Recent Trend of Pharmaceutical Regulations in Taiwan

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Outline

- Organization and Responsibility of TFDA
- Recent Trend of IND Regulations in Taiwan
- Recent Trend of NDA Regulations in Taiwan
- Recent Trend of Post-Marketing Management in Taiwan
- Future Prospects
Organization and Responsibility of TFDA
Establishment of Taiwan FDA, DoH

- Taiwan FDA (TFDA) was inaugurated on Jan. 1st, 2010
- Four Bureaus of Department of Health was integrated

- Food Safety
- Pharmaceutical Affairs
- Food & Drug Analysis
- Controlled Drugs

食品處
藥物食品檢驗局
藥政處
管制藥品管理局

10th Annual Meeting DIA Japan 2013
November 6-8 | Tokyo
Reorganization of Taiwan TFDA, MOHW

The Ministry of Health and Welfare (MOHW)

- Formed on July 23rd, 2013 from the Department of Health
- Following the restructuration of the Executive Yuan

To Promote The Health And Well-being Of All Citizens.
Our Vision and Mission

Vision

- To Safeguard National Health and Lead the Nation to a New Era of Food and Drug Management

Mission

- To Safeguard Food and Drug Safety
- To Begin a New Technology Era
- To Create a Safe Consumer Environment

Assure QUALITY, SAFETY, EFFICACY of Medicinal Products

Help to Speed the Development of Innovative Medicine
Pharmaceutical Regulation in Taiwan

- Life cycle management of medicinal products

**New Drug Discovery**
- Consultation

**Preclinical Testing**
- GLP/GTP

**IND**
- GCP
- IRB
- SUSAR Reporting
- Insurance

**NDA**
- GRevP

**Marketing**
- Safety & Quality Surveillance
- GPvP
- GDP
- GPP
- Drug Injure Relief

**Pre-Market Approvals**
- PIC/S GMP
- REMS/RMP

**Post-Market Management**

ICH –Based Regulations
Recent Trend of IND Regulations in Taiwan
Review Process for IND Applications

1. Hospital, Sponsor, CRO
2. TFDA
3. Integrated Medicinal Products Review Office (iMPRO)
   - Technical Section
     - Administrative Section
     - CMC
     - Pharm/Tox
     - PK/PD
     - Clinical
     - Statistics
   - TFDA+CDE
4. Assessment Report
   - Consult with AC Experts if needed
5. TFDA decision
6. Hospital, Sponsor, CRO

First-in-human, Ethnic & Ethical Concern, Cell/Gene Therapy, etc.

Advisory Committee
Establishment of Modern Clinical Trial Infrastructure in Taiwan

Goal

- Establish infrastructures for clinical trial conduction to meet international standard
- Strengthen quality of clinical trials and enhance IND review efficiency
- Introduce early-phase multi-national, multi-center trials, concurrently with global drug development
Establishment of Modern Clinical Trial Environment in Taiwan

- Enhance IND Review Efficiency
- GCP Inspection
- Training for Clinical Trial Professionals
- Government Funding Research Centers & Qualified Clinical Trial Sites for IND
- Enhance IRB Quality and Review Efficiency
Applicable for:
1. IND with the Same **US FDA-Approved** IND Number (July, 2004)
2. Multinational multicenter trials *simultaneously conducted in one of the medically advanced countries*; Taiwan’s medical center hospital also involved (Aug, 2010)
GCP Inspection in Taiwan

■ Routine inspection
  • Clinical trials for registration

■ For-cause inspection
  • Clinical trial with SAE occurred
  • Clinical trial with GCP violation and safety concern
    ► Protocol violation, mismanagement of investigational drug (IVRS error, Error packaging), or wrong delivery of study drug (human error)

■ GCP Inspector Training
Training for Clinical Trial Professionals

- **Regulation of Good Clinical Practice**
  - Article 14
    - All staff involved in clinical trial should be qualified by education, training, and experience to perform his or her respective tasks.

- **Pharmaceutical Affairs Act**
  - Article 41 (Jan, 2013)
    - The central competent health authority shall entrust professional medical groups to conduct educational training programs to cultivate talents in skills of clinical trial every year.

- **Regulation of Human Trials**
  - Article 4
    - A trial conductor should be a licensed physician, dentist, or traditional Chinese medicine physician with **5 or more years of experience in clinical treatment**.
    - The trial conductors are required to receive human trial related training of more than 30 hours, and medical ethic related courses for more than 9 hours within past 6 years.
Government Funding Research Centers & Qualified Clinical Trial Sites for IND

<table>
<thead>
<tr>
<th>Type of Clinical Research Centers</th>
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<tr>
<td>Excellent Center of Oncology#</td>
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<tr>
<td>General Clinical Research Center+</td>
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Qualified Clinical Trial Sites for IND: 134 Teaching Hospitals
Conformation to International Regulation on Protection of Human Subjects

- Declaration of Helsinki and ICH-GCP
- IRB inspection and Certification
- SCIDER/ FERCAP Recognition Program 2005-2012

<table>
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<tr>
<th>Country</th>
<th>China</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>Thailand</th>
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AAHRPP Accreditation

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<tr>
<th>Country</th>
<th>USA</th>
<th>South Korea</th>
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<th>Canada</th>
<th>Taiwan</th>
<th>China</th>
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</table>
Central IRB System

- To control IRB review time and synchronize the trial schedule in multiple sites.

IND application from Sponsors

Review by the Central IRB

20 Days

The position of Central IRB rotates among the 5 Excellent Center and the 2 Excellent Center of Oncology

Review Results

Sponsor

Inform

Abbreviate Review by the IRB of each clinical trial sites

Submission

10 Days

Results of Abbreviate Review

Since July 1st, 2013
Simultaneous Global Clinical Trials

- MOU between Taiwan Center of Excellence and International Pharmaceutical Company

Taipei Veterans General Hospital
  - 2009 Sanofi Aventis
  - 2010 GSK
  - 2011 Norvatis

China Medical University Hospital
  - 2010 Norvatis

Chung Gung Medical Hospital
  - 2010 Norvatis, MSD
  - 2011 Norvatis

National Taiwan University Hospital
  - 2007 GSK
  - 2009 Norvatis, Boehringer Ingelheim
  - 2012 Pfizer Bayer MSD

Chung Gung Medical Hospital
  - 2010 Norvatis
  - 2012 GSK
  - 2013 MSD
Case Sharing—Afatinib

- New Chemical Entity
- Indication: Target therapy drug for advanced non-small cell lung cancer
  - a selective, irreversible ErbB family blocker for the treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation
- First approved in the world (2013)
- Multinational Trial lead by Taiwan Principle Investigator
Recent Trend of NDA Regulations in Taiwan
Review Process for NDA Applications

Sponsors application

Integrated Medicinal Products Review Office (iIMPRO)  
TFDA+CDE

<table>
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<tr>
<th>Administrative Section</th>
<th>Technical Section</th>
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<tr>
<td>CMC</td>
<td>Pharmacology/Toxicology (Pharm/Tox)</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Clinical Pharmacology (PK/PD)</td>
</tr>
<tr>
<td>Clinical</td>
<td>Statistics</td>
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Consult with AC Experts if needed

Assessment Report

TFDA decision

Sponsors

PMF PIC/S GMP

Global New, NCE/Biological products, Biosimilar, etc.

Advisory Committee
Review Track for NDA

1. New drugs (except of NCE/NME, Biologics, Botanicals)
2. Domestic Manufactured Products; fulfill PIC/S GMP regulation

- **Priority Review**: NCE + Serious Disease + Unmet Medical Needs
- **Abbreviated Review**: NCE + US FDA & EMA Approved + No Ethnic Differences & Same Indication
Recent Regulations for NDA

- Publish Assessment Report for NCE/NME (Aug. 2010)
- Points to Consider for Review and Approval of NCE/NME (Nov. 2012)
- Risk Evaluation and Mitigation Strategy (REMS) or Risk Management Plan (RMP) (April, 2012)
- Implementation of eCTD (Oct. 2012)
- NCE-2 (April, 2013)
  - The review principle for the pharmaceutical drugs that has been marketed in the ten advanced countries for 10yrs, but is a NCE in Taiwan (except for biological products)
- Relaxation of CPP Requirements (May 2012)
- Accelerated Approval (Aug, 2013)
Relaxation of CPP Requirements

NCE Review

Non-CPP
- Full Technical Dossier
- Early Development in Taiwan
- GCP GLP GMP
- Preapproval Inspection
- REMS

1-CPP
- Full Technical Dossier
- CT in Taiwan
- REMS

2-CPP
- Any 2 of the 10 Medically advanced countries
- USFDA+EMA (Abbreviated Review)
- Full Technical Dossier
- REMS if Necessary
- Abridged Technical Dossier
- REMS if Necessary

CPP: Certification of Pharmaceutical Products
Case Sharing– Afatinib

- **New Chemical Entity**

- **Indication:** Target therapy drug for advanced non-small cell lung cancer
  - a selective, irreversible ErbB family blocker for the treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation

- **First approved in the world (2013)**

- **Review Track:** Non-CPP
Accelerated Approval

- Accelerating approval for drugs for serious conditions that fill an unmet medical need
  - Base on a surrogate endpoint
    - A laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit
  - Studies that demonstrate a drug’s effect on a surrogate endpoint must be “adequate and well controlled”

- Post-marketing (Phase IV) confirmatory trials are generally required to verify clinical efficacy
  - REMS/RMPs could be required.
Recent Regulations for NDA: For Special Categories of New Drugs

- **Botanical Products**
  - Guideline for Review and Approval of Botanical Products (Apr. 2013)

- **Biologics:**
  - **Biosimilar**
    - Guideline for Review and Approval of Biosimilar Products (2008)
    - Points to Consider for Review and Approval of Biosimilar Products (2010)
    - Guideline for Review and Approval of Biosimilar Monoclonal Antibodies (Sep. 2013)
  - **Vaccines**
    - Guideline for Review and Approval of Pandemic influenza vaccines (Oct. 2010)
  - **Cell and gene therapy products**
    - Guidance on investigational human cell/ gene therapy products
    - Content and format of investigational new drug (IND) applications for human cell and gene therapy products (Draft, Feb. 2011)
Quality Assurance for Drug Manufacturing

- 158 GMP Pharmaceutical manufactories in Taiwan
  - 44 factories are in compliance with PIC/S GMP
- 1055 Registered foreign manufactories
  - 757 factories have are in compliance with PICS/GMP

January, 2013
Join PIC/S

Starting from January 2015, all medicinal product manufacturers should be in compliance with PIC/S GMP
Regulatory Consultation System

Mission:
- To promote the public health by encouraging innovation and access to new drugs

Protect
Promote
Public Health

Assure QUALITY, SAFETY, EFFICACY of Medicinal Products
Help to Speed the Development of Innovative Medicine
Regulatory Consultation System

1. Domestic R&D
2. Innovative invention
3. Major public health contribution

(Draft, Oct. 2010)
Domestic Innovative Consultation

Pre-clinical | Phase I | Phase II | Phase III | NDA review

Rolling review

Approval

Regular path consultation

S: Sponsor meeting
KO: Kick-off meeting
P: Pre-filing meeting

<table>
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<tr>
<th>Total Cases (102.6.30)</th>
<th>NDA Approval</th>
<th>NDA Review</th>
<th>Phase III</th>
<th>Phase II</th>
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Recent Trend of Post-Marketing Management in Taiwan
Post-Marketing Safety and Quality Surveillance
—Risk Management

Post-marketing product quality and safety surveillance

Quality surveillance

Safety surveillance

Reassessment / Inspection
- Labeling change
- Withdrawal/Recall

Drug product quality defect reporting system

Passive

Therapeutic inequivalence reporting system

Active

National quality surveillance Program

Active

Global Safety Information Monitoring

Passive

Retrospectively Review Safety Issues from NHI Database

Passive

PSUR by Drug Companies

Active

National ADR reporting system
Active Assessment of Drug Safety

Health Datasets from National Health Insurance (NHI)

Potential safety signals

Signal refinement

Assessing the benefit-risk balance of drugs

Take regulatory actions

Verify causal-relationship of unclear signal

Evaluate the outcomes and implementations of the regulatory actions routinely

Pilot project since 2010
Taiwan Drug Injury Relief System

TFDA

Drug Injury Relief Review Committee

Drug Injury Relief Fund

Taiwan Drug Injury Relief Foundation (TDRF)

Drug Hazad Victim

Licensed Holders

Request for Review

Review and Determine Results

Relief Fund Payment

Levies

Drug Injury Relief Application

Review Notification, Relief Fund Payment

Levies Collection, Verification, Request, Return and Claim

Drug Hazard Victim

Licensed Holders
Future Prospects

Ensure Drug Quality, Safety & Efficacy

Promote Taiwan Brand Globally

International Harmonization on Medicinal Products Regulations

Industry
Academic
Medical center

Consumer

Government

FDA
Thank You For Your Attention!