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Cell- and tissue-based therapeutic product regulations in Singapore and regulatory convergence

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OUTLINE

- Current regulations (Medicines Act) – cell- and tissue-based therapeutic product
- Proposed regulations (Health Products Act) – cell, tissue and gene therapy product
- Asia Pacific Economic Cooperation – cell and tissue therapy product

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Current regulations (Medicines Act) – cell- and tissue-based therapeutic product

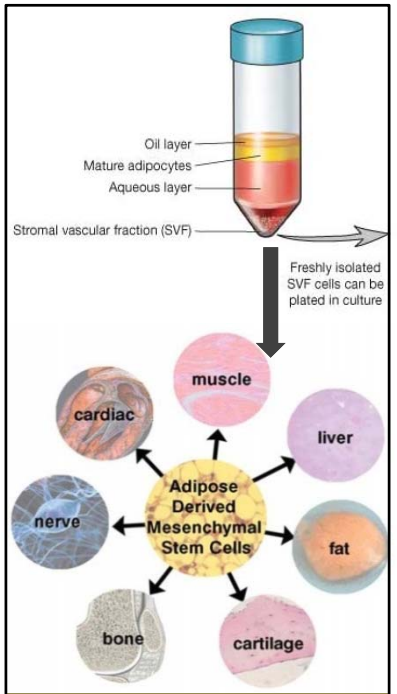
Proposed regulations (Health Products Act) – cell, tissue and gene therapy product

Asia Pacific Economic Cooperation – cell and tissue therapy product

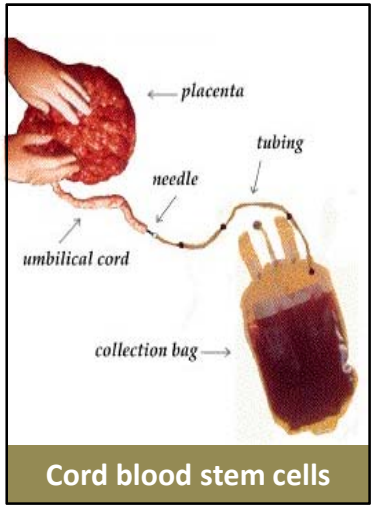
What is a cell- and tissue-based therapeutic product?

- Stem cells
  - bone marrow or cord blood
  - adipose (fat) tissue
  - embryo
- Cultured skin and cartilage
- Amniotic membrane with cells
- Cells grown on scaffold/matrix
- Genetically modified cells
- Viable animal cells

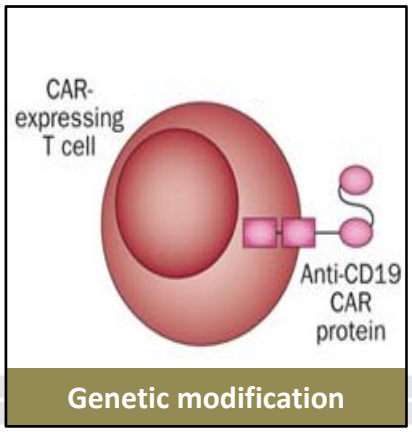
EXAMPLES



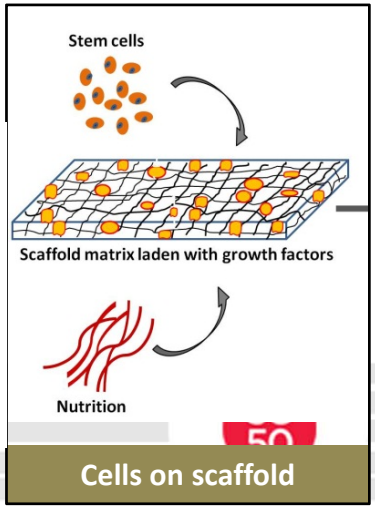
Fat stem cell and its application



Cord blood stem cells



Genetic modification



Cells on scaffold

Sources: http://www-bioon.qiniudn.com/industry/UploadFiles/201410/2014101317353859.jpg
http://www.plasticsurgerypulsenews.com/2/article_print.php?QnArticleID=34
http://www.usacordbloodbank.com/the-cord-blood-stem-cell-collection-process/

CURRENT REGULATIONS

DEFINITION

- **Cell- and tissue-based therapeutic (CTT) products are regulated as medicinal products under the Medicines Act**
- **CTT products are defined as *articles containing or consisting of autologous or allogeneic human cells or tissues that are used for or administered to, or intended to be used for or administered to human beings, for diagnosis, treatment or prevention of human diseases or conditions***

EXCLUSION

excludes –

- **any human organ intended for transplantation to replace a corresponding diseased organ;**
- **any cell- and tissue-based therapeutic product that is a whole blood or blood components intended for treating blood disorders and that**
  - **has not been subject to substantial manipulation; and**
  - **is intended solely for homologous use; or**
  - **is not intended for aesthetic procedures**

CTGTPs can be differentiated based on:

1. **The DEGREE OF PROCESSING → minimal vs. substantial manipulation**

2. **The FUNCTION they serve in the recipient → same function (homologous) vs. different function (non-homologous)**

3. **The COMBINATION with another product type → combined with a therapeutic product or medical device**

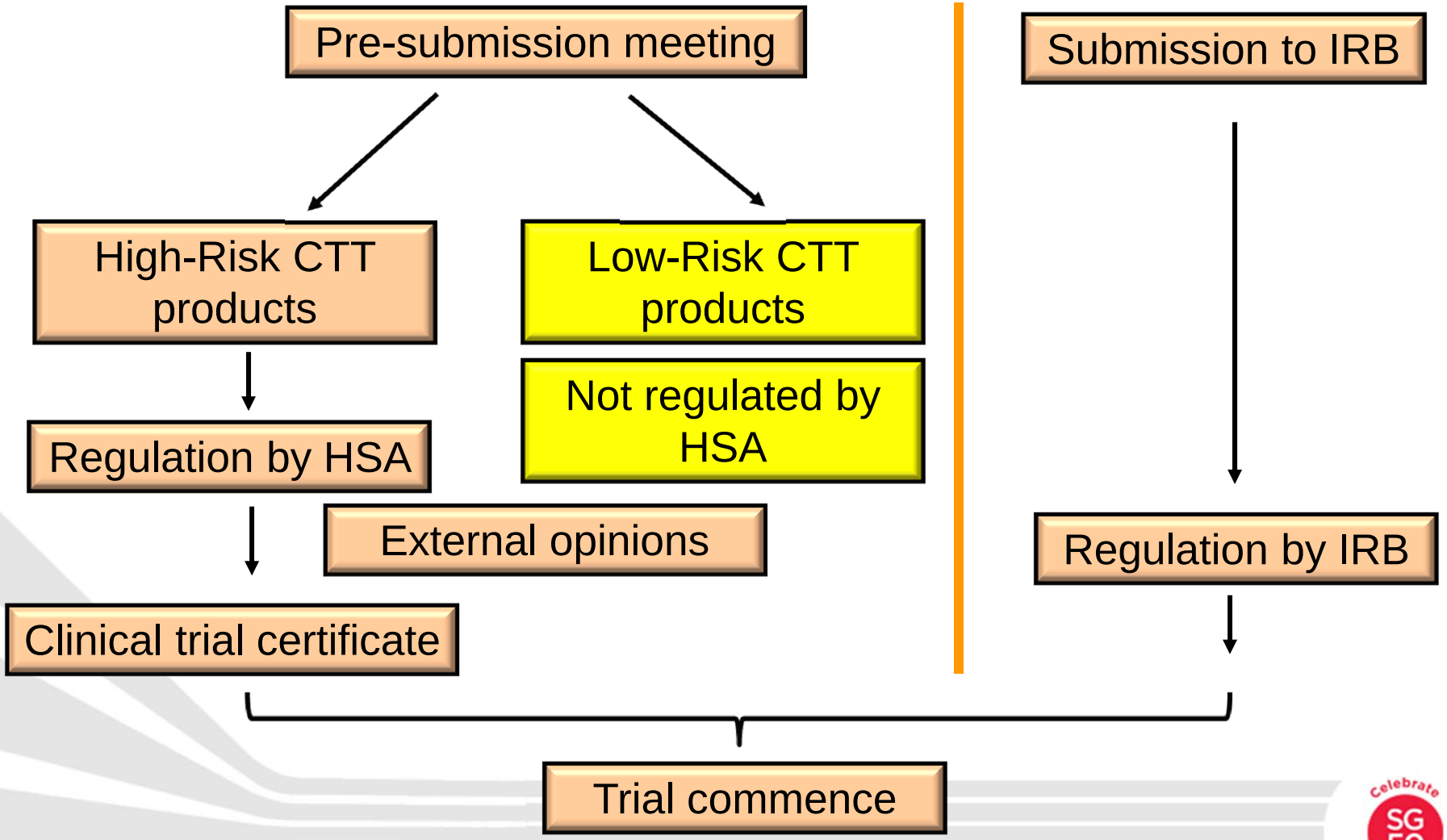
CURRENT REGULATIONS

RISK BASED

- **Phased-in regulation of CTT products**
  - **High risk CTT products are regulated**
  - **Low risk CTT products to be regulated in the new framework**
- **High risk CTT products are regulated to ensure they meet appropriate standards of safety, quality, and efficacy like other medicinal products**
  - **Clinical trial authorization**
  - **Product license for marketing**
  - **GMP compliance for manufacturing facilities**
  - **Applicable post-market obligations**
  - **Other duties and obligations**

CURRENT REGULATIONS

REGULATION OF CLINICAL TRIALS

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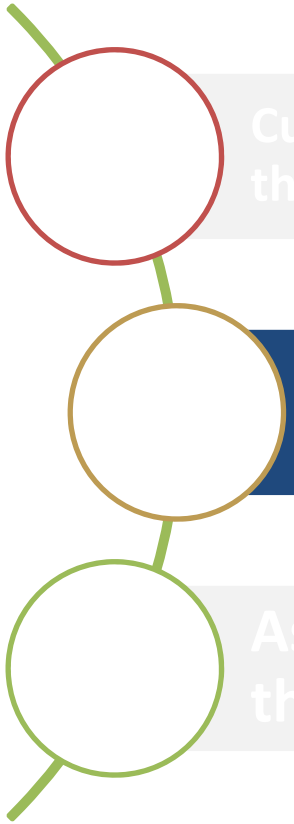
The HSA Clinical Trials Register is officially launched on 1 September 2012. The set of introductory slides presented at the Combined CRP-CRCS Forum on 22 Aug 2012 can be found here.
Please note that this register currently lists only active clinical trial sites in our applications database.
DISCLAIMER NOTE
All information available in the HSA Clinical Trials Register are maintained by the respective clinical trial sponsors conducting the research. Clinical trial status is updated by the sponsors at least every 6 months.
We seek your kind understanding on any non-current information reflected in the register.
Please click here to access the HSA Clinical Trials Register
Celebrate SG 50 Together

OUTLINE



Current regulations (Medicines Act) – cell- and tissue-based therapeutic product

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What is a cell, tissue and gene therapy product?

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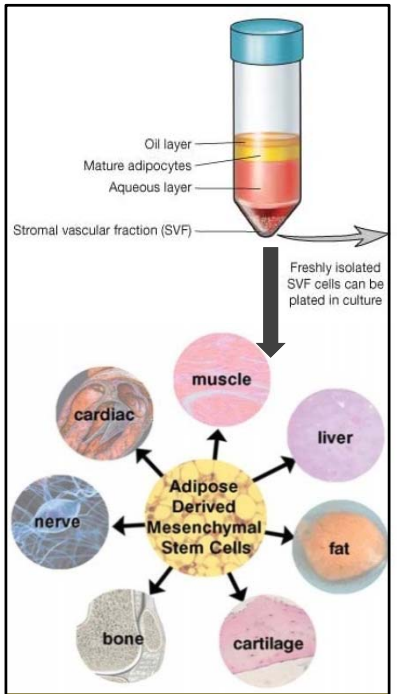
- Viable animal cells
- Recombinant nucleic acids



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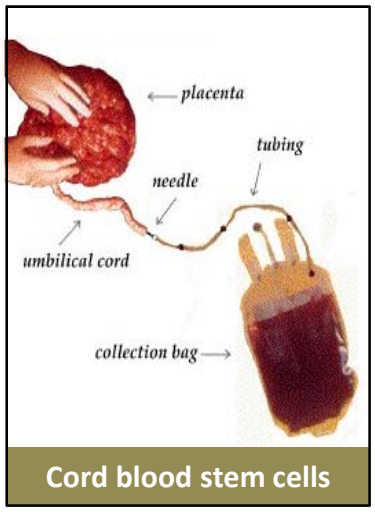

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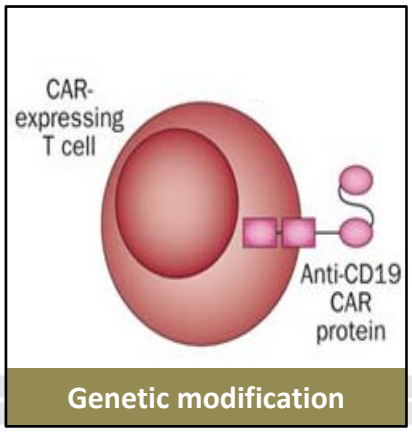

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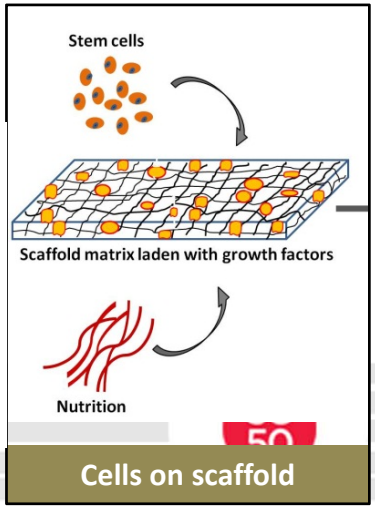

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THE NEED TO REGULATE

POTENTIAL RISKS

(i) Higher intrinsic risk

(i) transmission of infectious diseases (human, animal and recombinant microbial agents)
(ii) product may respond differently to the environment it is introduced
e.g. mesenchymal stem cells when implanted into knees will differentiate to cartilage, while the same cells become heart cells when injected into the heart
(iii) product sterility test results (e.g. bacteria/fungi require 14 days, mycoplasma 21 days) may not be available at time of release because of shorter shelf life (e.g. 18 hours)

(ii) Possible safety concerns to human health

(i) bio-compatibility issues with tissue engineered products
(ii) improper handling of CTGTP by end-user (e.g. grafting procedure, handling at the operation theatre)
(iii) unintended tumour formation by embryonic stem cells
(iv) genome integration and passing onto off-spring

(iii) Possible environmental contamination by gene therapy products

(i) risk to caregivers and environment at-large
(ii) generation of mutant viruses when not properly disposed

(iv) Need for record maintenance

(i) Long term patient follow-up for safety and efficacy

PROPOSED REGULATION

GUIDING PRINCIPLES IN REGULATING CTGTP

- To provide a **risk based framework**
  - level of regulatory control is tiered to the inherent risk of the product
- To **align with activity-based licensing framework**, where possible
  - manufacture, import, wholesale, registration and respective duties and obligations
  - advertisement control
  - regulation of clinical trials

Continue next page . . .

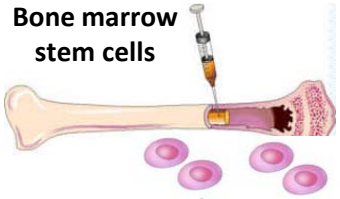
PROPOSED REGULATION

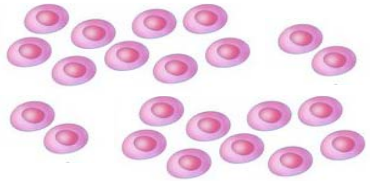
GUIDING PRINCIPLES IN REGULATING CTGTP

- To accommodate the rapidly developing field and be flexible to respond to novel technologies & new treatment modalities
- To leverage on approvals by other reputable reference agencies
- To adapt to future international harmonisation efforts and minimise duplication in regulations
- To ensure alignment with other regulatory controls such as practice control through premise licences or professional practice in the area of clinical care

MINIMAL MANIPULATION

SUBSTANTIAL MANIPULATION





CELL SEPARATION

cutting, dissecting, grinding, shaping, centrifugation, soaking in antimicrobials, sterilization, irradiation, flushing, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation,

CELL EXPANSION

Increase the number of cells – using culture techniques

Risks:
- Genome instability
- Use of enzymes and growth factors
- Cell morphology altered during culture

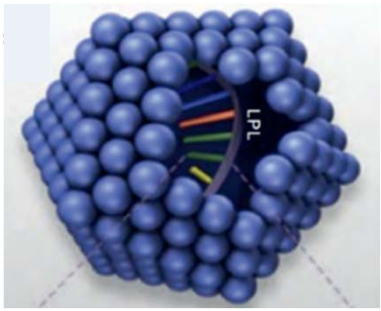
TISSUE ENGINEERING

Combined with a device (tissue engineered trachea)

Risks:
- Biocompatibility issues
- Requirement of specific rehabilitation post surgery

GENE THERAPY

Gene therapy for lipoprotein lipase (LPL) deficiency



Risks:
- Concerns with use of modified microorganisms
- Transmissibility to contacts, offspring and environment
- Development of unwanted gene mutations and/or tumors

Homologous use
e.g. treating leukaemia

Non-homologous use
e.g. treating heart attack

LOW RISK

- **Minimal manipulation AND**
- **Homologous use AND**
- **Not combined with drug or device**

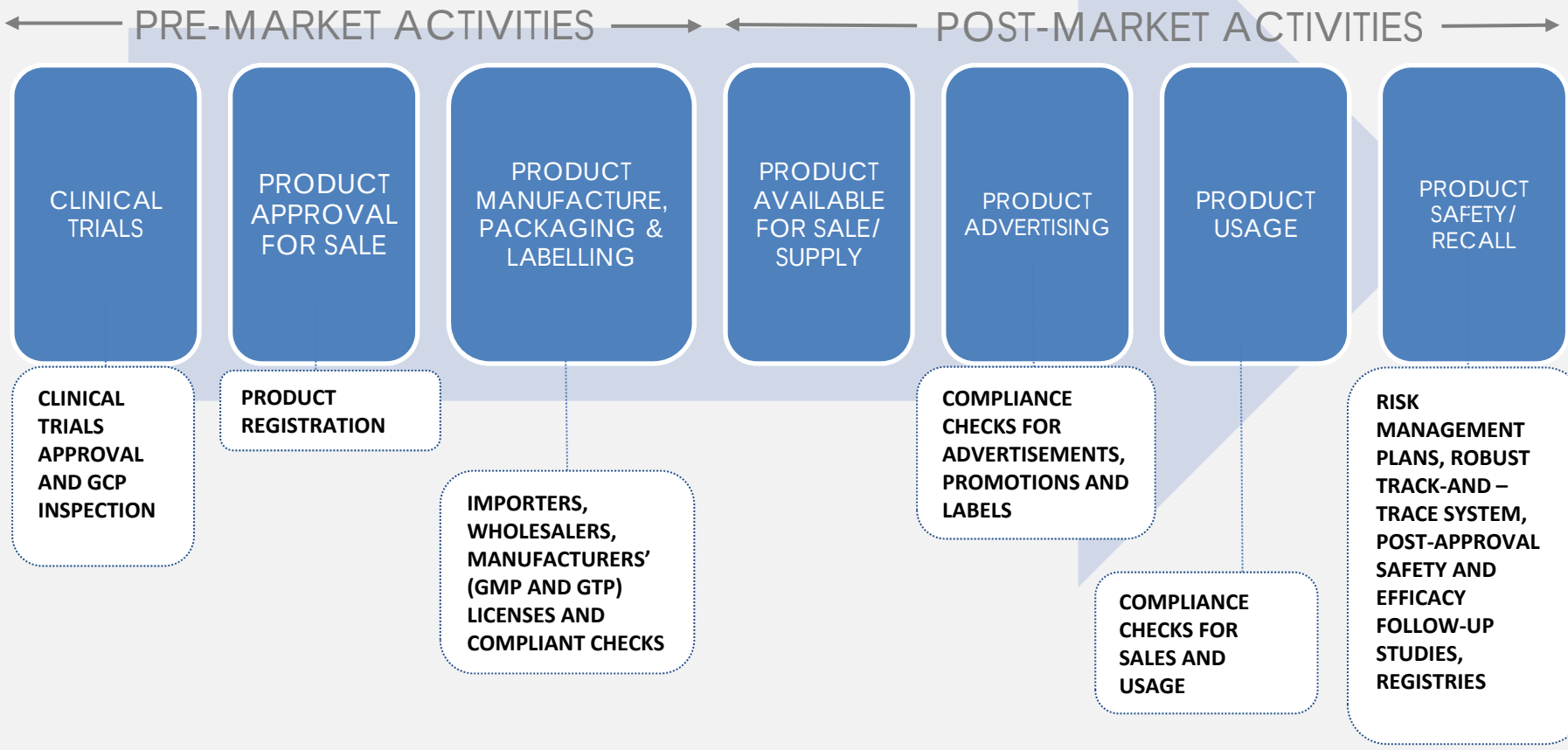
HIGH RISK

Human source:
- **Substantial manipulation OR**
- **Non-homologous use OR**
- **Combined with drug or device**

Xenogeneic, recombinant nucleic acid or recombinant microorganism

PROPOSED REGULATION

HP (CTGTP) REGULATORY TOUCHPOINTS



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ASIA PACIFIC ECONOMIC COOPERATION - APEC

APEC HARMONIZATION

Enabler of Prospective Regulatory Convergence and Cooperation – APEC Life Sciences Innovation Forum Regulatory Harmonization Steering Committee

Asia-Pacific Economic Cooperation

Regulatory Harmonization Steering Committee

Life Sciences Innovation Forum

ASIA PACIFIC ECONOMIC COOPERATION - APEC

RHSC FRAMEWORK

- **RHSC strategic framework endorsed by APEC leaders in 2011**
- **The multi-year strategic framework outlines steps towards achieving regulatory convergence for medical products by 2020**
- **Describes guiding principles and general multistep approach**
  - **doesn't produce harmonized guidance documents; rather, promotes use of existing international guidelines**
- **Includes definition of *regulatory convergence***

ASIA PACIFIC ECONOMIC COOPERATION - APEC

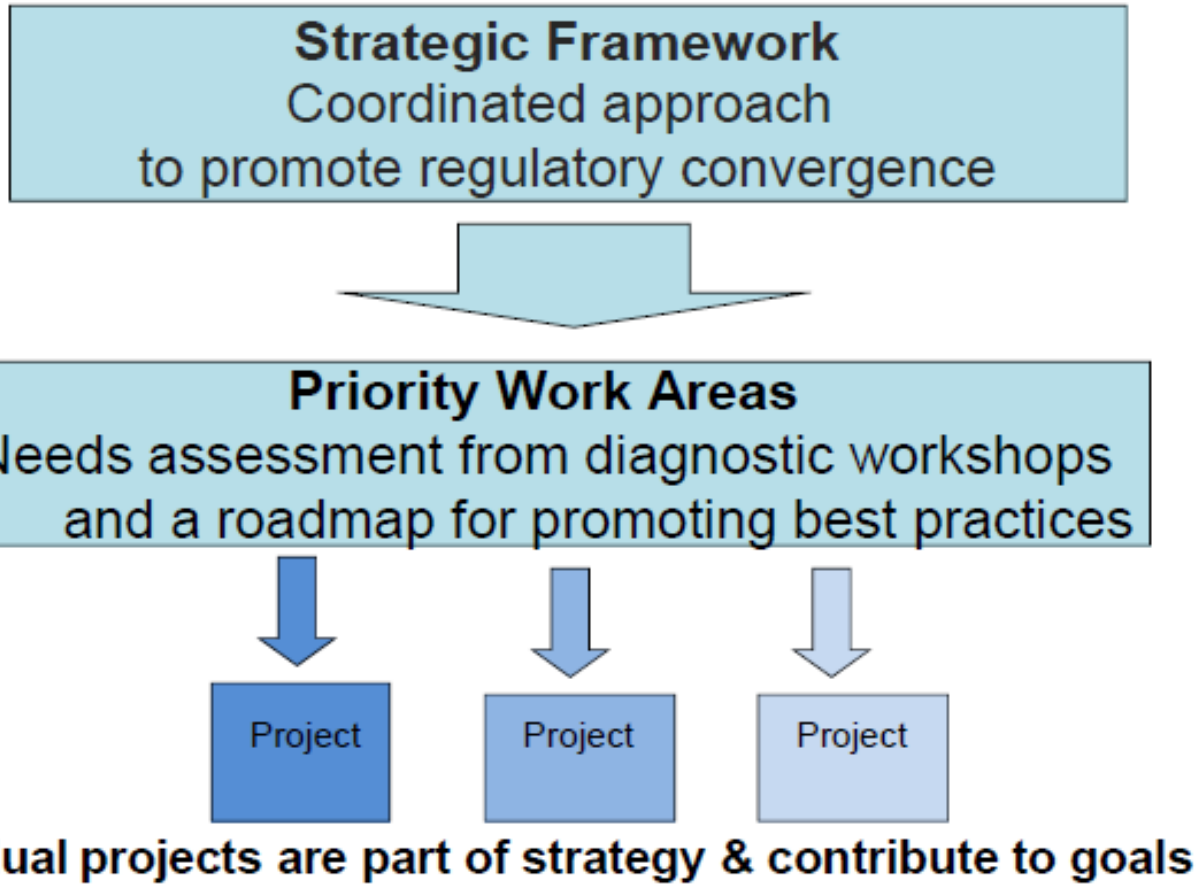
RHSC – REGULATORY CONVERGENCE

- *Regulatory convergence*, within context of APEC principles of voluntary action, represents a process whereby regulatory requirements across economies become more similar or aligned over time as a result of the gradual adoption of internationally recognized technical guidance documents and standards

- Does not represent the harmonization of laws and regulations, which is not necessary to allow for the alignment of technical requirements and greater regulatory cooperation

ASIA PACIFIC ECONOMIC COOPERATION - APEC

RHSC - FRAMEWORK



Individual projects are part of strategy & contribute to goals

ASIA PACIFIC ECONOMIC COOPERATION - APEC

RHSC ROADMAPS

- Global Drug Integrity and Supply Chain
- Good Review Practices
- Cellular Therapies
- Multi-regional Clinical Trials
- Good Clinical Practice Inspection
- Combination Products
- Pharmacovigilance
- Biotechnological Products

The RHSC include all APEC economies and a regulatory network inclusive of industry experts

CELL- AND TISSUE-BASED THERAPY PRODUCT ROADMAP

- One of the priority work areas under the auspices of LSIF RHSC
- Singapore is the Champion economy leading the development of a roadmap to stimulate and promote prospective regulatory convergence for cell- and tissue-based therapeutic (CTT) products
  - whereby the regulatory requirements become more aligned over time by gradual adoption of internationally recognized technical guidance documents, standards and scientific principles
  - It *does not* represent the harmonization of laws and regulations

CELL- AND TISSUE-BASED THERAPY PRODUCT ROADMAP

- The roadmap is to promote and advance prospective convergence of approaches for advanced therapeutic products within the APEC region
  - Cross border movement - not uncommon for human cells and tissues to be procured in one country, processed in another and transplanted in a third country
- Relevance: The roadmap will align with APEC LSIF's strategic plan to introduce safe and effective new and innovative medical products and promote regulatory convergence in the region (Honolulu Declaration 2011 "….commit to regulatory cooperation and convergence…"

CELL- AND TISSUE-BASED THERAPY PRODUCT ROADMAP

MILESTONES

- Priority work area endorsed – **Sep 2011**
- Concept note endorsed – **March 2012**
- Draft roadmap endorsed ‘in-principle’ – **Feb 2013**
- Final roadmap endorsed – **July 2013**

CELL- AND TISSUE-BASED THERAPY PRODUCT ROADMAP

GOALS

- Short-Term Goals:
  - To establish a mutual and harmonized understanding of cell- and tissue-based therapeutic products
  - To identify opportunities, develop relevant materials, and establish a training programme such as conferences/workshops on cell- and tissue-based therapeutic products for collaborative actions and information exchange
- Mid to Long-Term Goal:
  - To implement strategies to stimulate and promote prospective regulatory convergence and application of scientific principles to ensure and enhance the safety, quality and efficacy of cell- and tissue-based therapeutic products throughout the product life cycle

CELL- AND TISSUE-BASED THERAPY PRODUCT ROADMAP

PROGRESS

- Pilot workshop (Jul 2014) – HSA AHC workshop
  - Broader perspective focusing on regulatory approaches would help to identify potential avenues for regulatory convergence
    - product classification
    - academic facility GMP requirements
  - Clarity with specific examples on regulatory classification; substantial vs. minimal manipulation, and homologous vs. non-homologous use
  - Training of evaluators
  - Single platform for info sharing
- Work in progress
  - Understanding training needs for APEC member economies
  - Development of training curriculum – CMC, pre-clinical and clinical aspects
  - Targeted training to APEC member economies

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