Regulation of Cell Therapy Products in Taiwan
(台灣細胞治療產品管理現況)

藥求安全　食在安心

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http://www.fda.gov.tw/

Outline

- Organization and Responsibility of TFDA
- Regulation of Cell Therapy Products
- Regulatory Challenges
- Future Prospects

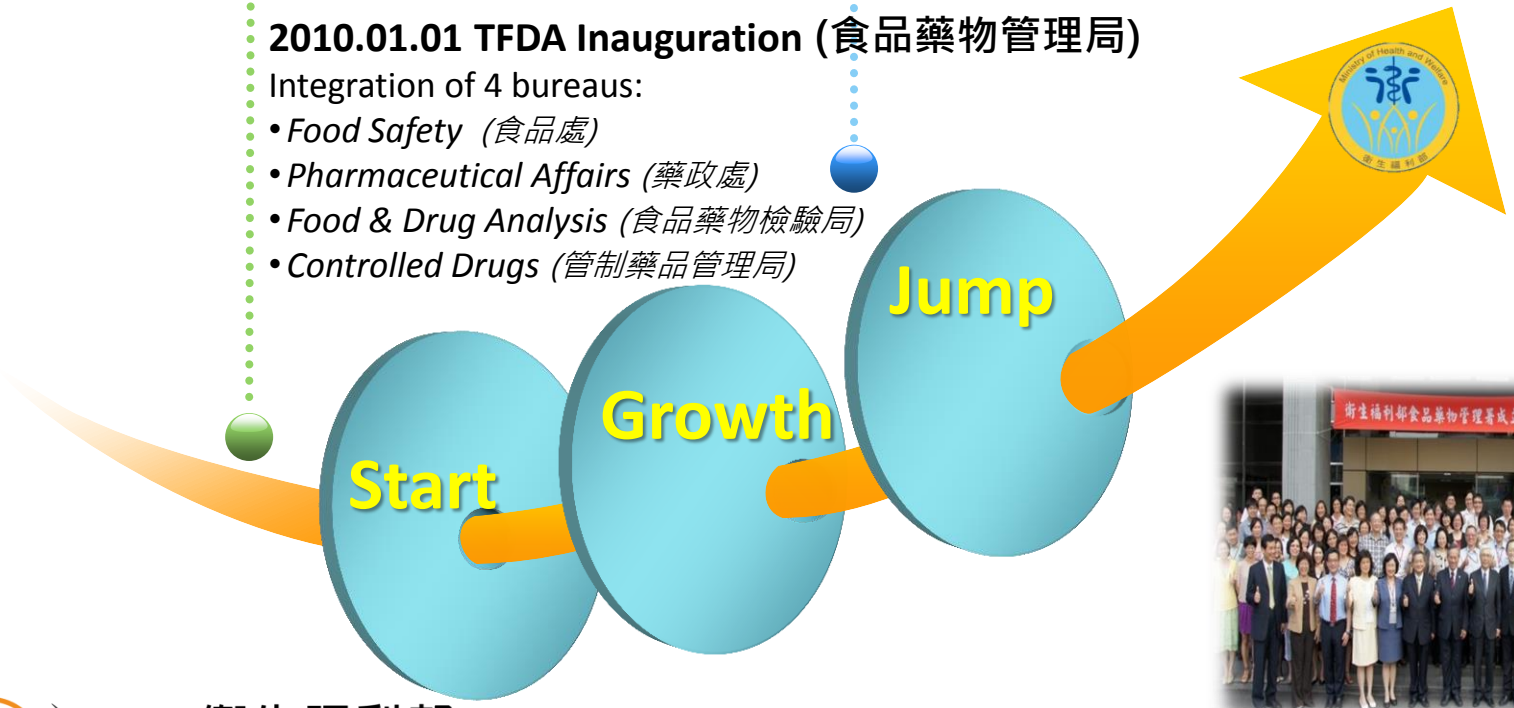
Establishment of TFDA

2013

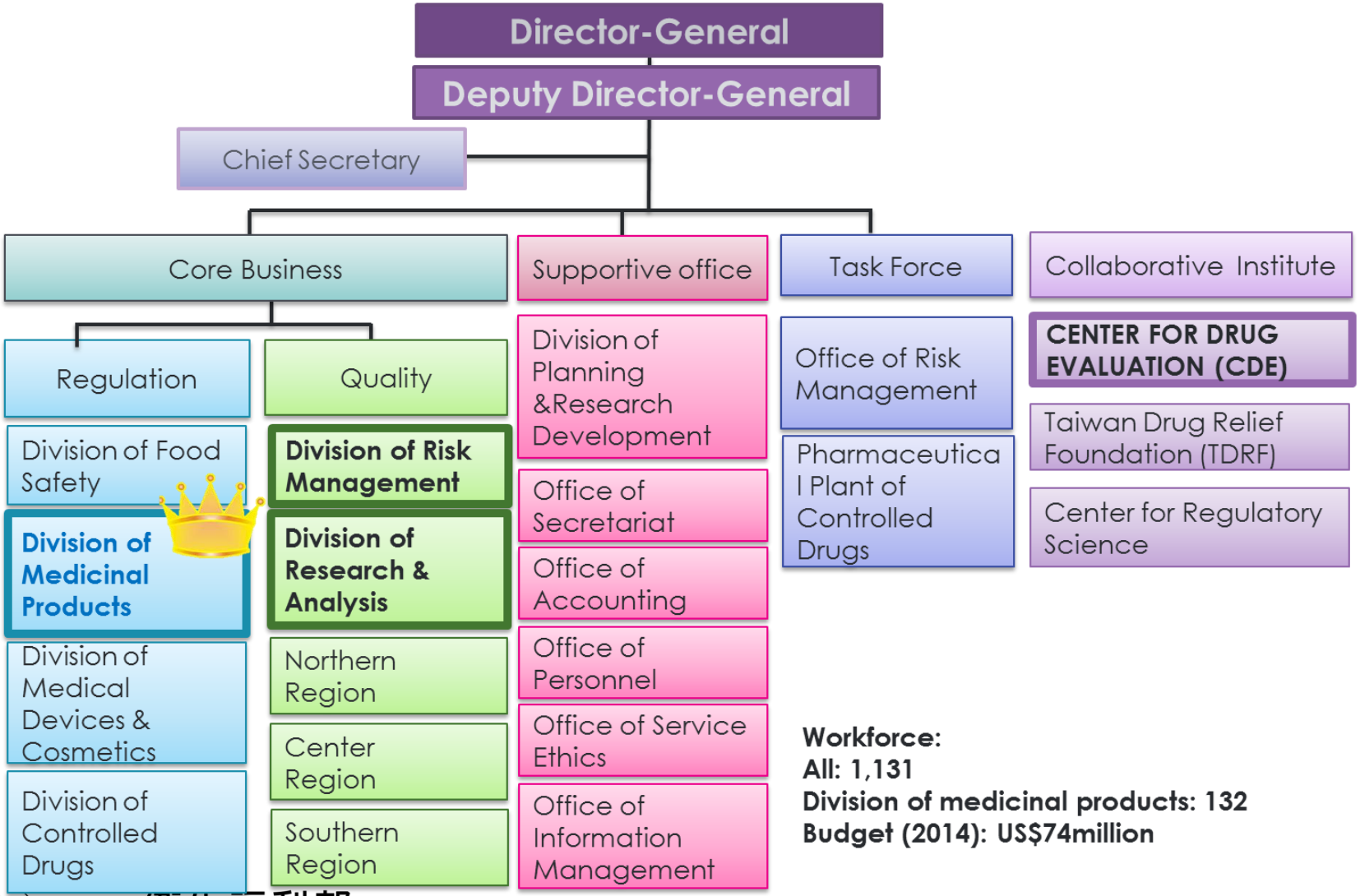
2013.07.23 TFDA Elevation (食品藥物管理署)
The *Ministry of Health and Welfare (MOHW)* was restructured from the Department of Health (DOH).

2010

2010.01.01 TFDA Inauguration (食品藥物管理局)
Integration of 4 bureaus:
- *Food Safety (食品處)*
- *Pharmaceutical Affairs (藥政處)*
- *Food & Drug Analysis (食品藥物檢驗局)*
- *Controlled Drugs (管制藥品管理局)*



TFDA Organization Chart



Workforce:
All: 1,131
Division of medicinal products: 132
Budget (2014): US$74million

Mission, Vision and Core Value

Quality and Safety of Food and Medical products
(藥求安全 食在安心)

To safeguard national health
(全民食藥健康守護者)
To lead the nation to a new era of food and drug management
(食藥安心消費環境)

- Profession (專業)
- Service (服務)
- Quality (品質)
- Innovation (創新)

Advisory Committee for Regeneration

2014.08.08 TFDA established Advisory Committee for Regeneration (再生醫學諮議小組)

Advisory Committee for Regeneration was established in 2014 and responsible to review and evaluate available data relating to the safety, effectiveness, and appropriate use of human cells, gene transfer products which are intended for transplantation, implantation, infusion and transfer in the prevention and treatment of a broad spectrum of human diseases.

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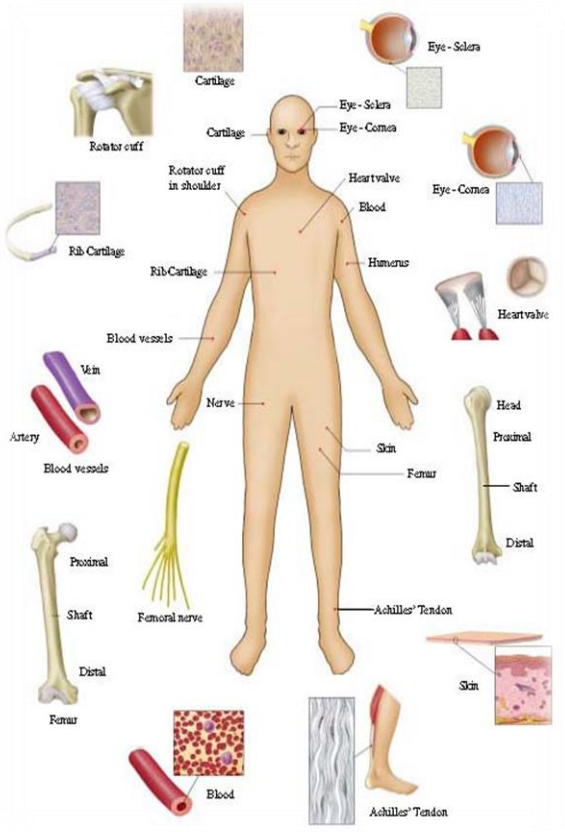
Regulation of Cell Therapy

Regulation of Cell Therapy

1. **Regulatory Evolution**
   From *Medical Practice* to *Medicinal Products*
2. **Current Regulatory Framework**
   - Guidance on Investigational Cell Therapy Products (2014.09.17公告)
   - Good Tissue Practice (GTP)
3. **Points to Consider on Cell Products**
4. **Application and Evaluation Process**
   - Consultation Mechanism
   - Review and Approval Process
5. **Current Status of Cell Clinical Trials**

Human Tissue is an important source of medical treatment



- Tissue for transplantation is recovered from *over 30,000* volunteer donors in US annually.
- The recovered tissue (or cells) is processed and distributed to *hospitals, surgery centers, and dental offices* for treatment of patients.

  - **Donated skin** is used in healing burn victims and for reconstructive surgery.
  - **Bone** implanted to replace tissue destroyed by trauma; or processed into powder used in dental surgery.

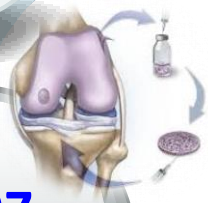
Development of medicinal Products

1899 Aspirin

Aspirin, made in 1899, was the most effective and popular anti-inflammatory drug and it opened the century of “Pharmaceutical products”.

1982 Insulin

Until 1982, the first genetic engineering medicine-Human insulin was approved and market. The century of “Protein Drugs” was coming.



1997 Carticel®

In 1997, the cell-based therapy product- Carticel®, **autologous cultured chondrocytes** is approved by US FDA. It is characterized as clinical “breakthroughs” and open-up a new revolution of new medicines development. ***“Cells” were Regulated as Medicinal Products***.

2012 Glybera®

The first GENE therapy product was approved in 2012. Look further ahead, drug development will follow **a “personalized medicine” approach- therapy** that tailored to the characteristics of specific types of patients.

Approved Cell Therapy Products

Japan (2)

JACE
JACC

EMA (3)

ChondroCelect
MACI
Provenge

Canada (1)

Prochymal

US (8)

Carticel
Provenge
Laviv
Gintuit
Hemacord
HPC
Ducord
Allocord

Korea (18)

Chondron
Holoderm
Kaloderm
Keraheal
CreaVax-RCC
Immuncell
NKM
Hyakgraft
Innolak
Adipocell
RMS Ossron
AutoStem
QeenCell
CureSkin
LSK Autograft
Hearticellfram
Cartistem
Cupistem

Australia (2)

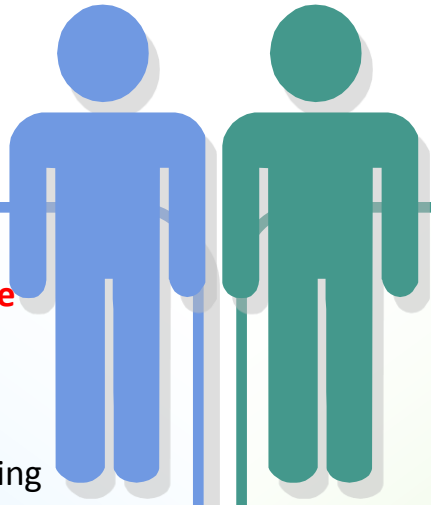
ReCell/CellSpray
Cartogen

New Zealand (1)

Prochymal

Regulatory Evolution in Taiwan-1

Before TFDA Inauguration (2010)



Tissue (cells) for Transplantation

Law and Regulation:

◆**Human Organ Transplantation Statute (人體器官移植條例)**

- ✓ Good Tissue Practice (GTP) (人體細胞組織優良操作規範)
- ✓ Regulation on Human Tissues Banking (人體器官保存庫管理辦法)
- ✓ Regulation Importation & Exportation (人體器官組織細胞輸入輸出管理辦法)

EX:

Bone, cartilage, ligaments, tendons, heart valves, skin, corneas, hematopoietic stem cells derived from peripheral blood and cord blood, etc.

Cultured Cells for Disease Treatment

Technology

Law and Regulation:

◆**Medical Care Act (醫療法)**

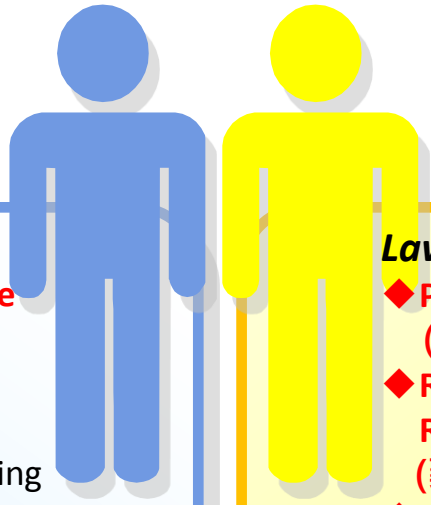
◆**Regulations on Human Trials (人體試驗管理辦法)**

- ✓ Guidance on Investigational Somatic Cell Therapy (體細胞治療人體試驗申請與操作規範)

Cell Therapy was regulated as New Medical Technology (新醫療技術). If several clinical studies could show Efficacy and Safety, new medical technology (cell therapy) would be transferred to Routine Medical Practice (常規醫療技術) conducted within hospital .

Regulatory Evolution in Taiwan-2

After TFDA Inauguration (2010)



Tissue (cells) for Transplantation

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EX:

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Cultured Cells for Disease Treatment

Products

Law and Regulation:

◆**Pharmaceutical Affairs Act (藥事法)**

◆**Regulation on Medical Products Registration** (Licensing to Drug) **(藥品查驗登記審查準則)**

◆**Regulation on GMP** (Licensing to Facility)

- ✓ Guidance on Investigational Cell Therapy Products
- ✓ Good Tissue Practice (GTP)
- ✓ Donors Eligibility *(draft)*
- ✓ Guidance on Registration Cell Therapy Products *(draft)*

Current Law, Regulation, Guidance

Tissue/Cells

LAW

Human Organ Transplantation Statute (人體器官移植條例)

Pharmaceutical Affair Act (藥事法)

Regulation

- Regulation on Human Tissues Banking
- Regulation Importation & Exportation

Regulation on Medical Products Registration (藥品查驗登記審查準則)

Guidance

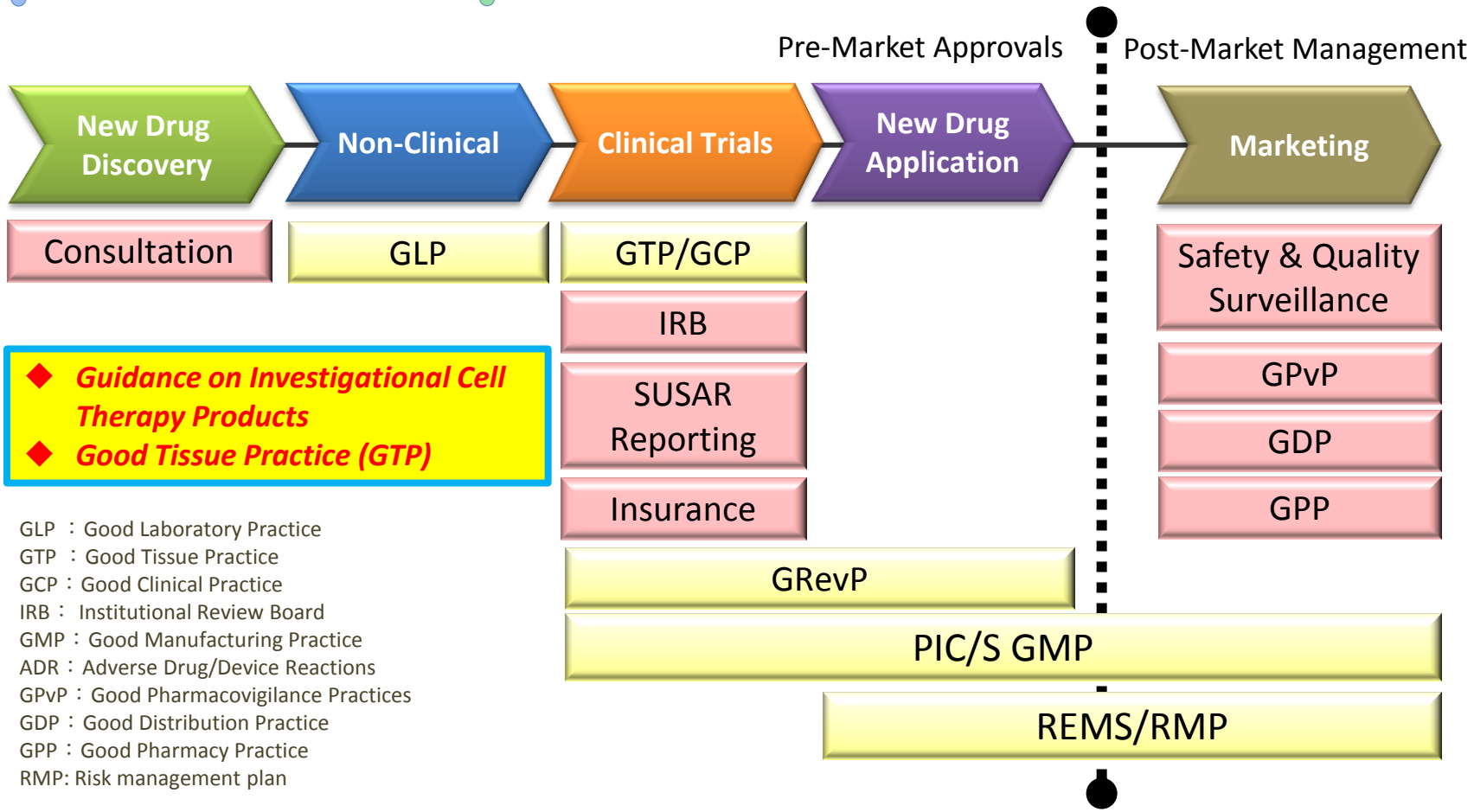
Good Tissue Practice (細胞組織優良操作規範)

- Guidance on Investigational Cell Therapy Products
- Good Tissue Practice (GTP)

Life Cycle Management of Medicinal Products

Cell regulated as Drugs…

Life cycle management of medicinal products (全生命週期之管理)
Safety, Effectiveness, and Quality (manufacturing consistency)



- ***Guidance on Investigational Cell Therapy Products***
- ***Good Tissue Practice (GTP)***

GLP ：Good Laboratory Practice
GTP ：Good Tissue Practice
GCP：Good Clinical Practice
IRB： Institutional Review Board
GMP：Good Manufacturing Practice
ADR：Adverse Drug/Device Reactions
GPvP：Good Pharmacovigilance Practices
GDP：Good Distribution Practice
GPP：Good Pharmacy Practice
RMP: Risk management plan

Guidance on Investigational Cell Therapy Products

◆ *2014. 09.17 TFDA announcement*

Application Process（申請作業)
Points to consider of Cell Therapy Products (審查考量)

◆ *Definition of Cell Therapy Products*

The autologous or allogeneic cells are used to treatment, prevent or diagnose diseases.

人類細胞治療產品（Human cell therapy products），係指使用取自人類自體（autologous）或同種異體（allogeneic）的細胞，施用於病人，以達到疾病治療或預防的目的。

◆ *Setup 4 criteria to ADJUST review process*

- Minimally manipulated (最小操作)
- Homologous use (同源使用)
- No combination (無合併其他物質)
- No systemic effects (無全身性作用)

Four Criteria to ADJUST review process

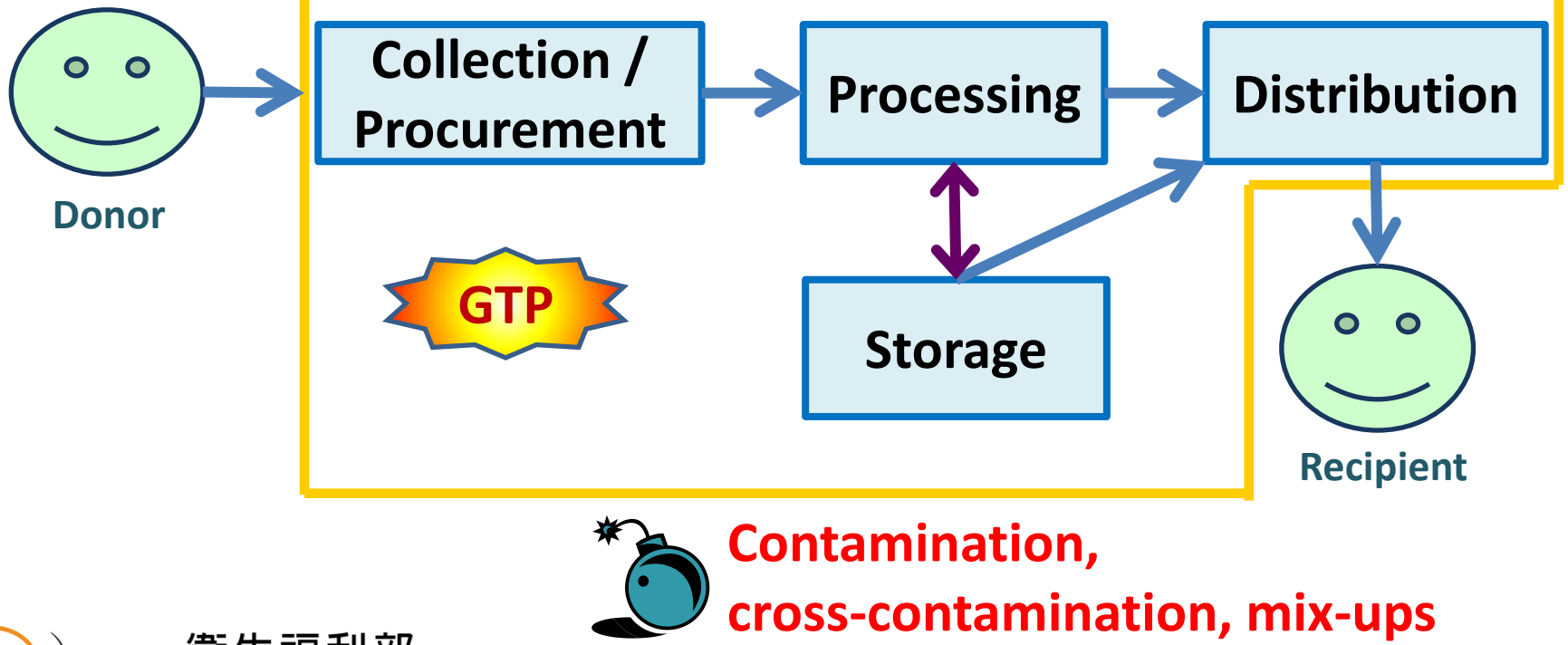
Minimal Manipulation	Homologous Use	No Combination	No systemic effects
• **NO CELL CULTURE** • Processing that does **NOT alter the relevant biological characteristics of cells** • ***Ex:***, centrifugation, cell selection, concentration, purification, irradiation, freezing, cryopreservation…	• The repair, construction, replacement, or supplementation of cells with a biological **that performs the same basic functions in the recipient as in the donor.**	• Not combine with another article, such as cells, medicine, medical device.	• Does not have a systemic effect (except for autologous, family-related or reproductive use)

Fast Track

Risks in Human Cell Products

Pathogen infection
Disease transmission

Adverse effects on the quality or safety Product (inflammatory/immune response)



Contamination,
cross-contamination, mix-ups

Good Tissue Practice (GTP)

2005 → 2007

Transition period

(宣導期)

- GTP Guidance announced on Dec.13, 2002
- A supplemental requirement to ensure safety and quality of cell, tissue, and cell/tissue derived products.

Counseling

(輔導期)

- Human studies or implantation using human origin substances

bone, cartilage, ligaments, tendons, heart valves, corneas, hematopoietic stem cells derived from peripheral blood and cord blood, epithelial cells, Cell therapy products etc.

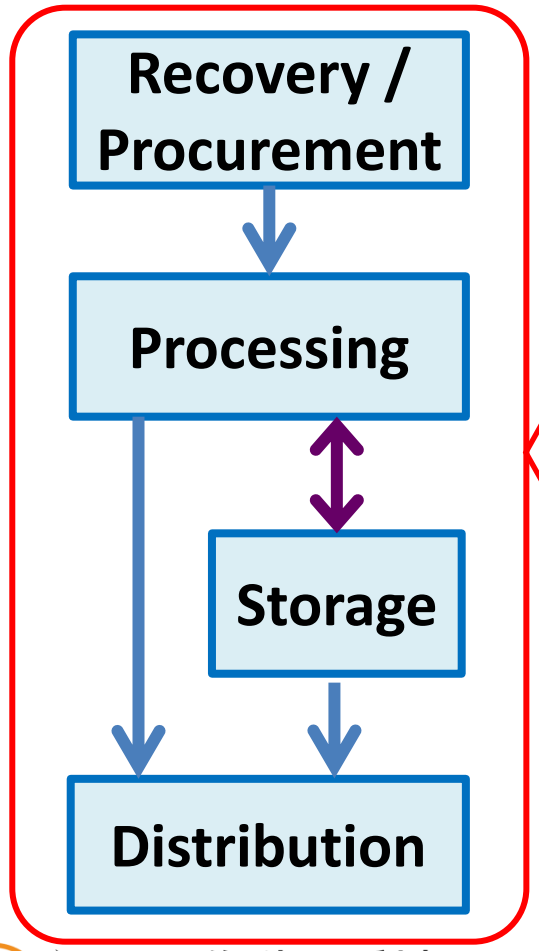
Enforcement

(執行期)

- To establish reliable quality assurance systems.
- To prevent the introduction, transmission or spreading of communicable diseases.

Content of GTP Guidance-1

Quality Management System

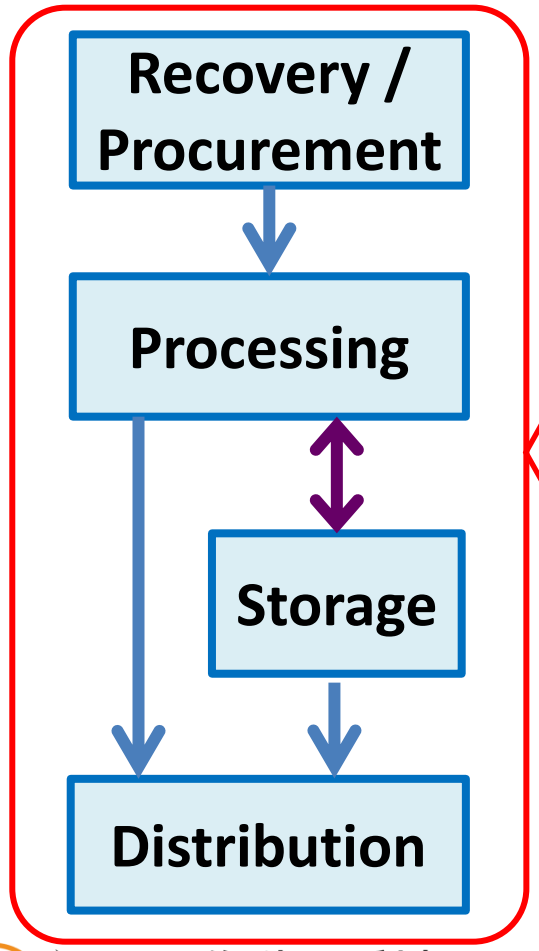


- 18 chapters; 64 articles
- Reference: US FDA 21 CFR 1271 part D

1. General Rules (總則)
2. Quality Programs (品質計畫之建立與維持)
3. Personnel and Organization (組織與人員)
4. Standard operation procedures (作業程序)
15. Records (紀錄)
16. Tracing Control (追蹤)
17. Complaint file (訴願檔案)
18. Enforcement (附則)

Content of GTP Guidance-2

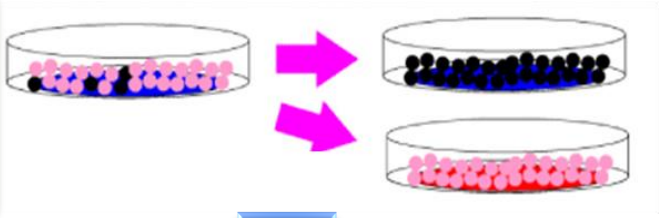
- 18 chapters; 64 articles
- Reference: US FDA 21 CFR 1271 part D



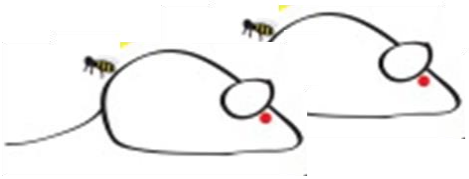
5. Facilities or Premises (設施與場所)
6. Environmental Control & Monitor (環境管制監控)
7. Equipment (設備)
8. Materials and Reagents (物料與試劑)
9. Process Control (製程管制)
10. Process Change (製程變更)
11. Process Validation (製程確效)
12. Labeling Control (標示管制)
13. Storage (儲存)
14. Receipt and Distribution (收送與配送)

Points to Consider on Cell Products-1

Quality and Safety
Cell source, Cell banks, Quality Control Testing

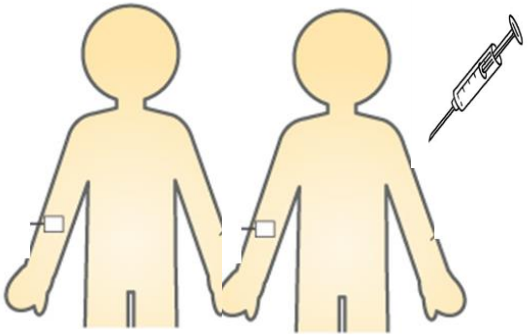


Pharm/Tox data
to support clinical trial design



Reports: Quality, Safety, and Efficacy of cell product for human use.

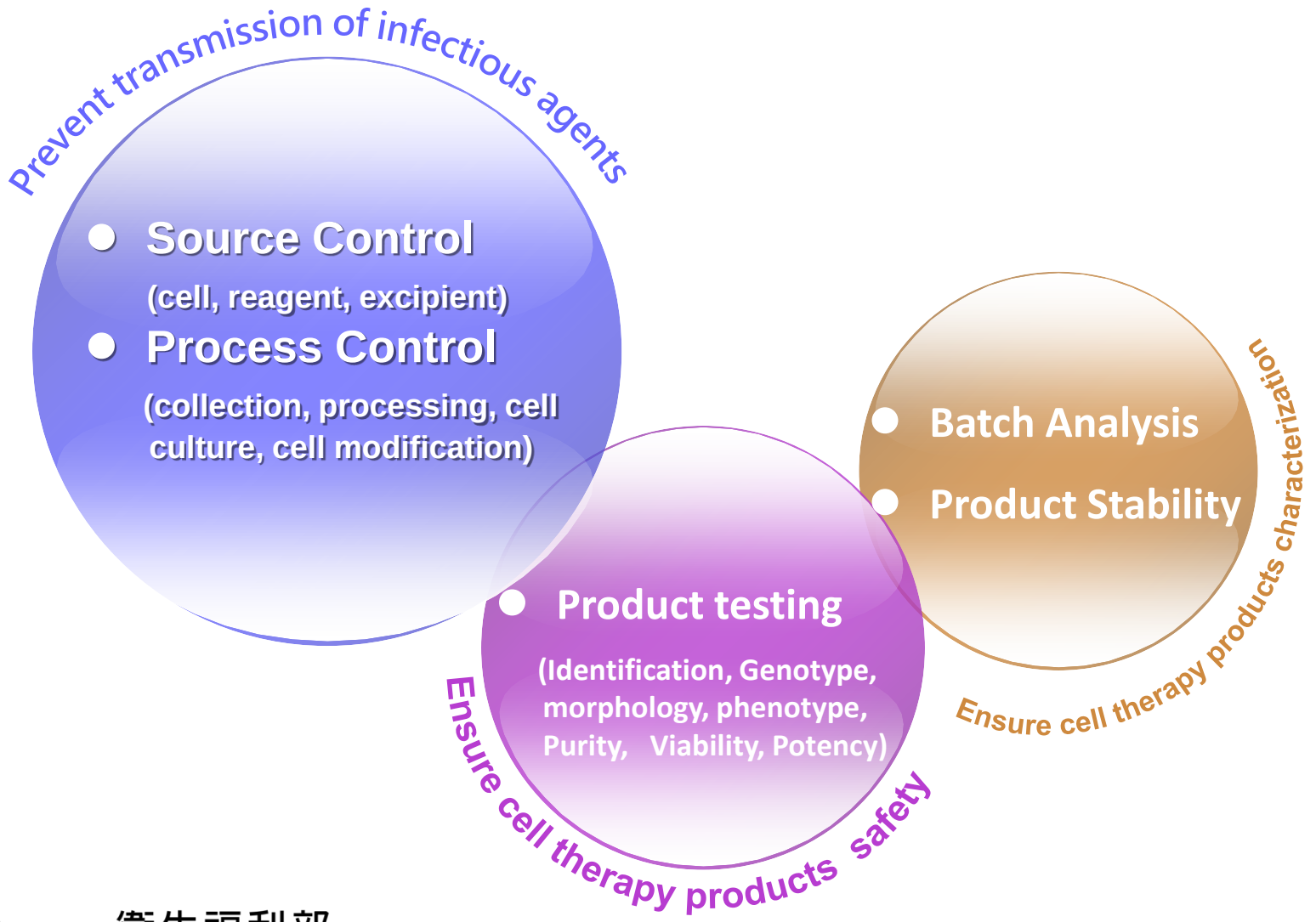
Safety and Ethical
Description of *Benefits/Risk* to subjects



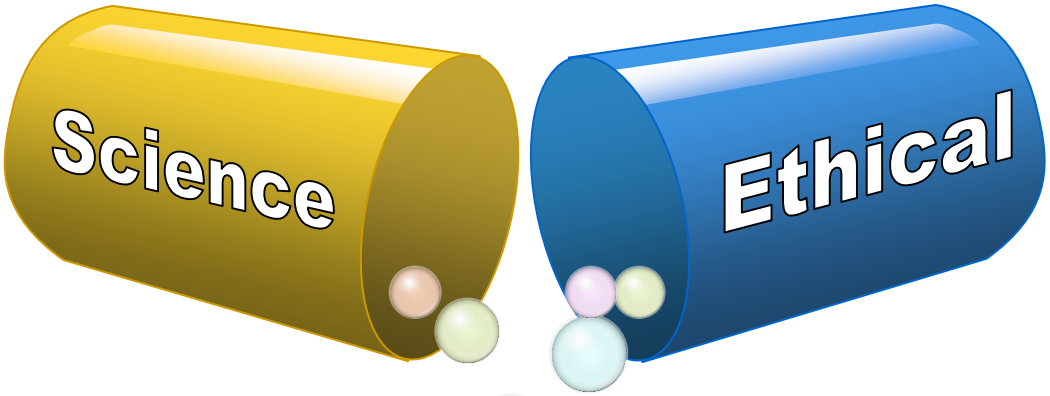
Points to Consider on Cell Products-2

CMC	Non-Clinical	Clinical
■Source Controls (Cells, Reagents, Excipients) ■Cell Banks (Size, Passage number) ■Manufacturing Control (in process; final release) ➢ Identity ➢ Purity/Impurities ➢ Safety • Sterility • Mycoplasma • Adventitious agent Testing ➢ Potency ➢ Tumorigenicity ■Stability (Consistency) ■Product Traceability and Labeling	■Pharmacology (relevant animal models of disease; injury if possible) ■Toxicology (relevant healthy animal species) ■Tumorigenicity ■Cell distribution studies ■Kinetic, migration, and persistence	■Preclinical experience ■Current clinical experience ■Objectives ■Study design (administration procedure, proposed dose levels, regimen, escalating) ■Selection of patients (inclusion/exclusion criteria) ■Safety evaluations ■Efficacy evaluations ■**Rights of subjects** ■Statistical considerations ■Traceability System

Considerations of CMC issues



Considerations of Clinical issues

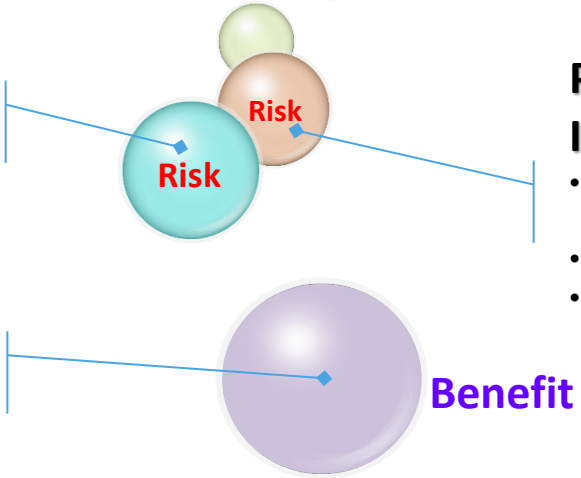


Population selection *vs.* Efficacy evaluation

Cell clinical trials are conducted in the disease population, not in healthy volunteers.

Customized products

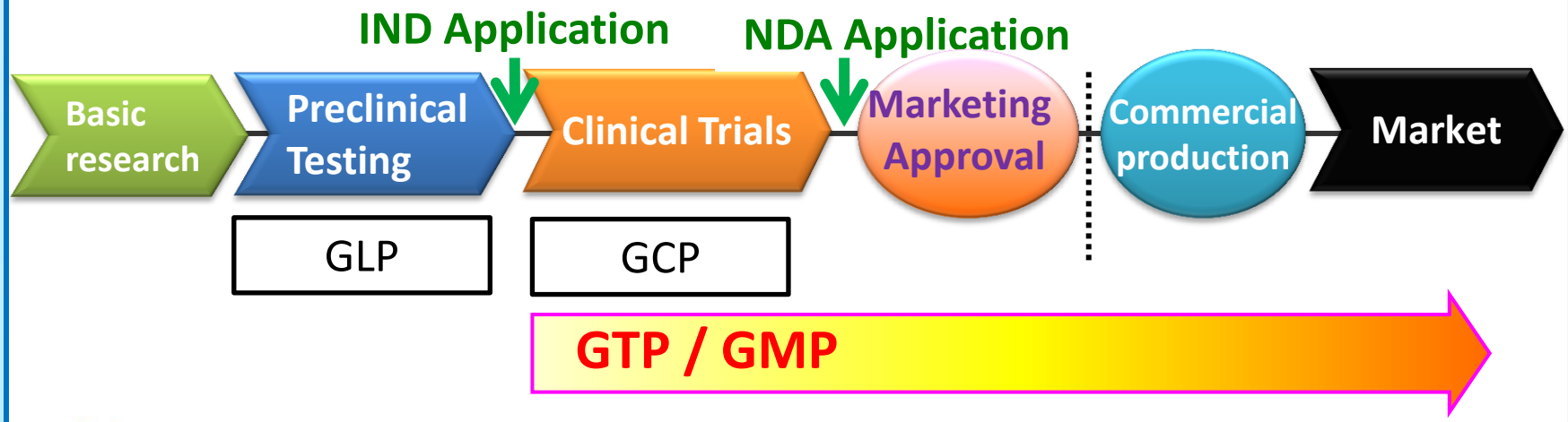
Cell therapy products for the treatment of the serious diseases that cannot be treated using conventional chemical or protein drugs.



Potential Risk *vs.* Informed consent

- Cell might persist for an extended period or produce a sustained effect
- Transformation and tumorigenesis
- Potential inflammatory and immune response

IND/ NDA Application



Consultation is necessary before IND or NDA application

Consultation
- Pre-filing meeting
- Sponsor meeting

Facilitate Application Approval
- ➢ Detailed manufacturing information
- ➢ Non-Clinical studies to show the safety and effect of cell products
- ➢ Clinical trials design supported by manufacturing, non-clinical data

Evaluation Process

Application submitted to TFDA

Documentation Evaluation

Integrated Medicinal Products Review Office (iMPRO)

Administrative part	Technical part			
	CMC	Pharm/Tox	Clinical	Statistics

Assessment Report

Advisory Committee For Regeneration

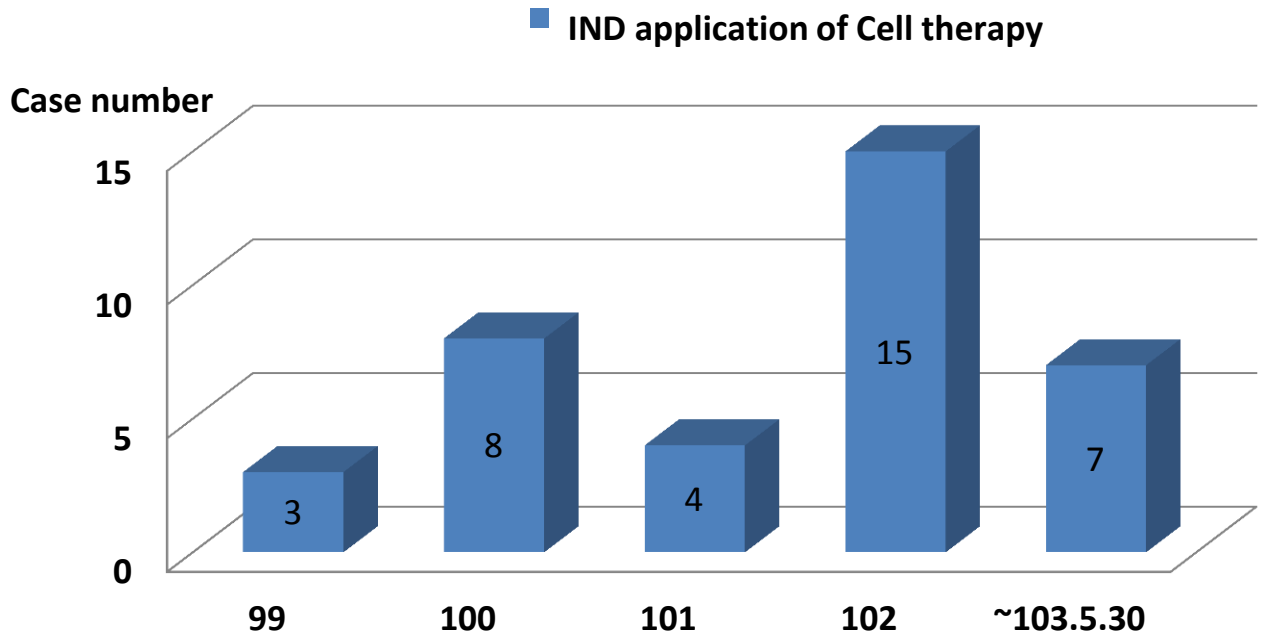
Asking for suggestion

When necessary

Providing opinion

Final Decision made by TFDA

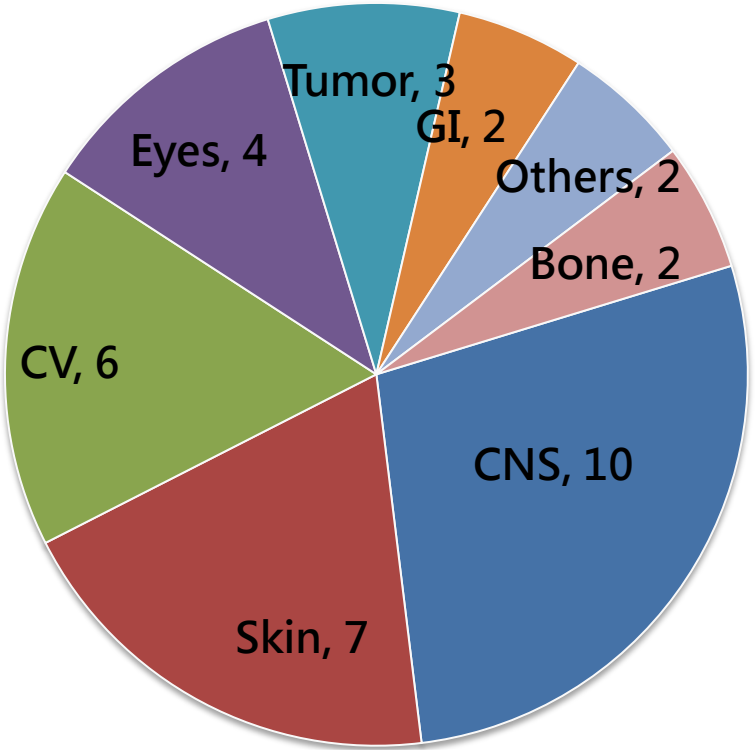
Application Statistics of Cell Therapy Clinical Trial in Taiwan -1



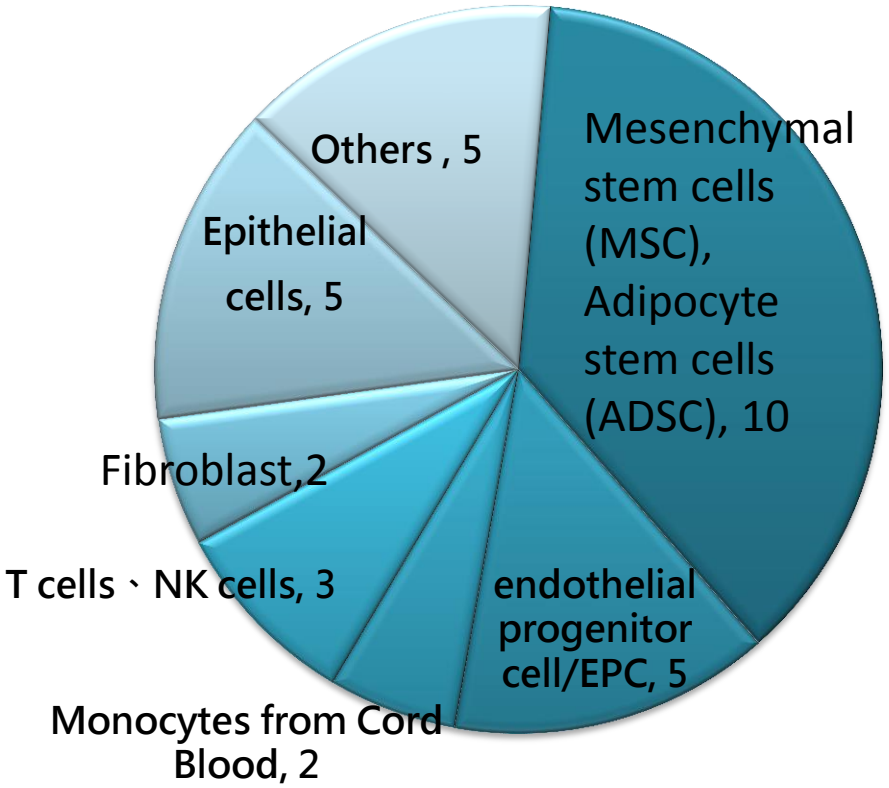
	Case number (2010~2014.5)	Approval rate	2013 review time (announcement time)
Cell therapy (IND)	36	52% (13/25) (disapproval: inadequate data)	126.6 days (150days)

Application Statistics of Cell Therapy Clinical Trial in Taiwan -2

Indications (case number)



Cell types (case number)



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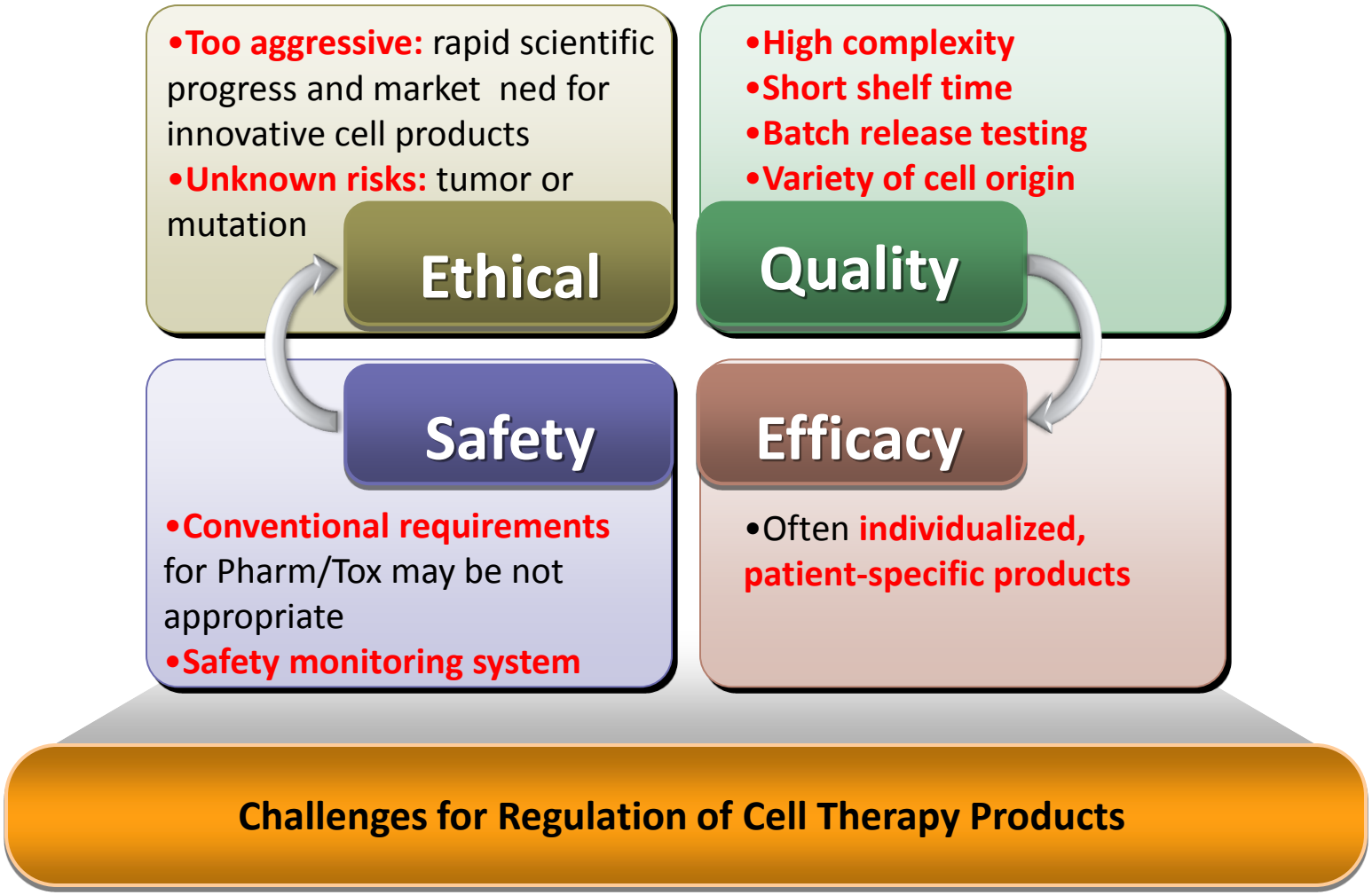
Challenges for Regulation



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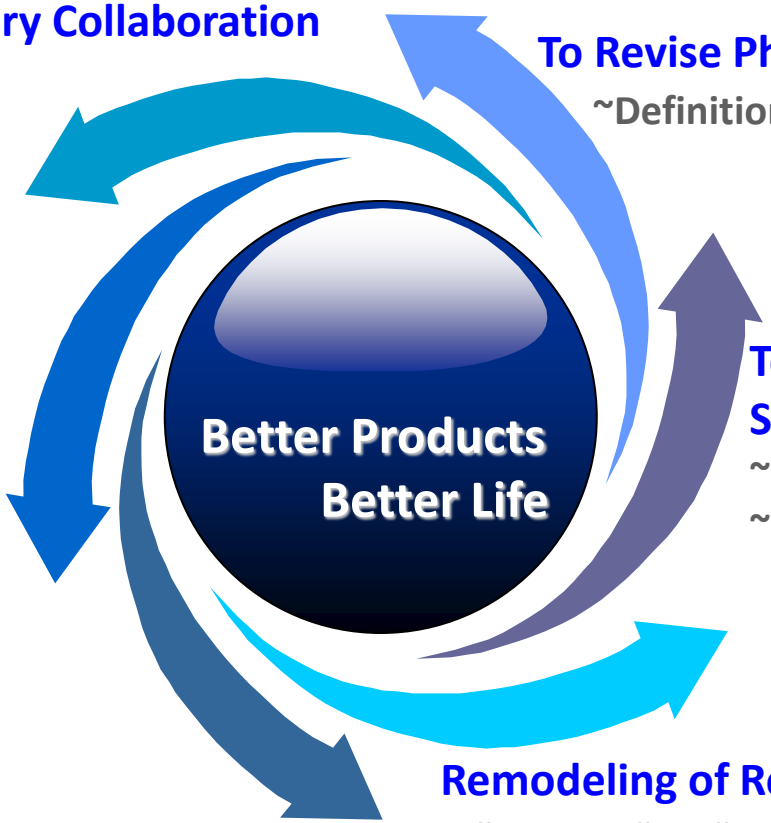
Future Prospects

To Enhance International, Regional and Cross-strait Regulatory Collaboration

To Revise Pharmaceutical Affair Law
~Definition of cell therapy products



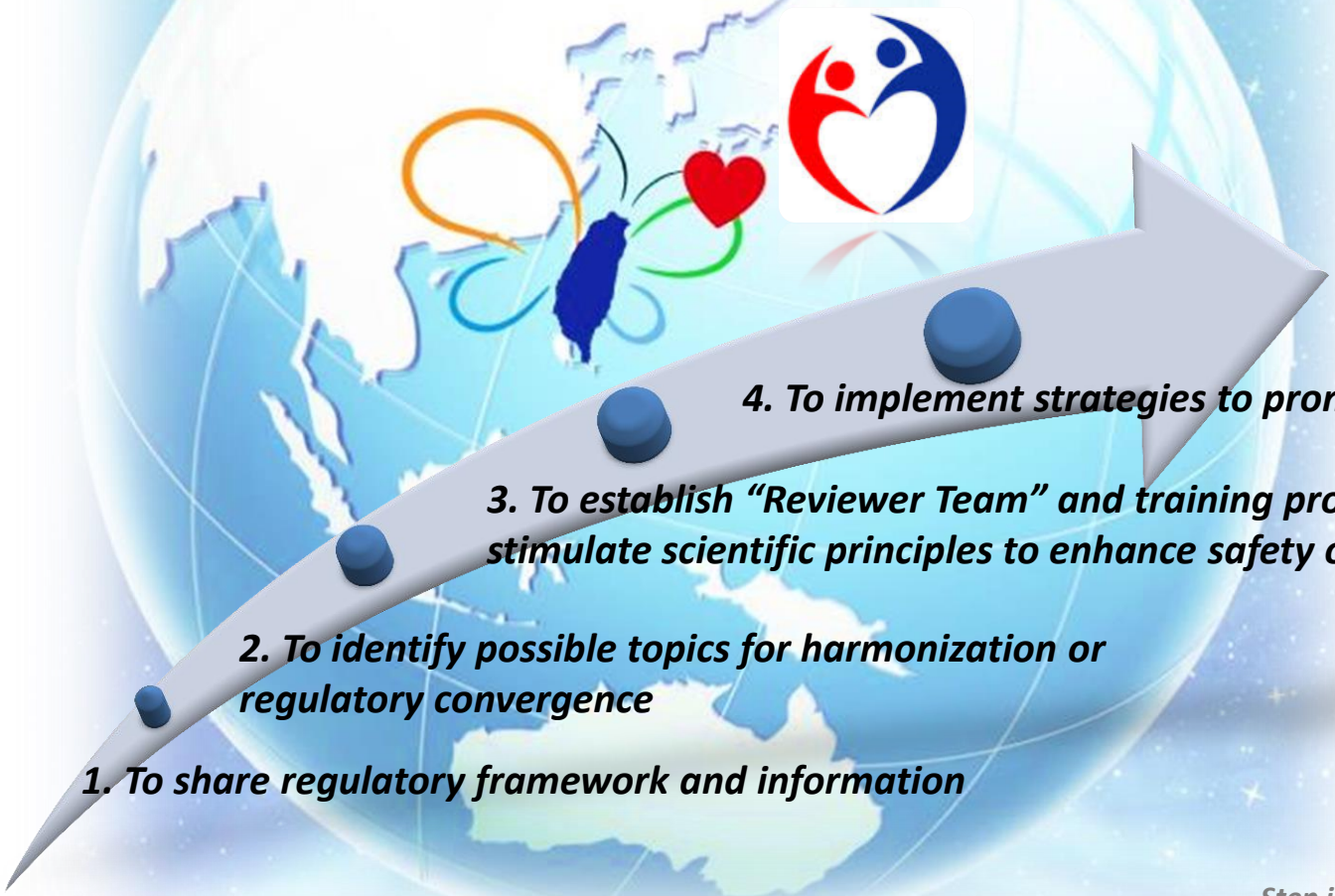
To Establish Training Programs
~ GTP, GMP, and Specificity of cell production process

To Continue Establishing Specific Guidance
~Donor eligibility
~Registration of cell products

Remodeling of Regulation of Cell Therapy
~ "Practice" or "Products"
~ "Technology" or "Medicine"

To Improve Consultation Mechanism

Image for the cooperation between Taiwan and Japan



4. To implement strategies to promote collaboration

3. To establish "Reviewer Team" and training program to stimulate scientific principles to enhance safety of products

2. To identify possible topics for harmonization or regulatory convergence

1. To share regulatory framework and information

Step in to Taiwan Today
Step out to the World Tomorrow

Future Prospects

Consumer Protection

Win-Win-Win

Government
Smart Administration

Industry
Competences Enhancement

Thank You for Your Attention

For more information

Website is at: http://www.fda.gov.tw