Regulation Strategies to Promote R&D of Biopharmaceuticals in Taiwan

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Outlines

- Recent Regulatory Strategies
- Regulatory Updates on Biological Products - biosimilars and cell therapy
- International regulatory involvements
Challenges of Taiwan

- Domestic market is too small to support huge R&D cost for new drug development
- Most of local companies are lack of financial and technical resources to become global pharma players
- Academician’s lack of genuine interest in helping industrial development and unfamiliar with regulatory requirements
- “Translational GAP” from basic research to clinical development
Strategies to Facilitate the Development of Biotech and Pharmaceutical Industry in Taiwan

**Funding**
- Tax Benefits
- R&D Grants Programs
- Joint Investment of the Government Fund
- Low Interest Loan
- Discounted rental fee for Loan 

**R&D Environment**
- National Research Program for Biopharmaceuticals (NRPB)
- Excellence GCRC program
- Taiwan Clinical trial Consortium

**Regulation**
- Consistent and Efficient Review Capacity with high Quality (GRP/ICH)
- Active consultation service

*by MOEA*

*by MOST*

*by MOHW*
Action Plans for Biotech Takeoff

- Basic R&D
- Commercial Exploitation
- Clinical Research
- Marketing

MOEA bridge basic R&D to commercial exploitation

Biotechnology Venture Capital (BVC)

National Development Fund attract non-governmental investment

Commercialization R&D Center (MOEA)

Si2C provide IP, technics and commercialization integrative service platform

Regulatory Environment Harmonized with International Standards

TFDA/CDE establish superior review capacity and provide active consultation services
Regulatory Infrastructure for Medical Products

MOHW

TFDA

CDE

TDRF
Framework of Marketing Approval Evaluation

Center for Drug Evaluation, CDE

IND Protocol Review & Consultation

NDA/ANDA/DMF Review & Consultation

Sponsor

TFDA

Arrows in red are for IND and NDA application. Arrows in blue are consultation.

CDE was established at 1998 by DOH (now MOHW) to assist TFDA to evaluate the marketing approval for pharmaceuticals and medical devices.
Framework of Drug Safety/Quality Surveillance

TFDA

Taiwan Drug Relief Foundation

National ADR Reporting Center (1998)
Medical Product Quality Defects Reporting Center (2004)

Industry (Periodic Safety Update Reports)

Hospitals, pharmacies, industries, and consumers

Local health authorities
Review Process for NDA

Sponsors Application

TFDA

TFDA + CDE

Administrative Section

- CMC
- Pharm/Tox
- PK/PD
- Clinical
- Statistics

Technical Section

Consult with AC Experts if needed

Assessment Report

PMF PIC/S GMP

TFDA Decision

Sponsors

Advisory Committee

Global new, NCE/Biological products, Biosimilar, etc.
Comprehensive and Multidisciplinary NDA Review in CDE, Taiwan

Team Approach
- Multidisciplinary
- Communication
- Consensus building

Decision Making
- Evidence-based
- Benefit-Risk Assessment

NDA Review Team in CDE
- Clinical Medicine
- Statistics
- Administration
- Project Manager
- Non-clinical CMC, Bio, Pharm/Tox, PK/PD
Principles of GRP are the Keys

**Efficiency**
- SOPs
- On-line tracking system
- QA meeting

**Quality Consistency**
- Competency building: 1-1 tutoring, case studies, seminars
- Electronic database
- Templates
- Internal/External QA System

**Clarity Transparency**
- Consultation
- Sponsor meeting
- AC meeting schedule announced on web
- Summary of review report for NDA of NCE published on-line
Risk-based Review Path for NDA since 2011

- **Accelerated Approval**
- **Review Path for NDA**
  - **NCE**
    - Regular Review: 360 Days
    - Abbreviated Review: 180 Days
    - Priority Review: 240 Days
  - **Non-NCE**
    - Regular Review: 200 Days

- **Abbreviated Review**: NCE + US FDA & EMA Approved + No Ethnic Differences & Same Indications
- **Priority Review**: NCE + Serious Disease + Unmet Medical Needs
- **Accelerated Approval**: NCE + Unmet Medical Needs → Surrogate endpoint CT
For imported New Drug, do they need to conduct clinical trials in Taiwan?

- Two key steps in New Drug Review
  1) BSE submission and review
     - Registration of Medicinal Products Article 22-1
     - assessment of ethnic difference based on ICE E5
     - grant waiver or not
  2) NDA submission and review

- If BSE is “NOT WAIVED”, Bridging Studies must be conducted in order to extrapolate foreign clinical data to Taiwan population.
Bridging Data Evaluation

- Comparison of PK profiles between Caucasian & East Asian
- Subgroup analysis of East Asian population from global trials (MRCT)
- Phase II dose-response data from East Asian (very useful !)
- Results of bridging study in East Asian
- East Asian phase III (confirmatory trial) data; beyond the scope of bridging study
Relaxation of CPP Requirements for Imported NCE Registration

- Regulations for Registration of Medicinal Products - Article 38-1, 38-2, 38-3, 38-4

NCE Review

 CPP: Certification of Pharmaceutical Products

**Article 38-1 (Non-CPP)**
- Full Technical Dossier
- Early Development in Taiwan (p1+p3 or p2+p3)
- + RMP

**Article 38-2 (1-CPP)**
- Full Technical Dossier
- + CT in Taiwan (p1 or p2 or p3)
- + RMP

**Article 38-4 (2-CPP)**
- Any 2 of the 10 Reference Countries
- USFDA+EMA (Abbreviated Review)

- Full Technical Dossier
- + RMP if Necessary
- + Abbreviated Technical Review
Incentives by NHIA Pricing Policy

- A 10% mark-up of reimbursed price for “local clinical trials” to address ethnicity-specific safety and efficacy
- Regulation for Registration of Medicinal Products - 38-1: (either one of following)
  - Phase I (10+) & Phase III (80+ with similar results)
  - Phase II (20+) & Phase III (80+ with similar results)

NHIA: National Health Insurance Administration
TFDA was the First Agency Approved Afatinib in the World

- **Approved Indication**: Indicated for the first line treatment of patients with locally advanced or metastatic non small cell lung cancer (NSCLC) with EGFR TK activating mutation
- **Review Track**: Non-CPP follow Regulations for Registration of Medicinal Products – Article 38-1
- **Pivotal Trial**: lead by global chief PI: Dr. James Yang (National Taiwan University Hospital)
- **Total review time**: 120 days
- **Taiwan approved**: May 17th, 2013 (US FDA approved: July 12th, 2013; EMA approved: October 16th, 2013)
- **Reimbursement price**: 10% mark-up
Regulatory Updates on Biological Products in Taiwan
Updates for Marketing Submission

- It is required to submit dossiers in ICH CTD format for new drug (NCE + biologics) applications (Nov. 1, 2012) and generic application (July 1, 2014).
Regulation for Biologics

Many guidance have been published to regulate the registration of biologics. Most of them follow the international best practice.

Not only to local guidance, review of biologics also take references from international regulations issued by ICH, WHO, US FDA, EU EMA, and Japan MHLW/PMDA.
Regulatory Framework Development for Biosimilar in Taiwan

Guidance for Review and Approval of Biosimilar Products (11/2008; amended draft 1/2012)

Points to Consider for Common Technical Documents (CTD) in Review and Approval of Biosimilar Products (8/2010)

Guideline for Review and Approval of Biosimilar Monoclonal Antibodies (9/2013)
Scope for Biosimilar

- Well-characterized recombinant peptides and protein products could apply for biosimilar medicine.
- Vaccines, allergen, blood- or plasma-derived and its recombinant substitution and other biological medicine (e.g. gene or cell therapy) are not suitable.
Reference Product

The same RP should be used throughout the head-to-head comparability studies.

The chosen RP must be authorized in Taiwan.

The active substance in molecular and biological terms should be highly similar.

The dosage form, strength and route of administration should be the same as that of RP.
Issues and Challenges on Reviewing Biosimilars

- Use of reference product not sourced from Taiwan
- Indication extrapolation
- Interchangeability
- Use of reference product not authorized in Taiwan??
  - New drug application with biosimilar package
  - Additional information based on scientific consideration (case by case)
Regulatory Evolution -1
Before TFDA Inauguration (2010)

**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.

**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.
Regulation of Cell Therapy

Regulatory Evolution -2
After 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

**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 of Cell Therapy Products (draft)
Current Law, Regulation, Guidance

- Human Organ Transplantation Statute
- Regulation on Medical Products Registration
- Pharmaceutical Affair Act
- Regulation on Human Tissues Banking
- Regulation Importation & Exportation
- Good Tissue Practice (細胞組織優良操作規範)
- Guidance on Investigational Cell Therapy Products
- Good Tissue Practice (GTP)
Application Statistics of Cell Therapy Clinical Trial -1

IND application of Cell therapy

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Application Statistics of Cell Therapy Clinical Trial - 2

Organ/Tissue, case #
- CNS, 10
- Skin, 7
- CV, 6
- Tumor, 3 (GI, 2)
- Others, 2
- Bone, 2

Cell types, case #
- Epithelial cells, 5
- Fibroblast, 2
- T cells, NK cells, 3
- Monocytes from Cord Blood, 2
- Endothelial progenitor cell/EPC, 5
- Others, 5
- Mesenchymal stem cells (MSC), Adipocyte stem cells (ADSC), 10
Guidance on Investigational Cell Therapy Products

◆ **2014. 09.17 TFDA announcement**

Application Process
Points to consider for the review of investigational Cell Therapy Products

◆ **Definition of Cell Therapy Products**

Human cell therapy products are the medical products using autologous or allogeneic cells to treat, prevent or diagnose diseases.

◆ **Setup 4 criteria to ADJUST review process**

- Minimally manipulated
- Homologous use
- No combination
- No systemic effects

**SCIENCE, ETHICAL, and SAFETY**
Roles of Regulatory Authority

**Main Goal:** assure the safety, efficacy and quality of the drugs available to the public

- **Public Health Protection**
  - Gate-keeper

- **Health Promotion**
  - Enhance accessibility

[Diagram showing the process of Review leading to Proactive Consultation, followed by Move Forward]
Regulatory Consultation Services

- Enhance transparency
- Facilitate application submission for medical product registration
- Facilitate medical product development

Potential candidates of medical products R&D projects from industries and R&D organizations
Index Cases Proactive Consultation Services

Case Selection:
1. Innovation
2. Contribution to public health
3. Regulatory Compliance

Confirmation

Consultation
Team Formed

Consultation

Research Projects from R&D Organizations/Companies

Recommended by Agencies

CDE Consultation Team:
Team Leader, PM, senior clinicians, senior statisticians, senior pharmaceutical scientists

Procedures:
Identify Objective → Assign Task → F2F meeting → Meeting Minutes

Response in Written Document
PIC/S member since 2012
All pharmaceuticals except herbal medicines have to meet the requirements of PIC/S GMP standards at the end of 2014.

ICH
- GC
  Expert working groups

IGDRP
For generic product regulation

APEC - RHSC
Good Review Practice

Bi-lateral
Taiwan – Japan

Cross-strait Agreement
Taiwan - China
Thank You for Your Attention