REGULATION OF CELL GENE THERAPY PRODUCT IN MALAYSIA

Presenter
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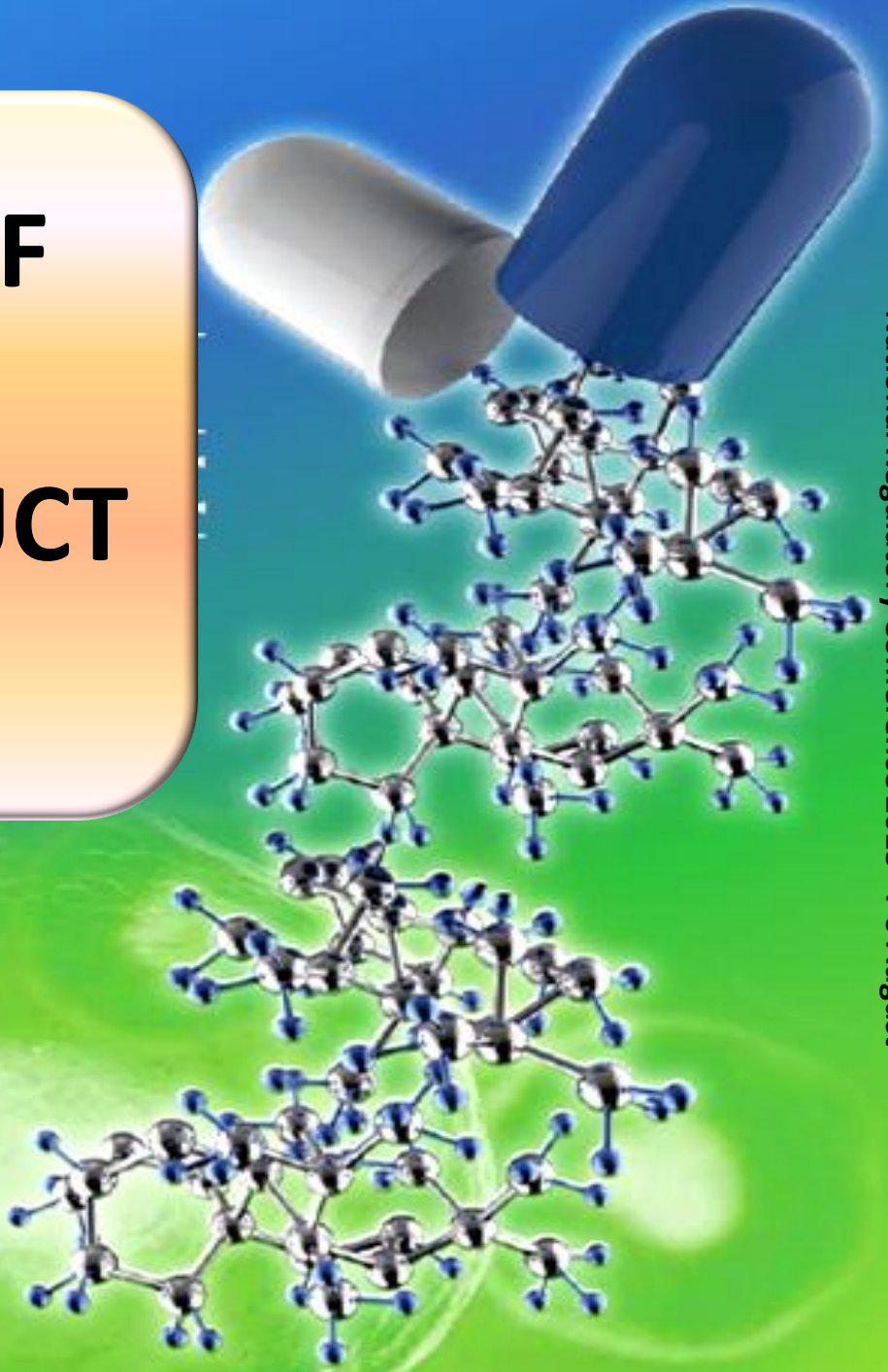


National Regulatory Conference 2015 4-6 August

Presentation Outline

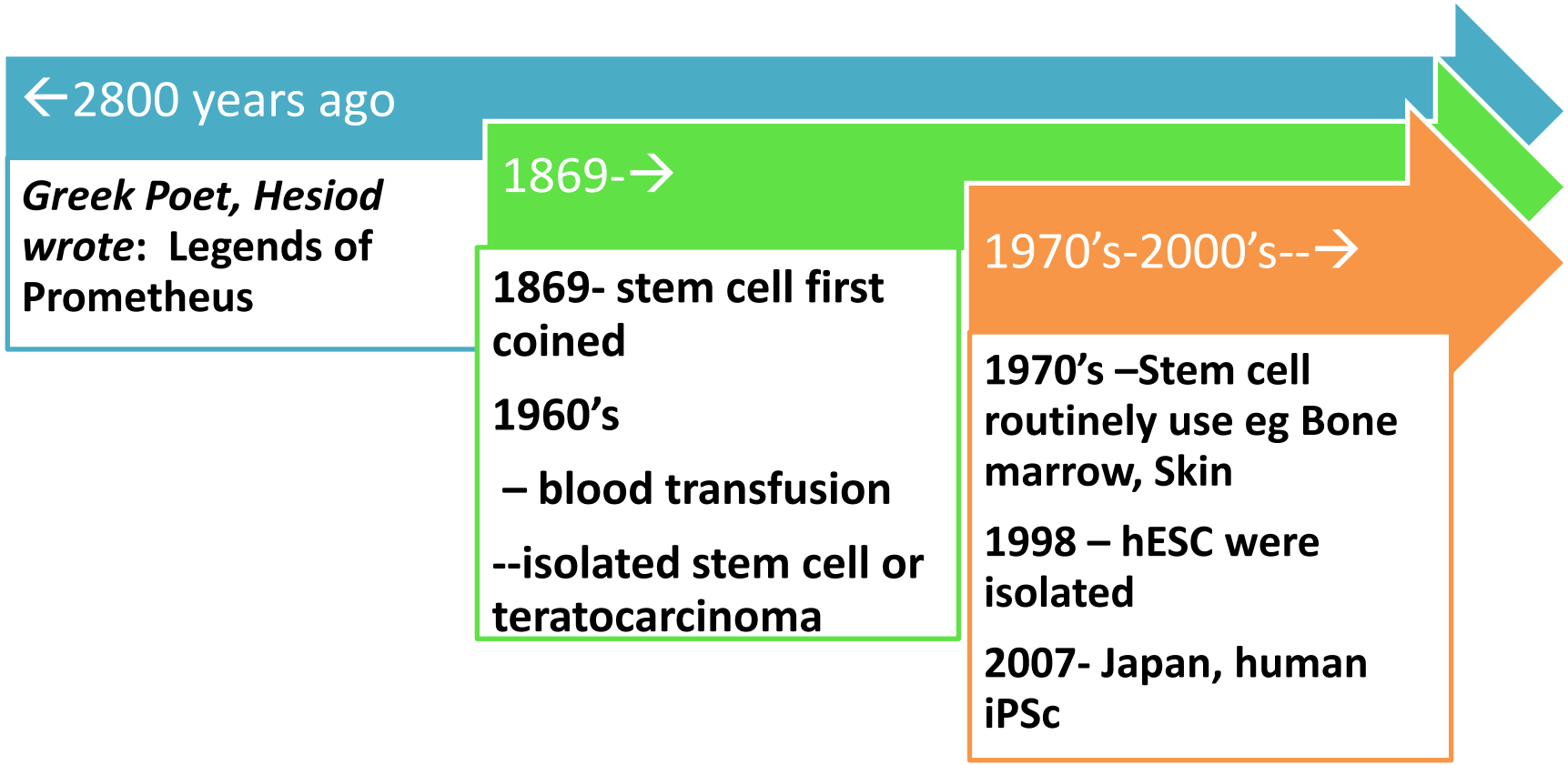
- Introduction
  - A story of Cell gene therapy
- Overview of Malaysia current regulatory control
  - Existing legislative framework
  - Regulatory authorities involved
- Scope of Guidelines
  - Which CGTPs applicable with this guidelines
- Regulating CGTP in Malaysia

A Story of CGTP

Sit back, Relax and Enjoy ….

CELL THERAPY- Utilization of cells for treatment of human diseases

History of Cell Therapy



Characteristic of different types stem cells

ESC	iPSC	SSM
Derived from Blastocyst	Derived from somatic cells	Isolated from post natal adult tissue
Pluripotent	Pluripotent	Multipotent
Ethical issues	non	Non
Differentiate in all cell types	Differentiate in all cell types	Differentiate in limited cell type
Significant teratoma risk	Significant teratoma risk	No teratoma risk
Cell lines will be allogenic	Less rejection if HLA match	Less rejection in autologous

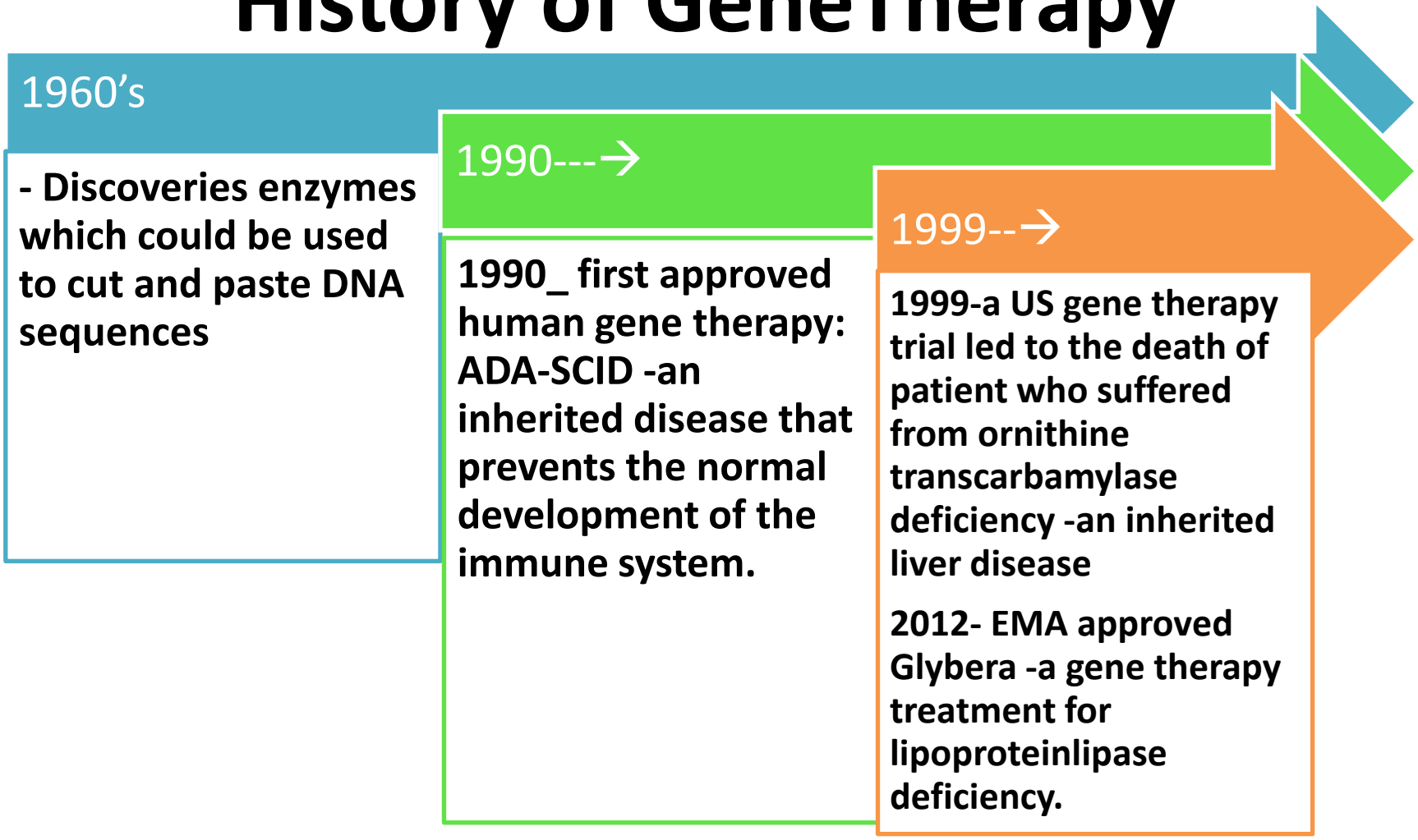
Term and definition:
Cell Therapy Approach

- **Autologous:**
  From a patient and back into the same patient. This is a patient-specific approach.

- **Allogeneic**
  From one or more donors and back into a patient who is different from the donor(s)

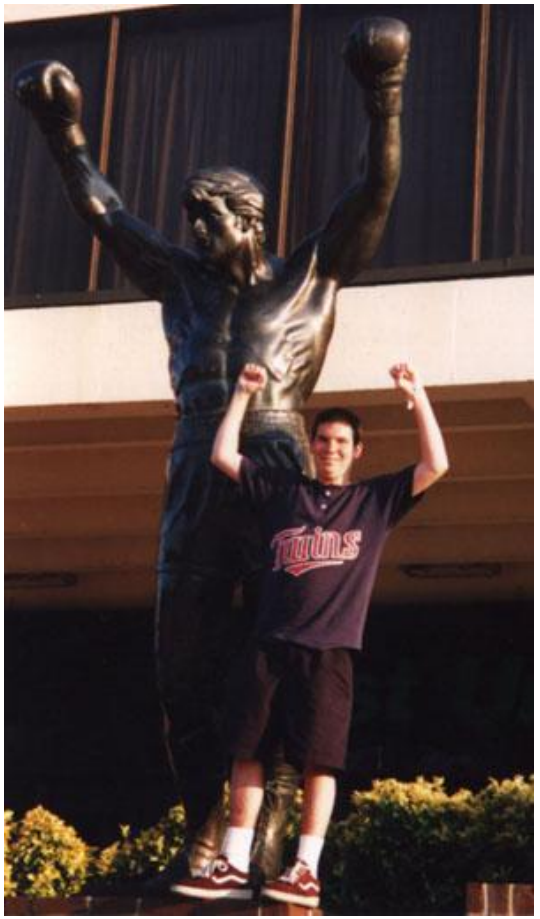
GENE THERAPY- Utilization of gene for treatment of human diseases

History of GeneTherapy



Jessie Gelsinger (1999)

- 18 y.o. with clinically mild form of ornithine transcarbamylase defiency
- Volunteered for clinical trial of gene therapy at U of Pennsylvania
- Adenoviral vector caused massive immune response, muti-organ failure, and death within 4 days
- All gene therapy trials placed on hold
- Multiple ethical issues raise
  - Informed consent
    - Adverse events in primate studies
    - Adverse events in 2 previous human subjects
  - Principal investigator conflict of interest
  - Inadequate evaluate patients



Gene therapy approaches

- IN VIVO: Vector administered directly to patient, and transfers genetic information to patient cells in vivo
  - Intravenously administered vector delivers gene for factor IX to patient with hemophilia B
- EX VIVO: Vector used to transfer genetic information to cells ex vivo, then cells are administered to patient
  - Vector that delivers gene for enzyme adenosine deaminase is incubated ex vivo with autologous lymphocytes of patient with ADA-deficient form of SCID (severe combined immunodeficiency), and genetically modified cells are infused to patient

Overview of current regulatory control

Current legislative documents

Current control on medicinal product:
Control of Drugs and Cosmetic Regulations 1984 (CDCR 1984**)**

Current Control on Cell Therapy

- Private Healthcare Facilities and Se
- Guidelines For Stem Cell Research A
  MOH/P/PAK/177.08(GU)
- National Standards For Stem Tran
  MOH/P/PAK/188.09(BP)
- National Guidelines For Haemo
  MOH/P/PAK/179.09(GU)
- National standards For Cord Bloo
  MOH/P/PAK/131.07(BP)
- Checklist For Research On Stem Cells RT 2009)
- Guidelines On Importation And Exportation Of Hu sue And/Or Body parts (CDC 2006)

Medicinal product must be registered and licensing
Authority body : DCA
Secretariate: NPCB
Relevant NPCB Guidance Document

Current Control on Medical Device

- Medical Device Act (2012)

CGTP

Medical Development Division

Medical Practice Division

Clinical use /medical procedure

Medical device Authority

Device

NPCB

Quality, efficacy and safety

Malaysia CGTP Guidelines

- Product that regulated by NPCB
- Complementary document: current legislative document & international relevant document (WHO, ICH, USFDA, EMA, TGA etc)
- At a 2nd draft stage
- Timeline
  - Dec 2015 – TWG meeting to review and comments
  - 1st Quarter 2016 – to be published
- A grace period will be given (at least 1 year)before implementation

Scope

- Cell Therapy
  - viable human cells of allogeneic or autologous origin undergoing a manufacturing process (ESCs, iPSCs, HSCs, PSCs)
  - May be combined with non-cellular components
  - The cell may be genetically modified (genetic engineering)

- Xenotransplantation- refer EMA and US FDA
- Gene Therapy
  - adopt the EMA and US FDA guidelines
  - Requirement registration- must be approved by any of the reference regulatory agencies (eg: US FD, EMA, Health Canada)

Scope Cell Therapy

INCLUDED

- Human stem cells
- Human tissue therapy products
- Human cellular therapy products
- Genetically modified cellular products
- Cancer vaccines and immunotherapies
- Dendritic cell, lymphocyte-based therapies, cancer cell based therapies, peptides, protein

NOT INCLUDED

- Fresh viable human organ
- Fresh viable human haematopoietic stem/ progenitor cells
- Fresh blood and blood component
- Unprocessed reproductive tissue
- Secreted or extracted human products
- Sample of human cells or tissue
- In-vitro diagnostic device

Regulating CGTPs

Cell Gene Therapy Products (CGTP)

DRUGS OR MEDICAL DEVICE?

DRUG

- 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

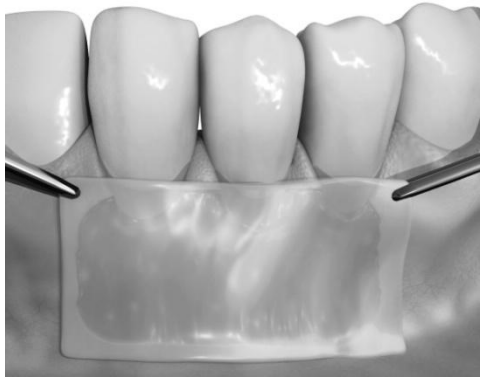
Medical Device

- 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

Examples 1

GINTUIT

- Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen
- allogeneic cellularized scaffold product
- indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults.
- Increased keratinized tissue at the treated site
- MOA: not Known



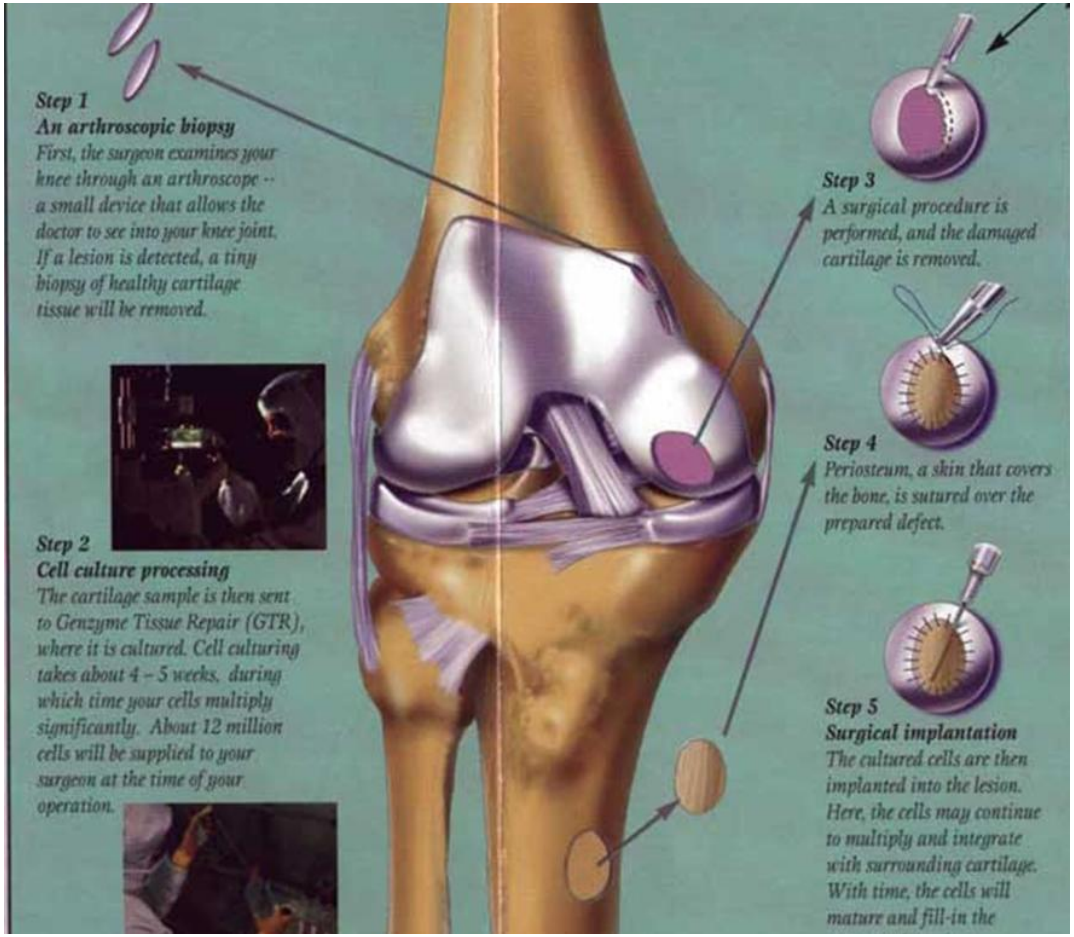
Cellular Product regulate by MDA

Examples 2

Carticel®

- autologous cultured chondrocytes for Implantation
- indicated for the repair of symptomatic cartilage defects of the femoral condyle

Cellular Product regulate by NPCB

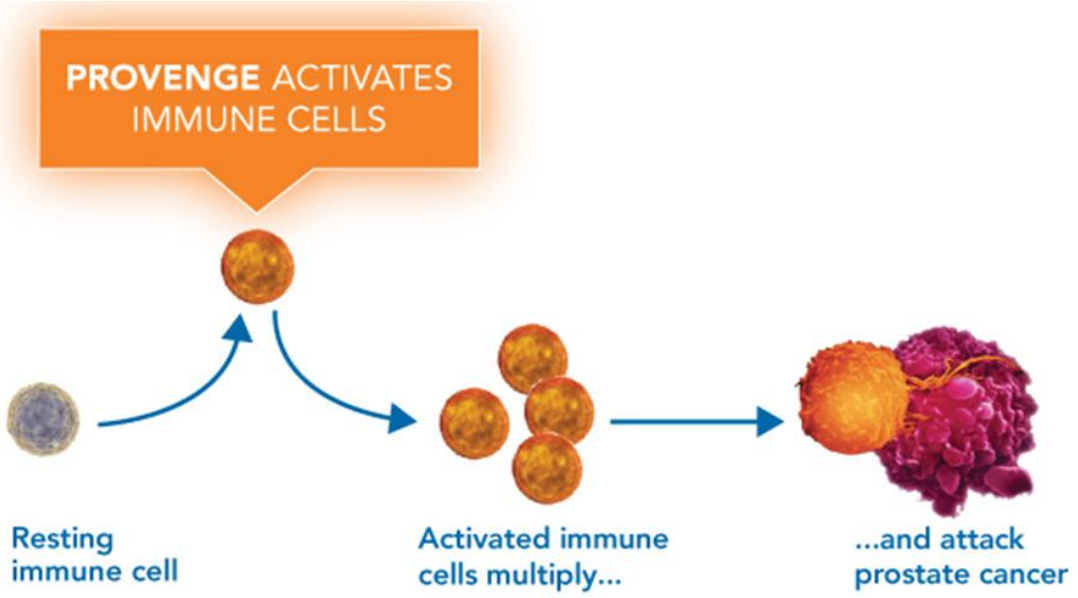


Examples 3

PROVENGE (autologous cellular immunotherapy)

- indicated for hormone refractory prostate cancer.
- Contain activated autologous CD54+ cells (patients immune cell cultured together with antigen on the cancer cells and protein known to stimulate the immune system)
- MOA: activate the immune system => kill cancer cells

Cellular Product regulate by NPCB



Examples 4

Integra Allograft Cancellous Bone

- Crush bone or chips
- Indication: use as bone void filler for bridging gaps in bone. Act as a scaffold for new bone growth

Cellular Product regulate by MDA

Examples 5

Glybera

- Adeno-associated viral vector engineered to express lipoprotein lipase in the muscle for the treatment of lipoprotein lipase deficiency

Gene Product regulate by NPCB

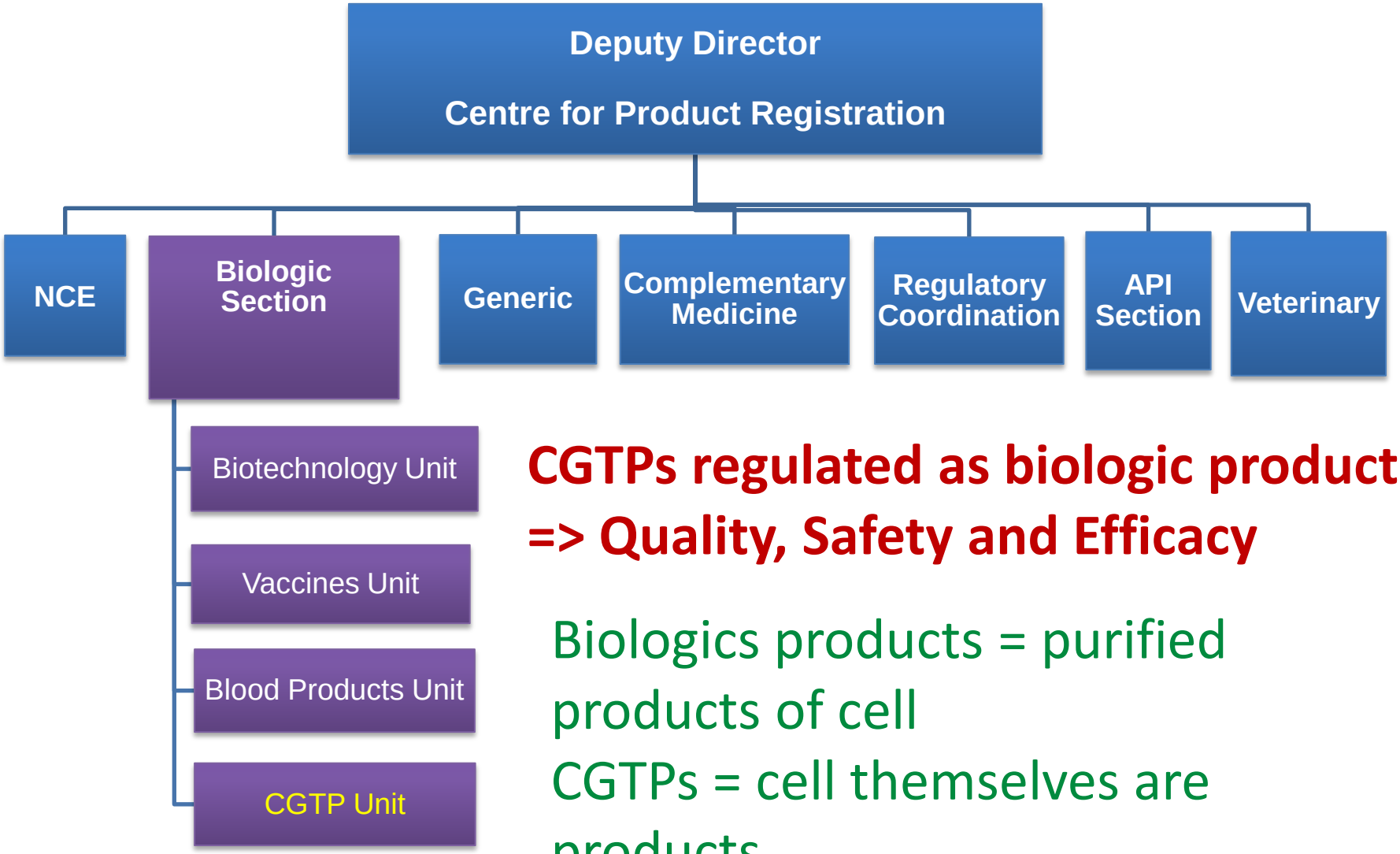
Product Classification

- Classification by NPCB
- For interface product: Classification by NPCB base on Medical Device – Drug –Cosmetic Interface (MDDCI) Committe decision
- For combination product: may evaluated together but contol of product only by one agency – MDA or NPCB => jurisdiction is based primary mode of action

Information required for classification

- The way the product is to be used
- Source of the product
- A clear, step by step, description of how the product is processed from the time of recovery to the point of use

Centre for Product Registration, NPCB

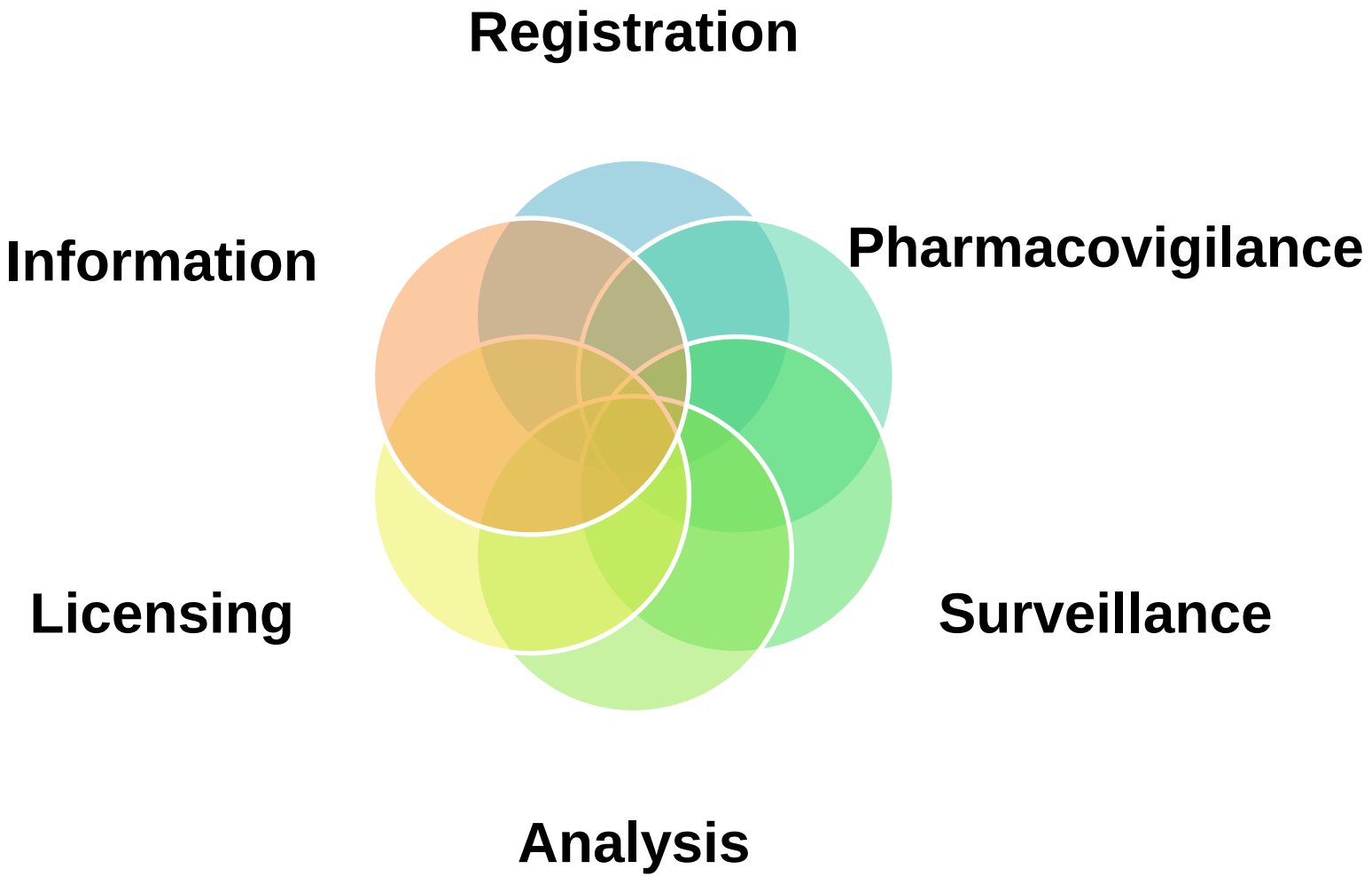


CGTPs regulated as biologic product => Quality, Safety and Efficacy

Biologics products = purified products of cell

CGTPs = cell themselves are products

Regulatory components



Principle elements

- Good Tissue Practice
  - Prevent product from infectious disease agent
  - Maintain their integrity & function

(***Good Tissue Practice Guideline published by the Centre for Compliance & Licensing, 1st Edition, January 2015)***

- Good manufacturing practice
  - Safe, quality and effective products
  - Process control and product characterisation
- Quality, Safety and Efficacy same standard as other registered biological products
- Tiered risk based approach: based on the degree of risk posed by the products.

Regulatory framework 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 surveilance:
  - ✓ 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 surveilance

Class I Cell Therapy Products

Must have ALL following criteria:

- Minimal manipulation (not activated, encapsulated, expanded in vivo or genetically modified)

  For structural tissues:

  Process not alter the original relevant characteristic of the tissue relating to the tissue's utility for reconstruction, repair or replacement

  For cells or non-structural tissues:

  Process not alter the relevant biological characteristic of cells or tissues

- Homologous use
- No combination with drug/device
  - Except water, crystalloids or sterillising, preserving, or storage agent
- No systemic effect and is not dependent upon metabolic activity of living cells for it primary function
  - except autologous use

Homologous use

- Performs the same basic function(s) in the recipient as the donor.
- Eg non homologous use:
  - using adipose or bone marrow MSCs to treat neurological conditions
  - using an adipose-derived MSC product as a bone graft substitute for the repair, replacement, or reconstruction of musculoskeletal defects
  - using a human amniotic membrane product for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects

Minimal manipulation

- The main function of the HCT/P, in the donor, determines which definition of minimal manipulation applies.
- Structural tissue: structural components and cells, and those cells are part of the structural tissue
  - adipose, skin, amniotic membrane
- Cells or nonstructural tissues:those who serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions
  - Reproductive cells or tissues (eg oocytes), cord blood, Amniotic Fluid, Bone marrow aspitate, lymph nodes,

Minimal manipulation? For structural tissues Example …

Amniotic membrane

- Original relevant characteristic: tissue's physical integrity, tensile strength and elasticity
- Process: mechanically and chemically to remove cells and packages it in sheet as decellularized amniotic membrane

Cellular product is minimal manipulation because the removal of cellular component does not alter the utility of the product to serve as membranous barrier

Minimal manipulation? For structural tissues Example …

Amniotic membrane

- Original relevant characteristic: tissue's physical integrity, tensile strength and elasticity
- Process: grinds and lyophilised and packages it as a powder

Cellular product is more than minimal manipulation because the processing alters the membrane's physical integrity, ensile strength, and elasticity that allow it to serve as membranous barrier

Minimal manipulation? For structural tissues Example ……..

Adipose Tissue

- Original relevant characteristic: to pad and cushion against shocks
- Process: removing cells, which leaves the decellularized extracellular matrix portion of tissue products

Cellular product is more than minimal manipulation because the process alters the ability of adipose tissue to provide padding and cushion

Minimal manipulation? For structural tissues Example …

Bone

- Original relevant characteristic: compressibility and strength
- Process: Threading to create bone dowels, screw and pins

Cellular product is minimal manipulation because the process do not alters the bone's inherent physical properties

• Process: to create bone dowels and bone chips for repair, reconstruction, or replacement of periodontal bone

- Minimal manipulated because the bone's inherent physical properties are not altered

Minimal manipulation? For cells or non-structural tissues Example …

Hematopoietic stem/progenitor cells (H/P stem cells)

- Original relevant characteristic: ability to repopulate the bone marrow by self renewal and by differentiating along myeloid and lymphoid tissue
- Process: cell selection on a mobilised peripheral blood apheresis product to obtain higher concentration of H/P stem cells.

Cellular product is minimal manipulation because the process did not altered their relevant characteristic

Minimal manipulation? For cells or non-structural tissues Example …

Cord blood stem cells

- Original relevant characteristic: ability to repopulate the bone marrow by self renewal
- Process: cell selection on a mobilised peripheral blood apheresis product to obtain higher concentration of H/P stem cells. Incubates the selected cells in a labarotory vessels containing culture media and growth factor .

Cellular product is more than minimal manipulation because the process affects the production of intracellular or cell-surface protein and other marker of cell lineage, activation state and proliferation -> alter their multipotency and capacity of self renewal

The extent of document in dossier
(Risk base approach)

- The data organized according to the ACTD
- One size fits all" is not applicable –risk based approach is recommended (may refer EMEA draft risk based approach guidelines)
- Risk – unfavourable effect related to CGTPs use
  – concern to the patients /other population
- Examples - unwanted immunogenicity
  - disease transmission
  - tumor formation
  - treatment failure
  - unwanted tissue formation
  - an advertant germ line transduction
  - toxicity

Example : Stem cell therapy

Risk : Tumour formation

Factor identified:

- Type of cell use (potency)
  - ESC vs iPSC vs SSC
- Culture condition/genetic stability /manipulation of the cells (CMC)
  - Limit to population doubling, Process validation, analytical procedure
- Site of injection (non-clinical/clinical)

Summary

- Cell and gene therapy poses unique opportunities and challenges
- One size does not fit all
  - Lower risk => lower regulatory burden
  - Higher risk=> more stringent regulation and oversight
- Multiple regulators involved

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Thank you

Together we advance