The importance of regulatory aspects for global commercialization

Tim Oldham PhD, Chief Executive Officer
Cell Therapies Pty Ltd

Dominic Wall PhD FFSc (RCPA), Chief Scientific Officer
Cell Therapies Pty Ltd

Chair Legal and Regulatory Committee - ISCT ANZ region

Operations Director - Pathology & CBCT
Peter MacCallum Cancer Centre
Regulatory challenges with cells and tissues

- Small molecule 0.5nm
- Therapeutic antibodies 5nm
- Viral vectors 50nm
- Eukaryotic cell therapies 50,000nm
Regulatory issues and global commercialization

• Manufacturing and product risks
• Inherent challenges to a “fit” in a regulatory scheme
• Regulatory risks - exemptions

• A robust harmonised regulatory framework with minimal exemptions is a precondition for developing a global cell therapy program: how is Malaysia positioned?
Inherent challenges for cell & tissue products

**Medicinals**
- No collections/donors
- Large lots
- High throughput
- Terminal sterilization
- Automated
- Control of starting materiel
- Stable protocol
- Unknown recipient

**Cells and Tissue**
- Donors and collections
- Single product lots, high value batches
- Low throughput
- Partial closed system, no term sterile
- Traditionally labour intensive
- Limited control of starting materiel
- Evolving research based protocols,
- Known recipients
Regulators are concerned about product risks

Unexpected toxicity?  Malignant transformation?  Inappropriate differentiation?

Spontaneous Human Adult Stem Cell Transformation

Daniel Rubio1, Javier Garcia-Castro1,2, Maria C. Martín3, Ricardo de la Fuente1, Juan C. Cigudosa2, Alison C. Lloyd4 and Antonio Bernad1

Potential risks of bone marrow cell transplantation into infarcted hearts
Martin Breitbach et al
Blood 2007 110: 4 1362–9

Two fight for lives after drug trial poisoning

BY PHILIPPA NAUGHTON AND AGENCIES

The distraught girlfriend of one of two men fighting for their lives in a London hospital after being poisoned in a drug trial today said she had barely recognised him because his head was so swollen.

Myfanwy Marshall, 35, said that her boyfriend looked "like the Elephant Man" after being given a dose of the drug, TGN 1412.
Novel cell therapies can cause severe toxicity

---

**Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma**

Regulators are concerned about materials

Biomaterials?

Diabetes. 1997

Animal derived materials…

Enzymes? Serum?

... bare-handed workers at Yuan Intestine & Casing Factory, untangle and flush pig intestines that will be used to make heparin...
Regulators are concerned the origin of the cells

Why allo, is it as effective as auto?

Hare JS et al Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy- The POSEIDON Randomized Trial
*JAMA*. 2012;():1-11 First online 6 Nov 2012

The mesenchymal stromal cells dilemma—does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road?

**JACQUES GALIEPAU**

*Departments of Hematology & Medical Oncology and Pediatrics, Emory University Winship Cancer Institute, Atlanta, Georgia, USA*

*Cytotherapy*. 2013;(15) 2-8

Errors with cell identity

Clinically sourced patient ID errors RCPA KIMMS QAP 2012

- Mismatch of documents & samples 0.06%
- Australian surgical biopsy data
  - Median of 1% have incorrect transcription of Patient ID
- 0.25% of specimens rejected due to ID errors
  - Unlabelled 0.07%
  - <2 identifiers 0.04%
Regulatory issues and global commercialization

• Manufacturing and product risks

• Inherent challenges to a “fit” in a regulatory scheme

• Regulatory risks - exemptions

• A robust harmonised regulatory framework with minimal exemptions is a precondition for developing a global cell therapy program: how is Malaysia positioned?
Donor materials for international use

• How to design one cell bank for international use?
• Multiple retention samples to allow re-testing
• Consistent internationalised donor assessments
• Broad consent, including for retesting & follow up
• Some issues can’t be addressed
  ▪ Paid donors
  ▪ Unconsented donors
  ▪ Unscreened donors
  ▪ High risk donors
Harmonised GMP Inspection is essential

Is there a cGMP suitable for cells and tissues?

Some specific differences in facility requirements and quality systems in the current code of GMP vs US GMP.

Manufacturing vs diagnostic quality systems? ISO vs GMP? PIC/S vs local codes of GMP?

“Where required, applicable code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products should apply.”

New facilities are expected to harmonize to PICs Annex 1 facility requirements.
PICS as the global inspection standard

...declared goal of developing and disseminating harmonised GMP standards and guidelines

First FDA application in 2009 failed - 5 absent and 18 partial requirements out of 89

During the upcoming PIC/S Conference in November 2010 in Kuala Lumpur (Malaysia), the PIC/S delegation will recommend to the PIC/S Committee Meeting to accept the FDA as a full member. This is according to a statement by Benda Holman (Executive Director, ORA Strategic Initiatives, ORA, FDA) during the PDA/FDA Joint Regulatory Conference on 14 September 2010 in Washington. This could mean that in future the number of foreign FDA inspections will be significantly reduced to only include countries that are not yet members of the PIC/S inspection community.

2012 Indonesia
2013 New Zealand
2015 Japan & Sth Korea (applied 2013)
Trials

• Trial data for multiple authorisations
  ▪ Exporting trial outcomes to more than one market
  ▪ Avoiding duplicating Phase 3 studies
  ▪ Objective endpoints and manufacturing control
  ▪ How will manufacturing be controlled (inspection by a competent authority - EU)

• Strategic considerations for sponsors
  ▪ Focus on trials in markets with regulatory credibility
  ▪ Bridging markets - using approvals in one market to break into other markets
  ▪ **Avoid** unregulated markets/ excessive medical exemptions
A model for bridging markets

• Use a credible regulator to bridge data from one market to a local marketing approval
• Use a regulator in good standing with PIC/S
• Use a regulator with a track record in approving pivotal data for US and EU markets
• Use a market with a tailored risk adapted framework designed for cells and tissues
• Use a regulator who cites EU and US or similar pharmacopeias
Regulatory issues and global commercialization

- Manufacturing and product risks
- Inherent challenges to a “fit” in a regulatory scheme
- Regulatory risks - exemptions

A robust harmonised regulatory framework with minimal exemptions is a precondition for developing a global cell therapy program: how is Malaysia positioned?
How to obtain rapid access

• Exemption frameworks must be stringently controlled....
  ▪ By location (products developed within sovereign state only – Japan)
  ▪ By product (homologous...levels of manipulation- US, EU, AU)
  ▪ By practitioner (authorised medical practioners- AU)
  ▪ By benefit and indication (breakthrough, expedited access- US, AU, EU, Japan)
  ▪ By institution (Hospital based -EU, Japan)
  ▪ By frequency (Occasional, -EU)
  ▪ By stage of product development (initial human studies, conditional approvals -US, EU, Japan)

Most markets have some form of rapid access BUT poor control of exemption causes significant market distortion
Risks with exemption frameworks

• Rapid Availability of novel therapies, versus
• NO marketing approval or manufacturing oversight
• Risk and harm to patients and markets
• Competitive neutrality and market damage
• Loss of ‘real’ investment in innovation
• Trials vs exemptions
• Reimbursement/payment?
• Most schemes have special access
Regulators wish to restrict unproven cell therapies

The Adult Stem Cell Foundation's Mission is to provide information about new technologies, breakthrough treatments and natural products related to the role that Adult Stem Cells play in helping to manage and prevent degenerative diseases including cancer. This website is dedicated to providing more information for patients, doctors and researchers alike.

Potential uses of Stem cells:
- Stroke
- Traumatic brain injury
- Learning defects
- Alzheimer's disease
- Parkinson's disease
- Missing teeth
- Amyotrophic lateral-sclerosis
- Baldness
- Blindness
- Deafness
- Myocardial infarction
- Muscular dystrophy
- Diabetes
- Bone marrow transplantation (currently established)
- Spinal cord injury
- Osteoarthritis
- Rheumatoid arthritis
- Crohn's disease
- Multiple sites: Cancers
Controlling risk...

• Manufacturing risks – controlled by an inspectorate or quality framework.
• Inherent unexpected product risks - unanticipated risks - controlled usually by means of a prospective product market authorisation regime.
• Exploitation of vulnerable subjects - by an independent ethical oversight process and informed consent.
• Appropriate access to innovation - usually by means of a trial or expedited access regime
• Competitive neutrality - by means of a widely followed framework providing certainty and a consistent cost model
Regulatory issues and global commercialization

• Manufacturing and product risks
• Inherent challenges to a “fit” in a regulatory scheme
• Regulatory risks - exemptions

A robust harmonised regulatory framework with minimal exemptions is a precondition for developing a global cell therapy program: how is Malaysia positioned?
Components of a regulatory strategy

Regulatory system

- Market access pathways
- Promotional standards
- Post market surveillance
- Product (safety, efficacy)
- Manufacturing (quality)

Product regulatory strategy

- Product formulation
- Starting materials
- Manufacturing locations
- Indications
- Markets
- Bridging
- Speed vs market potential vs protection
- Pricing/HTA

Regulatory agency resourcing and skills
How should a framework operate?

- How fast will it be?
- Will there be an orphan scheme?
- Will it allow for expedited or conditional approvals?
- Will it facilitate international harmonization?
- Is it protecting local companies/practices or encouraging global two way biotech trade?
- What resources are needed to deliver appropriate regulation and effectively manage risk and benefit?
- How much will it cost?
  - AU Examples
    - Best case 1 year for review
    - Regular audit fee $13,500
    - Annual fee of $5,500 per Class 2-4 biological
    - Initial ARTG evaluation
      - $120,000 for a Class 3 product
      - $195,000 for a Class 4 product
      - $28,500 major variation
Conclusion

• The local market is a global market
• Exemptions are a major global regulatory risk
• Materials, donors and testing are challenging to harmonise, but this is possible
• A well designed ethical study should facilitate approvals in multiple markets
Further enquiries...

Dominic Wall PhD
Chief Scientific Officer

t +61 3 9656 1069
m +61 417 301 356
e DominicWall@celltherapies.com.au
www.celltherapies.com.au
Effective clinician exemptions - difficult to control

- EU still requires GMP & competent authority oversight
- ‘non-routine’- but variably applied across EU and has been reviewed due to significant regional differences
- Other markets have failed to regulate- TGA unrestricted compared to EU provisions

EC 1394/2007

There are two narrowly drawn exemption schemes available in the UK that may allow the supply of unlicensed ATMPs (ie ATMPs that are not the subject of a marketing authorisation granted by the European Commission).

1) The hospital exemption
If an ATMP is prepared within the UK on a non-routine basis for use in the UK only in a hospital in accordance with a medical prescription for an individual patient it may fall under the hospital exemption inserted as Article 3 (7) of Directive 2001/83/EC by Article 28 (2) of the ATMP Regulaation.

2) The 'specials' exemption
The existing exemption from the requirement to hold a marketing authorisation provided by Schedule 1 (the 'specials' exemption) of the Marketing Authorisation Regulations (SI 1994/3144) as amended, may also apply to an unlicensed ATMP if it is "supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility in order to fulfil the special needs of those patients..."

It should be noted that a qualified person (QP) is not required under either of these.
Challenges

• High cost products require high benefits vs risk
• Can autologous cells be manufactured and reimbursed profitably
• Use the right comparator for health economic analysis

• Competitive neutrality is essential to prevent market damage and loss of ‘real’ investment in innovation
• Poorly controlled exemption schemes are a global issue
Export

• Export concessions are vital for a viable CMO industry
  ▪ Needs to consider bilateral approvals
  ▪ Manufacturing should be still locally regulated
  ▪ But avoid dossier for safety & efficacy
  ▪ Still requires cGMP and mandatory standards
Commercial impacts of exemption

• Cost of “real” market approval vs Insertion of manufacturing into clinical centre

• Why develop a product in unregulated markets?
• Medical tourism “therapeutic haven” vs evidence-based product development

• Investment in product characterisation & automation
• Competitive neutrality
• Regulatory credibility is paramount for the market to be viable as a development site