wants**
- **T-cells**: collection efficiency, minimise undesirable impurities
- **Collection efficiency for CD3**

**Other factors to consider**

- Impact of specialised requirements on standard unit operations
- Ability/willingness to collect additional data
- Characterising variability and impact on manufacturing

### Granulocyte contamination: peripheral blood apheresis

![Granulocyte contamination chart]

### Cryoprotectant variability

<table>
<thead>
<tr>
<th>Cryomedium content</th>
<th>Number of EU sites (n=14)</th>
<th>Number of JP sites (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSA + heparin + N.S.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HSA + N.S.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ACD-A</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HES/Voluven</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Plasmalyte + HSA + ACD-A</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>HSA + ACD-A</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Plasmalyte + HSA + HES</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cryostor 10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serum + N.S.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MEM</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Cell therapy products are often variable

Variable dose for autologous product

- Is the product the same from each donor?
- How many donors do you need?
- How many are there?
Collection Process and Variables

• Multiple sources of variability and risk (Inter-collection centre):

• High donor variability, especially when the patient is un-mobilised
  • Bone marrow function
  • Procedure tolerance
  • Venous access

• Moderate operator variability
  • Knowledge and experience, particularly for specialised collections – tweaking?
  • Collection efficiency and product purity
  • Equipment

• Microbial contamination risks from skin
Collection Process and Variables

• Multiple sources of variability and risk (Intra-collection centres):

  • Multiple collection centres
  • Variable equipment makes used for collection
  • Variable consumables
  • Multiple cryopreservation labs
  • Differing cryoprotectants and control rate freezer models
  • Multiple quality systems
  • Highly complex logistics, inexperienced logistics personnel
Cell Therapies / Peter Mac Model

Apheresis unit managed as a manufacturing facility
- CTPL QMS oversees apheresis and cryopreservation in hospital
- GMP trained clinical staff
- Full equipment/process validation
- Full GMP QMS operating within apheresis unit
- GMP compliant collection facility, including HVAC
- Full records traceability
- Full materials and supplier control
- Quality separate from Manufacturing (clinical collection) org structure
- Dedicated Quality resource embedded within apheresis unit
- Product Quality unit independent from hospital Quality unit
- Clear delineation of responsibility for product and patient
- Weekly/quarterly Quality review meetings which include clinical staff

Outcome:
PeterMac first hospital approved in Australia for Kymirah for treatment of DLBCL
Alternative Model

Risk Evaluation and Mitigation Strategy (REMS)

- Typical manufacturer / supplier model
- Moves burden from regulator to manufacturer
- Allows manufacturer to apply own quality standards over each collection facility

Issues:
- Apheresis units audit fatigue
- High risk for error due to competing Quality requirements from different manufacturers
GMP - Good Aseptic Practice
GMP - Good Aseptic Practice

CTPL Manufacturing Facility

- Unclassified
- Grade D
- Grade C
- Grade B
GMP - Good Aseptic Practice

CTPL Manufacturing Facility

Unclassified
Grade D
Grade C
Grade B
<table>
<thead>
<tr>
<th>Expected</th>
<th>Actual</th>
<th>Solution</th>
</tr>
</thead>
</table>
| Tightly controlled process parameters         | Large process variables, large specifications e.g.  
- Transduction efficiency: >5% (10-35%)  
- Vector Copy Number: 1 – 3  
- Cell viability >70% >80% >90% >10%  
- Impurity profiles, different batch to batch. Exacerbated by unmet clinical need. | Justification in clinical trial or product registration                  |
| Tight specification for starting material     | Large process variables in starting material                                                                                                                                                         | None, accepted as process variable                                      |
| High quality starting material                | Starting material of variable quality e.g. cell viability, high levels of debris, cells impacted by various patient treatment regimes - ‘happy’ cells                                                                                                                                 | None, accepted as process variable                                      |
| Material used in validation replicates those intended to be used in released product | Ethical issues around collecting patient material                                                                                                                                                     | Using healthy donor collections as surrogate                             |
## GMP - QC of Final Product

<table>
<thead>
<tr>
<th>Expected</th>
<th>Actual</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tightly defined QC test methods, no opportunity for operators to manipulate data</td>
<td>Due to patient to patient variability, cell scatter changes for each batch. Difficult to define generic flow cytometry gating protocols</td>
<td>Lock method, audit trails and procedures in place on gating changes</td>
</tr>
</tbody>
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<thead>
<tr>
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<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full safety testing of product prior to release e.g. - replication competent testing for vectors by cell culture - sterility testing - particulate visual inspection</td>
<td>- Cell culture testing takes 10 weeks in the US. Patient will expire prior to release of product - Cell culture sterility test takes 2 weeks, patient may expire - Not possible to perform to opaque nature of cell based products</td>
<td>TGA approval to release prior to testing. Approval for alternative test methods e.g. qPCR or rapid microbial testing (BacT). Validate process for particles.</td>
</tr>
</tbody>
</table>
# GMP - Release of Final Product

<table>
<thead>
<tr>
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<th>Actual</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full testing of product prior to release</td>
<td>Limited test results, including safety tests. Especially applicable to fresh release products</td>
<td>TGA approval. Take additional safety tests earlier in the process. Monitor and ensure other risk controls are operational e.g. aseptic qualification, staff culture. Conduct post release testing.</td>
</tr>
<tr>
<td>Rejection of product not meeting specification</td>
<td>Allowed if treating clinician determines that the benefit of administration outweighs the risk</td>
<td>Procedure in place to allow for transfer of responsibility for release to clinician.</td>
</tr>
<tr>
<td>Expected</td>
<td>Actual</td>
<td>Solution</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Product remains integral and efficacious until administered to patient</td>
<td>Compliance but with difficulties to be managed:</td>
<td>- Quality agreements with transport couriers</td>
</tr>
<tr>
<td></td>
<td>- Product needs to shipped at $&lt;140^\circ$C</td>
<td>- Only using couriers with guaranteed slots on flights</td>
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<td></td>
<td>- Shipper tipping over during transport</td>
<td>- Only using couriers with preapproved customs clearance</td>
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<td>- Loss of data monitoring during shipping</td>
<td>- Shippers with networked remote monitoring</td>
</tr>
<tr>
<td></td>
<td>- Shipper not maintaining temp</td>
<td>- Shippers with tilt sensors</td>
</tr>
<tr>
<td></td>
<td>- Shipper getting stuck at customs</td>
<td></td>
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</tbody>
</table>
# GMP - Post release

<table>
<thead>
<tr>
<th>Expected</th>
<th>Actual</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product remains integral and efficacious until administered to patient</td>
<td>- Difficulties in storage of product at point of infusion</td>
<td>- Storage considerations reviewed as part of site selection, responsibility for storage defined, pharmacy or ward?</td>
</tr>
<tr>
<td></td>
<td>- Difficulties in management of thawing of product:</td>
<td></td>
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<td></td>
<td>- water bath vs automated</td>
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<td></td>
<td>- over heating of product</td>
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<td></td>
<td>- extended time since thawing</td>
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<tr>
<td></td>
<td>- Quality agreement in place with hospital</td>
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<td></td>
<td>- Extensive training of clinical staff</td>
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<td></td>
<td>- Escalation pathway to manufacturer for deviations during administration (especially applicable during commercial phase)</td>
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</tbody>
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CAR-T cell, complex logistics

**Clinical Team**
- Patient is identified, and Clinical Trial/Commercial access eligibility is reviewed
- Clinical Trial eligible
- Commercial Program eligible
- Patient is enrolled onto Clinical Trial
- Communication with manufacturing facility
- Patient information form is approved and patient consent form is completed
- Communication with manufacturing facility
- Haem & Clinical Trial Co-ordinator
- Patient is referred to Apheresis for collection

**Apheresis**
- MNC(A) Product transported to Cryopreservation
- Standard MNC(A) procedure is performed
- Standard patient screening and consent is performed
- Cell Therapies Specialist Nurse
- CAR T Nurse Consultant

**Cryopreservation**
- Storage occurs within Tank 3 utilising rack system
- Communication of product attributes to manufacturing facility
- Co-ordination of slot and shipper/label arrival
- Product remains in storage until hangtags and shipper arrives
- Product is packaged and shipped to manufacturing facility. Communication with manufacturing facility of product arrival.
- CAR T-Cell product manufactured at external facility
- Shipper (final product) is received
- Cryopreservation staff and CAR T-Cell Project Manager transport final product to Apheresis
- Final product is transferred to tank 3 racking system
- Final product is transferred to PMCC dry shipper
- Patient not for immediate infusion
- Patient for immediate infusion

**Apheresis**
- Patient is consented for CAR T infusion and inpatient admission
- Apheresis staff thaw and infuse final product (via CHARM pathway)
- Communication with manufacturing facility
- CAR T Nurse Consultant
- Cell Therapies Specialist Nurse
- Patient is transferred to ward

**Clinical Team**
- Communication with manufacturing facility
- Clinical adverse events are reported to client by Clinical Team
- CAR T Nurse Consultant
- Haem & Clinical Trial Co-ordinator
- Patient is monitored for Adverse Events

3 December 2019
Future – Code Change

TGA to move to PIC/S Annex 2a?

Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products

Version 1.0 April 2013

Annex 2A
Manufacture of Advanced Therapy Medicinal Products for Human Use

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, genome editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this annex. In a medicinal product, the genetically modified cells can be presented alone or combined with medical devices. This annex provides additional and specific guidance on the full range (as defined in the glossary) of ATMPs and the active substances that are used in their manufacture. Although one of the objectives of this present revision was to prepare a document that would stand for several years the field is quickly changing; it is recognised that amendments may be necessary to accommodate technological
• **A $105 million** co-investment from the Australian government, CTPL & Peter Mac Foundation

• **New Manufacturing Capacity**

  Commitment to build 1700 m$^2$ additional commercial manufacturing capacity at Peter Mac to support clinical and commercial CAR-T cell therapies for Australian patients

• **Increased Clinical Capabilities**

  Create a new 14 bed/chair clinical unit focused on cellular immunotherapy treatments

• **Increased trials activity**

  Additional clinical and pre-clinical research resources to support new treatment candidates, and for eligible Australian projects, to fund CTPL manufacturing for Pilot/Phase 1 studies
thank you