INTRODUCTION

How we regulate Cell and Gene Therapy Product?

Presented by Azizah Ab Ghani
National Pharmaceutical Control Bureau
CGTP
Multidisciplinary approach
MOH

Medical Development Division
Medical Practice Division
Medical device Authority
NPCB

Clinical use /medical procedure
Device
Quality, efficacy and safety
• Product that fit under Sales and Drug Act 1952 and sale of drug Act 1952
  – The purpose of products to maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function
  – The principal mode of action of the product is by means physiological action (eg: pharmacological, immunological or metabolic...)

• Regulate by NPCB
Medical Device

• Product that fit under definition under Section 2 Medical Device Act 2012 (Act 737)
  – The principal mode of action is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions ...)

• Regulate by MDA
Control of product only by one agency

Jurisdiction by NPCB base on primary mode of action

Drug Authority (NPCB)  

Medical Device Authority
### Legislation and guidance

#### Control on medicinal product:
- Sales of Drugs Act 1952
- Control of Drugs and Cosmetic Regulations 1984 (CDCR 1984)
- Drug Registration Document/ Application for Clin Trial Import Licences & Clin Trial Exemption
- Good Tissue Practice 2015

#### Control on Health care Practice
- Private Healthcare Facilities and Services Act 1998 (Act 586)

#### Control of Cell & Tissues
- Guidelines For Stem Cell Research And Therapy 2009 MOH/P/PAK/177.08(GU)
- National Standards For Stem Transplantation 2009 MOH/P/PAK/188.09(BP)
- National Guidelines For Haemopoietic Stem Cell Therapy 2009 MOH/P/PAK/179.09(GU)
- National standards For Cord Blood Banking And Transplantation 2008 MOH/P/PAK/131.07(BP)
- Checklist For Research On Stem Cells and cell Based Therapies (NCESRT 2009)
- Guidelines On Importation And Exportation Of Human Tissue And/Or Body parts (CDC 2006)

#### Control on Medical Device
- Medical Device Act (2012)
CAR-T Cell Therapy
Manufacturing and delivery pipeline of genetically modified T-cell therapies.

(i) Collection of PBMCs and transfer to GMP manufacturing facility

(ii) Viral gene transfer of TCR or CAR into PBMCs

(v) Precondition patient (e.g., chemotherapy) and transfuse T-cell therapy

(iv) Transfer cells from manufacturing centre to patient

(iii) Propagate genetically modified tumour-reactive T cells

Screening

Cells (starting material) accepted by GMP facility

Genetically modified TCR T cell

CAR T cell

Cell product released by GMP facility

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Screening Tissue collection – NPCB Jurisdiction

• Donor eligibility determination not required
• Sample testing – ? infective marker
• Good Tissue Practice:
  - Sterile technique
  - Tracebility
  - Quality Management System in place

• Challenges
  - Number of T cell => inability to achieve sufficient dose
Manufacturing and delivery pipeline of genetically modified T-cell therapies.

Handling issues:
• Stored?
• Preserved?
• Transport?
• Process at clinical site? GMP

Manufacturing and delivery pipeline of genetically modified T-cell therapies.

1. Collection of PBMCs and transfer to GMP manufacturing facility
2. Viral gene transfer of TCR or CAR into PBMCs
3. Genetically modified TCR T cell
4. Transfer cells from manufacturing centre to patient
5. Precondition patient (e.g., chemotherapy) and transfuse T-cell therapy
6. Cell product released by GMP facility
7. Propagate genetically modified tumour-reactive T cells


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Quality of the product

- Failure of manufacturing product lot
- Delivery product to wrong patient
- Not enough blood
- Production schedule constraint
- Sterility
- Purity
- How to evaluate quality
How we regulate CAR-T in Malaysia

• Mechanism of action= exert tumor-killing responses in a human leukocyte antigen-independent manner. This MOA fits Drug definition
• Vector production and gene transduction
  ✓ regulate as gene therapy
  ✓ Bio safety Act → Environment assessment risk
• Engineered T Lymphocyte
  ✓ regulate as cell therapy class II
CAR-T Regulatory Pathway

Clinical Trial

Document

Product Registration

References

- Malaysia Guideline for Application of CTIL/CTX, 6th Edition
- Guidance Document and Guidelines for Registration of Cell and Gene Therapy in Malaysia
- Drug Registration Guidance Document- Appendix 3: Guidelines on Registration of Biologics
Typical Process Chain for Autologous Cell Therapy

- **PBMC Collection**
- **Patients**
- **Manufacturing**
- **Product return to patients**
- **Export/Import**
Transferring Cell for Further Manufacturing: NPCB Perspectives
Jurisdiction Consideration

- To export/import PBMC
  - All imported stem cells/tissue products for use in clinical trials and therapy shall be GMP certified and registered by the NPCB (*Guidelines Stem Cell Research*)
  - To export biological product the laboratory must obtain export permit from Disease Control Division, Ministry of Health or KLIA health office. (*Standard operation procedure for transporting of biological specimen in Malaysia*)
Jurisdiction Consideration

• To bring in unregistered products for the purpose clinical trial – NPCB jurisdiction
  – Import
    ✓ Clinical Trial Import License (CTIL)
  – Manufactured
    ✓ Clinical Trial Exemption License (CTX)
  – Requirement for CTIL/CTX
    ✓ Register with National Medical Research Register (NMMR)
    ✓ Letter of Authorisation
    ✓ Approve by ethic committee (EC) which is registered to Drug Control Authority
    ✓ PIC/S GMP Compliance
    ✓ Investigator Brochure
Jurisdiction Consideration

- To import/manufacture products for the purpose of marketing (NPCB)
  - New Biologics Application Cell Therapy Class II
- Who can apply
  - must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Commission of Malaysia (with the scope of business related to the health/ pharmaceutical product)
  - known as the Product Registration Holder (PRH)
Low Risk Product (Class 1)

Must have ALL following criteria:

• Minimal manipulation (not activated, encapsulated, expanded in vivo or genetically modified)
• Homologous use
• No combination with drug/device
  – Except water, crystalloids or sterilising, preserving, or storage agent
• No systemic effect and is not dependent upon metabolic activity of living cells for its primary function
  – except autologous use

Does not meet any criteria above=> product will be classify as high risk (Class II)
Market approval for CGTPs
(Risk based approach)

Lower risk:
- Class 1 CTP
- Must be registered and listed with NPCB
- Regulated by:
  - GMP regulation (listing)
  - Donor screening and testing
  - Good Tissues Practice
  - Labelling
- Post marketing surveillance:
  - Adverse event reporting
  - Inspection and enforcement

Higher risk:
- Class II CTP or Novel cell and gene therapy
- Regulated as biologic products:
  - GMP licensing
  - Good Tissues Practice
  - IND frame work
    - Complete CMC
    - Pre-clinical
    - Clinical trial
- Post-marketing
  - Active surveillance
Jurisdiction Consideration: Quality Addurance

• Quality Assurance: GMP PIC/S
  ✓ Annex 1: Manufacturing od Sterile Medicinal Products
  ✓ Annex 2: Manufacture of Biological Medicinal Products for Human Use
  ✓ Annex 11: Computerised System
  ✓ Annex 13: Manufacture of Investigational Medicine Products
  ✓ Annex 14: Human Blood and Plasma Products
  ✓ Annex 15: Qualification and Validation
    ▪ Application of cGMP not include Donation, procurement and testing of starting tissues/cell

• Good Tissue Practice Guidelines 2016
Typical Process Chain for Autologous Cell Therapy

- **PBMC Collection**
- **Manufacturing**
- **Product return to patients**
- **Patients**

**Import**: K.Lumpur to Singapore
Jurisdiction Consideration

• The transport of cell and products must be controlled with documentary evidence of adherence to the specific storage and transport condition (data time and temperature to support shelf life)
• Traceability
• Preservation and thawing do not affect product quality
• Stability
• Product release: if a complete release testing cannot be tested before product is administer to the patient due to time restriction:
  ✓ A critical set of essential tests that can be performed in the limited time prior to clinical use
  ✓ Whenever feasible, retention samples should be stored for future analysis
Jurisdiction Consideration

- HSA-Singapore cover manufacturing of these cells for a trial. The product to be use in Malaysia as standard of care
Thank You