2014 50th Annual Meeting

Current Status of Pharmaceutical Regulations and the direction of international collaboration in Taiwan

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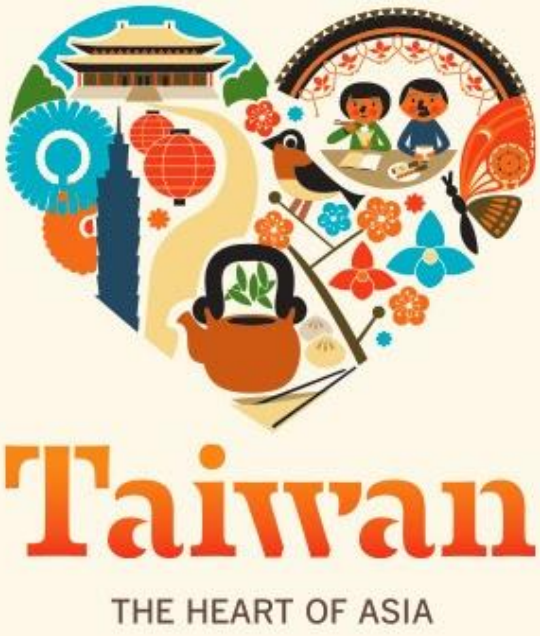
Outline

- Taiwan Profile
- Organization and Responsibility of TFDA
- Current Status of IND Regulation in Taiwan
- Current Status of NDA Regulation in Taiwan
- Current Status of Post-Marketing Management in Taiwan
- Direction of International Collaboration
- Future Prospects

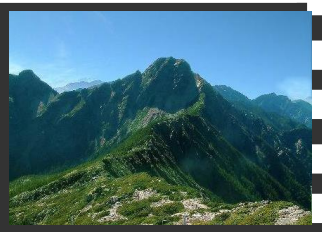
IND: investigational drug
NDA: new drug application



Taiwan Profile

Taiwan Profile

- Area: about 36,000 sq.km.
  (14,400 square miles)
- Capital: Taipei City
- Population: 23 million
- 99.8% Citizen Covered by NHI – a Single Payer and Single Database (IC Card)
- Pharmaceuticals Market:
  NT$ 82.4 Billion(US$ 2.75 Billion) in 2013





Organization and Responsibility of TFDA

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Establishment of TFDA

2009.6.3 TFDA Organization Act → 2010.1.1 TFDA Inauguration → 2011~2013 MOHW Restructure → 2013.7.23 TFDA Elevation

4 bureaus:

- Food Safety 食品處
- Pharmaceutical Affairs 藥政處
- Food & Drug Analysis 藥物食品檢驗局
- Controlled Drugs 管制藥品管理局

FDA

2013.07.23 TFDA

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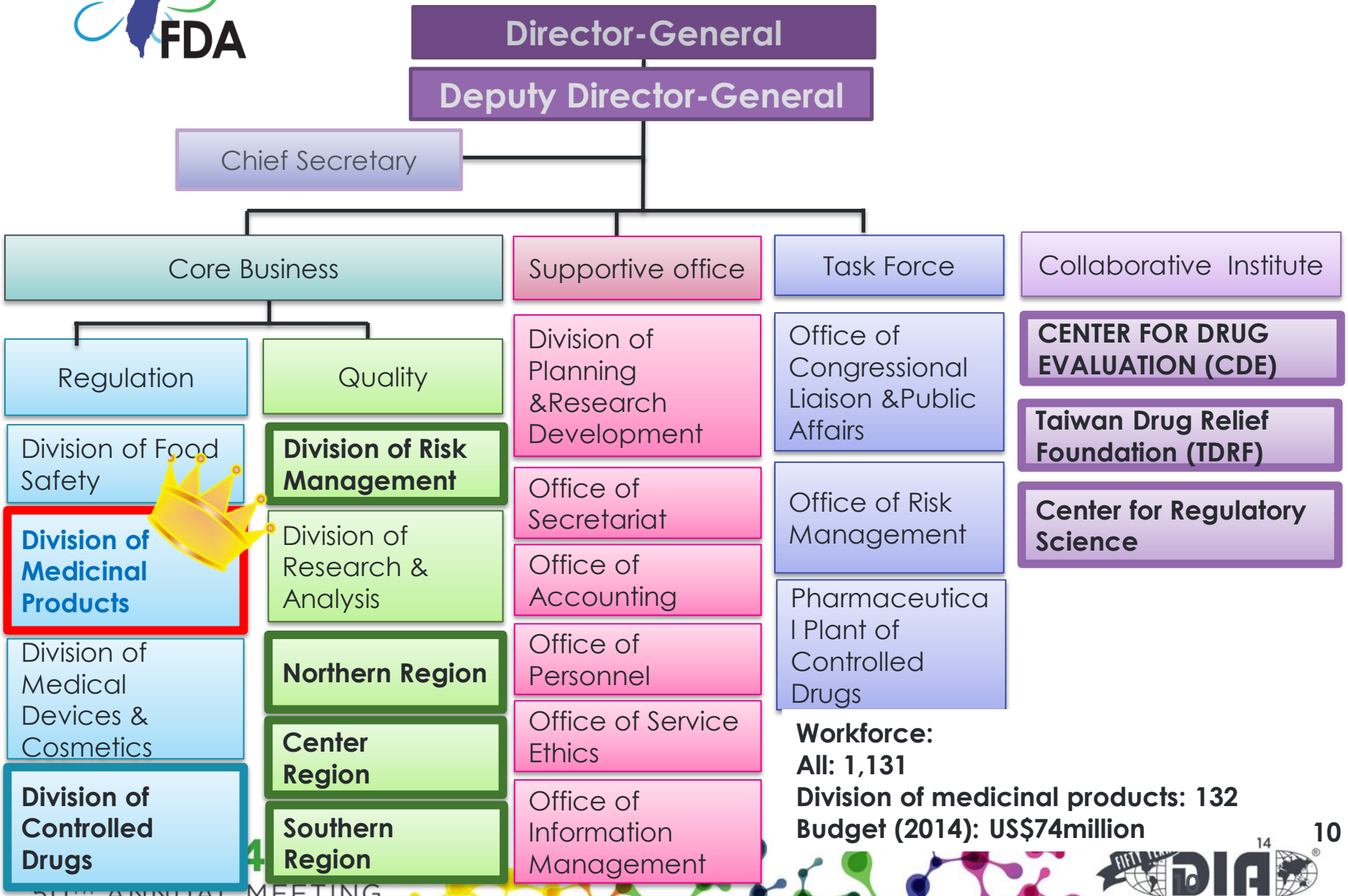
Vision & Core Value

Safe Food

Safe Drug

Food and Drug Safety Management System

TFDA Organization Chart



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

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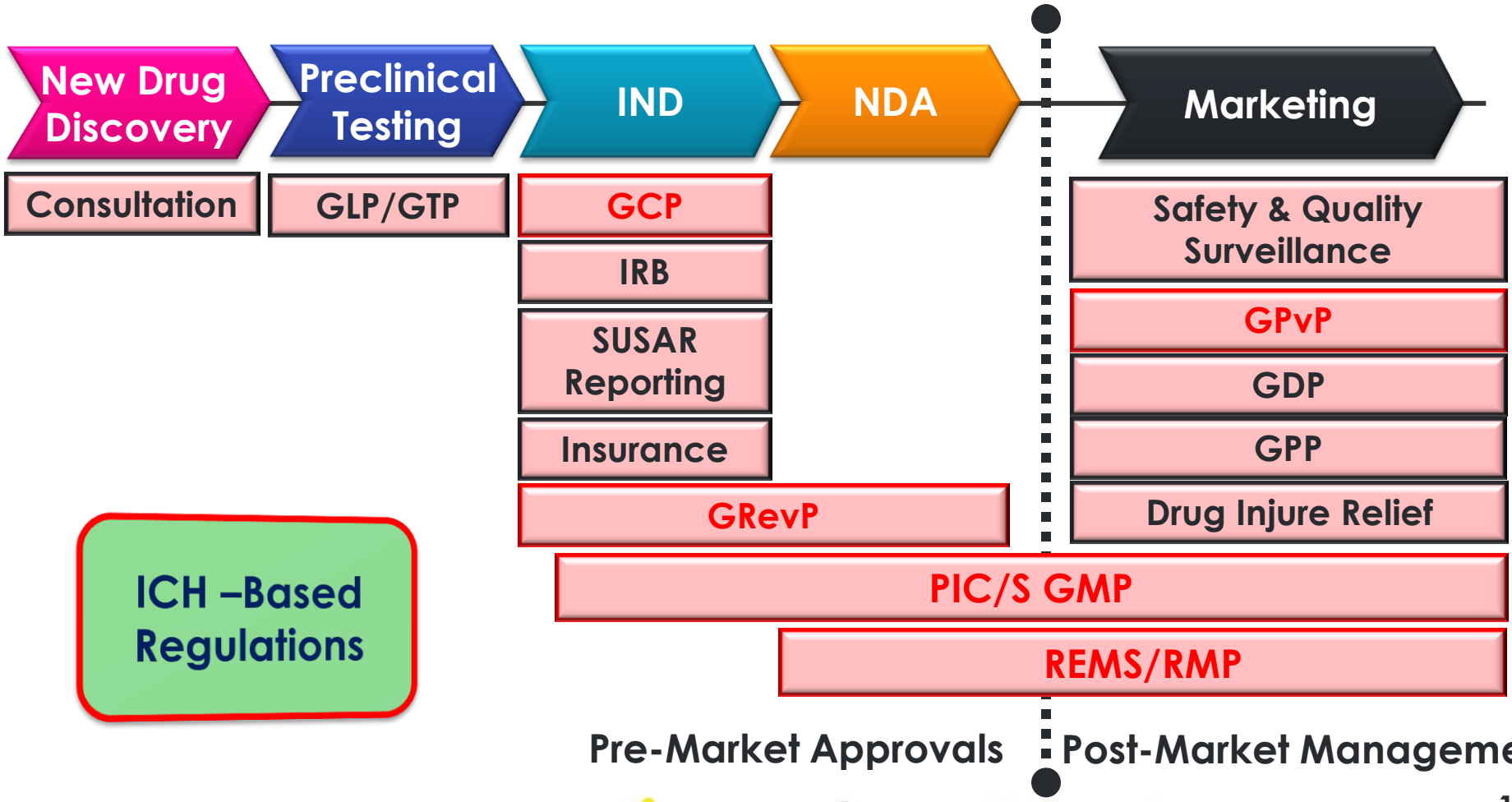
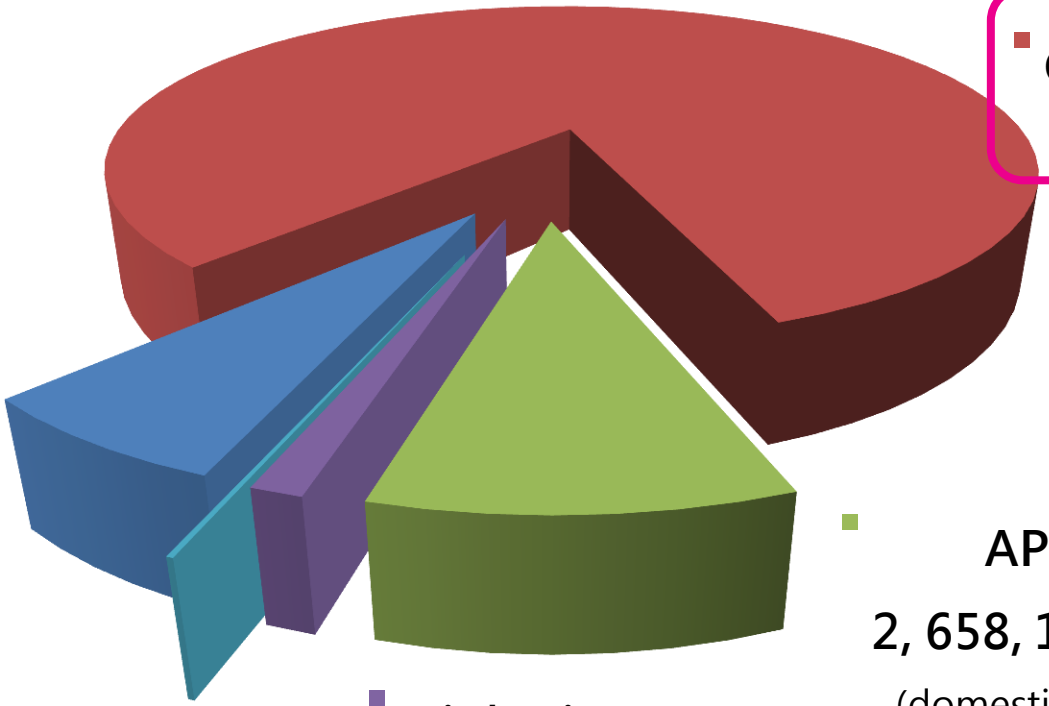
Pharmaceutical Regulation in Taiwan

- Life cycle management of medicinal products



Statistics on Pharmaceutical Licenses in Taiwan (up to date) <26,654>



Generic Drugs, 21,814; 82.0%
(domestic 19, 638; Import 2, 176)

New Drugs 1, 767, 6.6%
(domestic 492; Import 1,275)

API 2, 658, 10.0%
(domestic 582; import 2, 076)

Orphan Drugs 49, 0.2%
(domestic 9; Import 40)

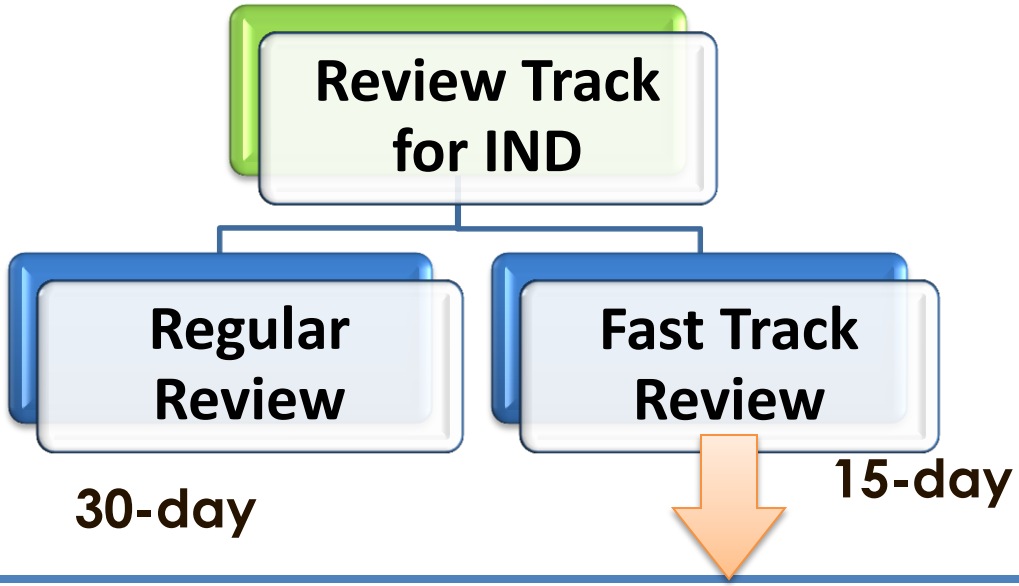
Biologics 357, 1.3%
(domestic 21; Import 336)

Current Status of IND Regulation in Taiwan

Current Status of IND Regulation in Taiwan

- Objectives
  - To enhance IND **review efficiency**
  - To strengthen **clinical trial quality**
  - To promote international collaboration of clinical trials
    - encouraging multi-regional clinical trials (**MRCT**), and early phase trials in Taiwan

Enhance IND 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)

Strengthen clinical trial quality -GCP Inspection in Taiwan

ICH-GCP

- **Regular inspection**
  - First-in human, pivotal, phase IV (30 ~ 40 cases/ yr)
  - with 1~2 cases/yr unacceptable (3~7% unaccepted)
- **For-cause inspection** (~3 cases/yr)
  - Clinical trial with GCP violation and safety concern
  - Clinical trial with serious adverse event (SAE) occurred

Strengthen clinical trial quality -Qualified Clinical Trial Sites for IND

- 131 teaching hospitals (Qualified sites) in Taiwan
  - 26 sites with government funding

Total Teaching Hospitals (qualified clinical sites) , 131					
Excellent Center*	6	Excellent Center of Oncology*	8	General Clinical Research Center*	12

- **International recognition certificate and accreditation**
  - 23 sites (Ethics committees and IRB) in Taiwan have received SIDCER # / FERCAP# Recognition certificate (2005-2012)
  - 2 sites in Taiwan have earned AAHRPP# Accreditation (~2013)

#SIDCER: Strategic Initiative for Developing Capacity in Ethical Review
#FERCAP: The Forum for Ethical Review Committees in the Asian and Western Pacific Region
#AAHRPP:The Association for the Accreditation of Human Research Protection Programs

International collaboration in Clinical Trials

- MOU between Taiwan Centers of Excellence and the International Pharmaceutical Companies

Taipei Veterans General Hospital

- 2009 Sanofi Aventis
- 2010 GSK
- 2011 Norvatis

National Taiwan University Hospital

- 2007 GSK
- 2009 Norvatis, Boehringer Ingelheim
- 2012 Pfizer, Bayer, MSD

China Medical University Hospital

- 2010 Norvatis

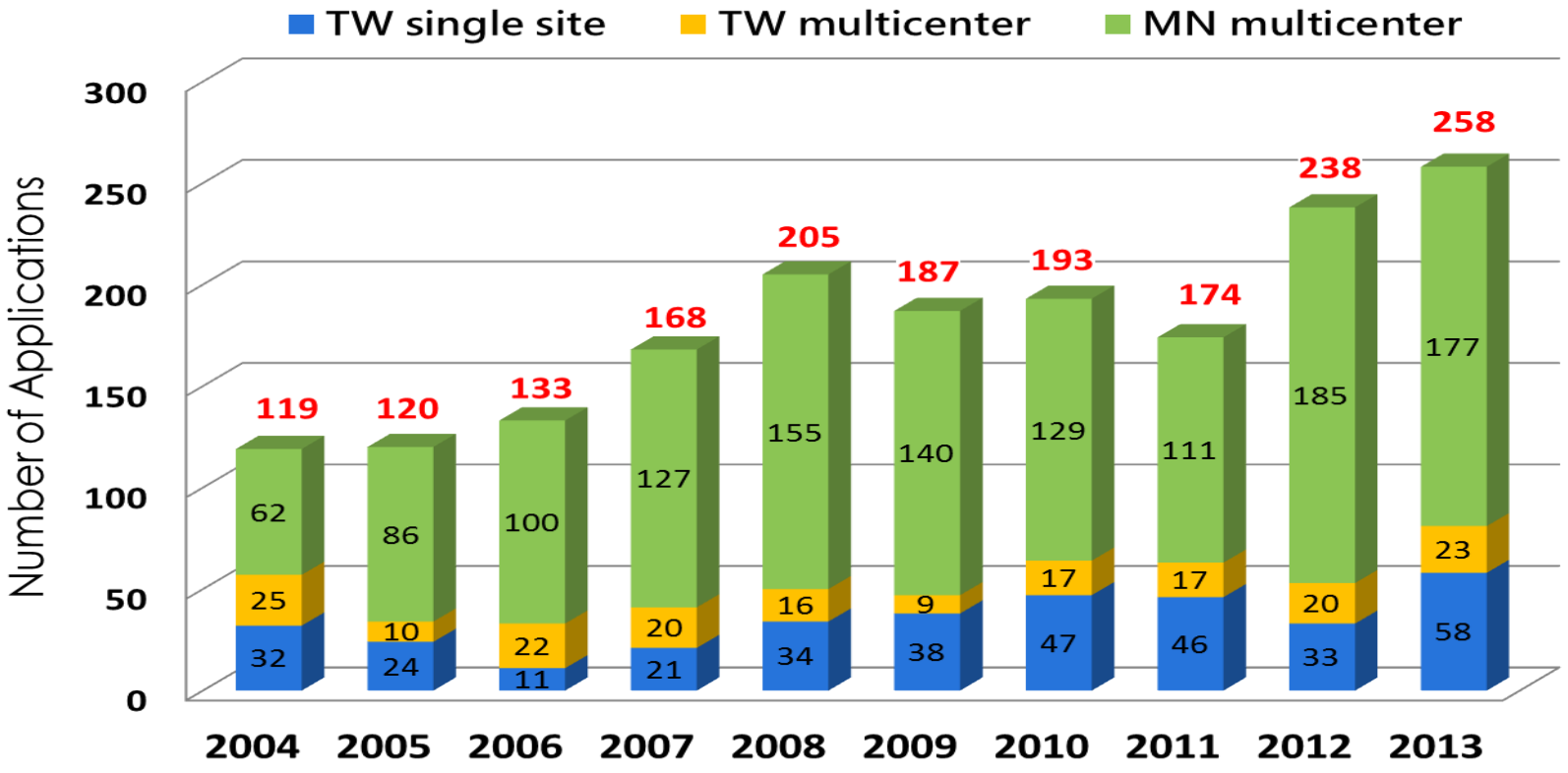
Chung Gung Medical Hospital

- 2010 Norvatis
- 2012 GSK
- 2013 MSD

Chung Gung Medical Hospital

- 2010 Norvatis, MSD
- 2011 Norvatis

IND Applications in Taiwan

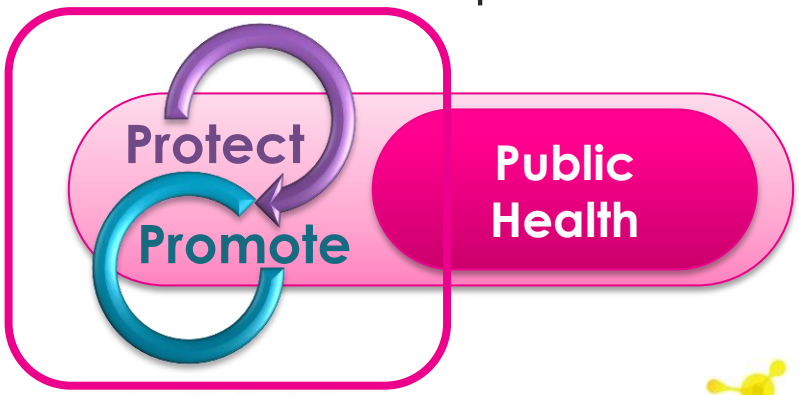


Increase of multiregional trials

Current Status of NDA Regulation in Taiwan

Current Status of NDA Regulation in Taiwan

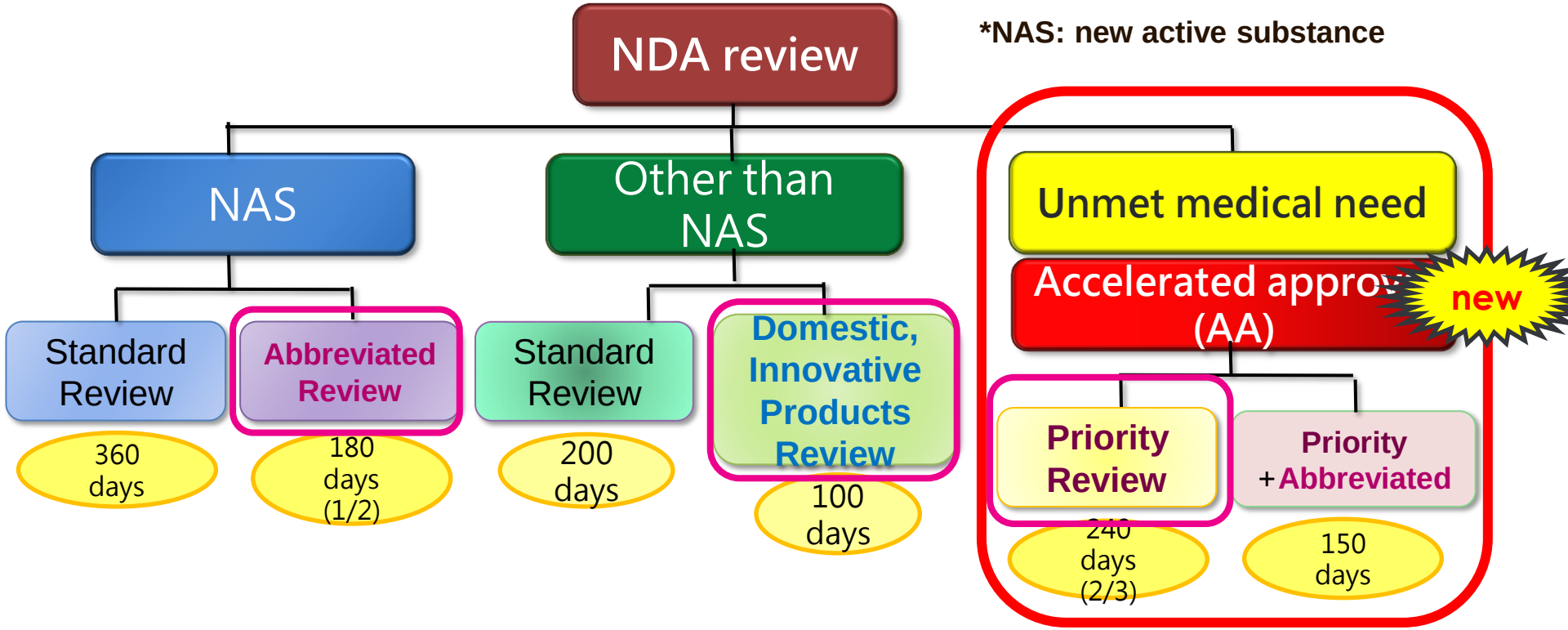
- Objectives:
  - Refine NDA review strategy
  - Optimize NDA regulations
  - Facilitate innovative medicine industry
    - Regulation Paradigm shift
      - ➢ from protection to promotion



Assure QUALITY, SAFETY, EFFICACY of Medicinal Products

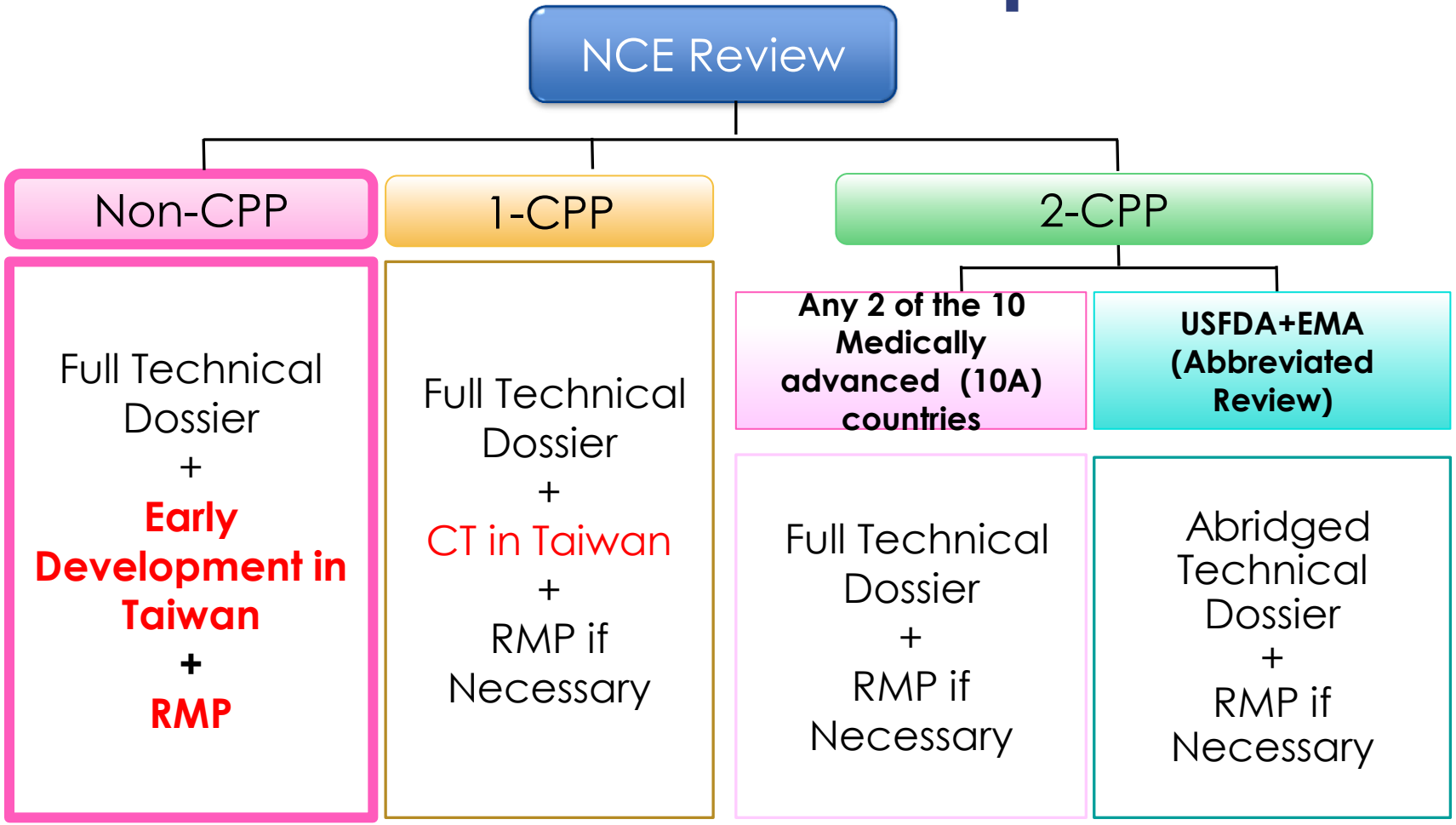
Help to Speed the Development of Innovative Medicine

Refine NDA review strategy



- Standard Review：NAS +US FDA and EMA approved + no ethnic issue
- Priority Review：NAS+unmet medical need
- Domestic, Innovative Products Review：Other than NAS+PIC/S
- AA: unmet medical need→ Surrogate endpoint CT

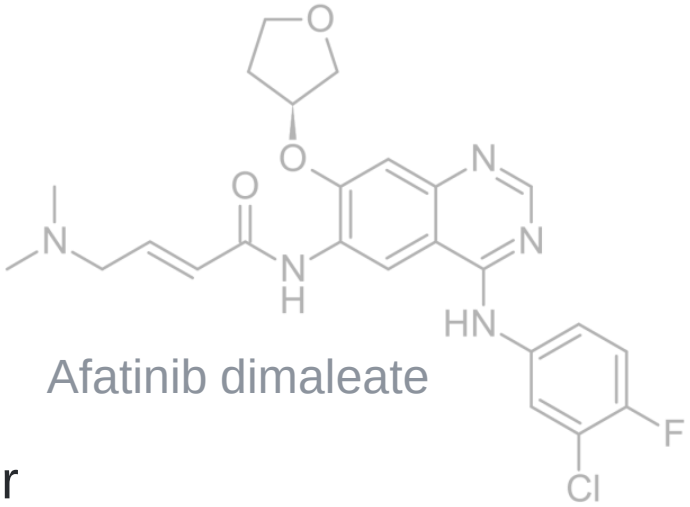
Optimize NDA regulation -Relaxation of CPP Requirement



CPP: Certification of Pharmaceutical Products
RMP: Risk Management Plan

Case Sharing– Afatinib

- New Chemical Entity
- non-small cell lung cancer with epithelial growth factor receptor (EGFR) mutation
- **First approved in the world (May 2013)**
- **MRCT** lead by Taiwan Principle Investigator
- 80% of the subjects in phase II and 20% of subjects in phase IIB/III were from Taiwan
- **Non-CPP Review Track**
- **Review time: 120 days**



Afatinib dimaleate

Facilitate innovative medicine industry -Regulatory Consultation System

Regulatory Consultation System for Medicinal Products

- **Online Information**
- **Consultation by Request**
- **Active Consultation**
  - **Domestic Innovative Consultation** (Early Harvest Lists)
    - Aug. 2011
  - **National Research Program for Biopharmaceuticals (NRPB)**
- **Industrial Communication Platform**


FDA


memo

Facts and Opportunities

TIME

Fair! not longer than ICH countries

Quick !

Parallel IRB and fast track

COST

Fair!

Definitely **cost down** than in Europe

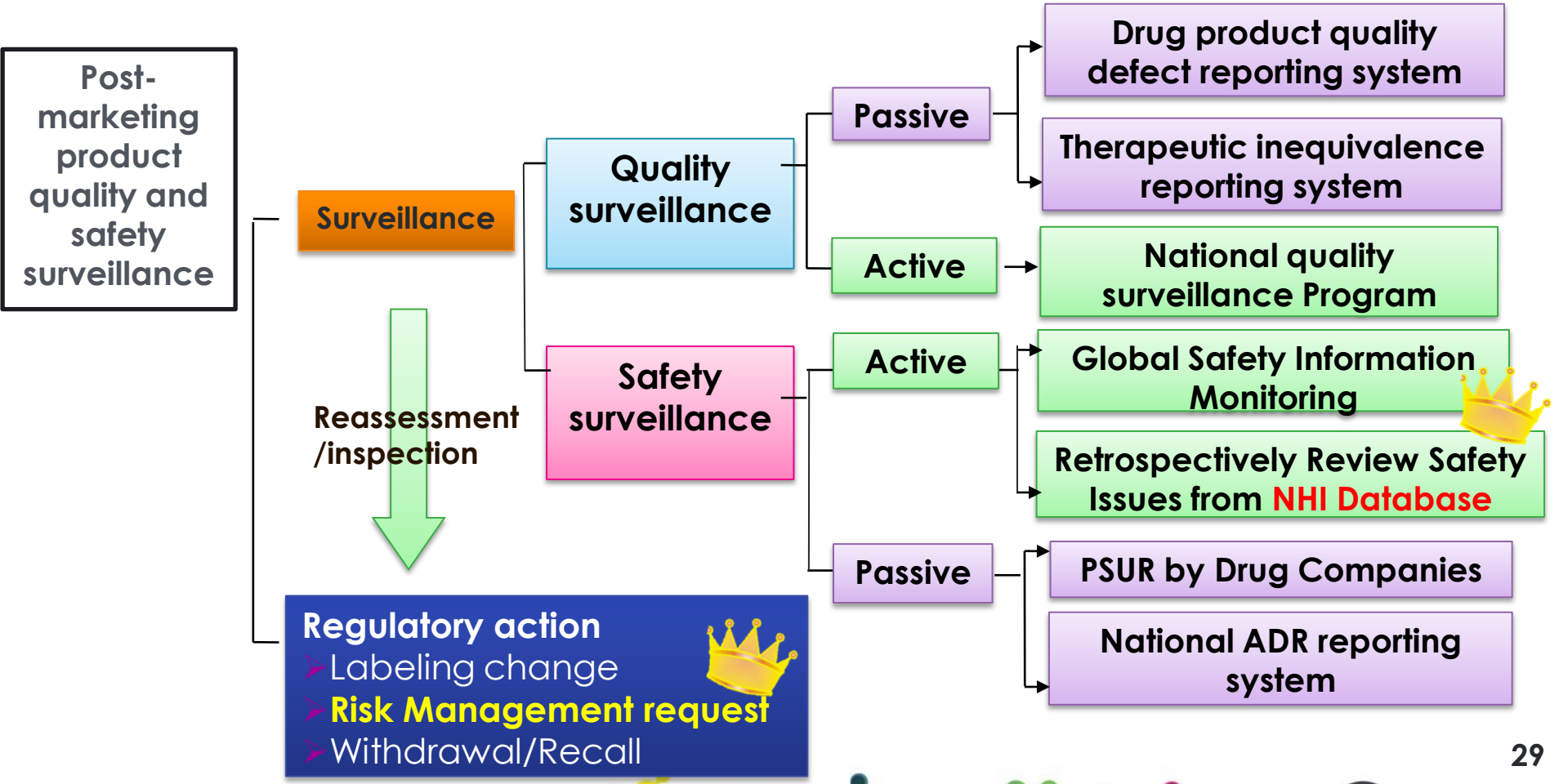
QUALITY

Good! With no doubt !

Come and conduct clinical trials in Taiwan.

Current Status of Post-Marketing Management in Taiwan

Post-Marketing Safety and Quality Surveillance —Risk Management



Risk Management Plan

By careful design, monitor and control, the implementation of Risk management plan :

- Provides early access to new drugs (especially in non-CPP cases)
- Prevents marketed drug withdrawn
- Ex. Currently 29 NDAs and 4 marketed ingredients (Carbamazepine, TNF-Alpha Blockers, Rosiglitazone, Pioglitazone) in Taiwan require RMP conduction.

Carbamazepine(CBZ) Risk Management by Government

Signal Detection

- 3rd cause of drug injury relief cases
- SADR : Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Refinement and evaluation

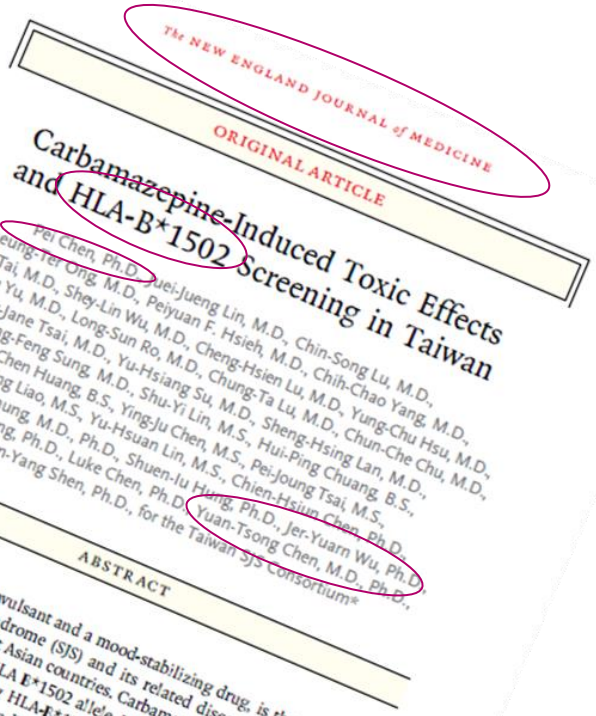
- off-label use?
- HLA-B*1502 genotype and SJS?
- Health Care Professional remind the patients with the ADR?

Risk Management

- approved indications unified, labeling revision, black boxed warning added…(2004、2007、2008、2010)
- HLA-B*1502 gene screening included in NHI(2010.06)
- Mandatory printed labels, Pharmacists are required to remind the patients of potential side effects when fill out the prescriptions (2010.07)
- Revision of Drug Injury Relief Act (2011.05)
- RMP by pharmaceutical companies (2011.09)

Carbamazepine and gene screening By researcher

The New England Journal of Medicine


THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Jui-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Fer Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., ing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., heng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D., Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jer-Yuarn Wu, Ph.D., hang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., hen-Yang Shen, Ph.D., for the Taiwan SJS Consortium*

ABSTRACT

onvulsant and a mood-stabilizing drug, is the main cause yndrome (SJS) and its related disease, toxic epidermal ast Asian countries. Carbamazepine-induced SJS–TEN is HLA-B*1502 allele. We sought to prevent carbamaze- ng HLA-B*1502 screening to prospectively identify condition.

recruited 4877 candidate subjects who had not ed DNA purified from the subjects' peripheral ied the HLA-B*1502 allele. Those testing posi- were advised not to take carbamazepine and advised to continue taking their prestudy) were advised to take carbamazepine. We a week for 2 months to monitor them rical incidence of SJS–TEN as a control.

cts; more widespread rash developed SJS–TEN did not develop in any carbamazepine-induced SJS–TEN (0.22

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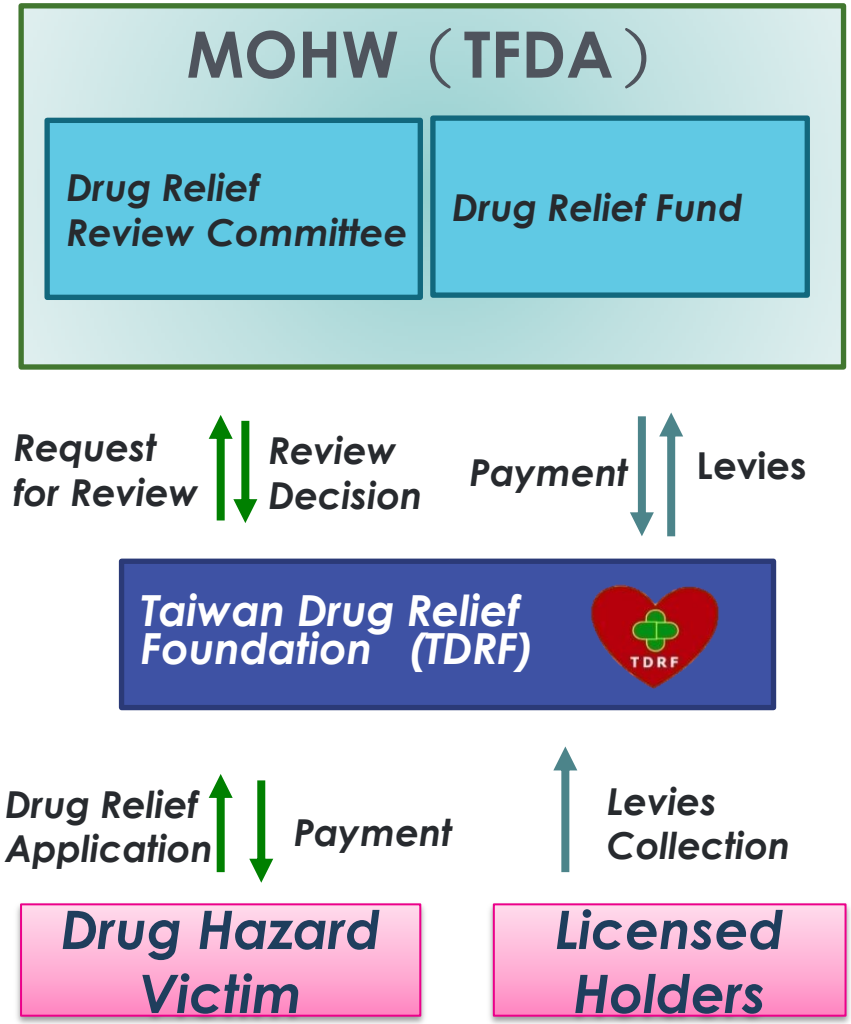
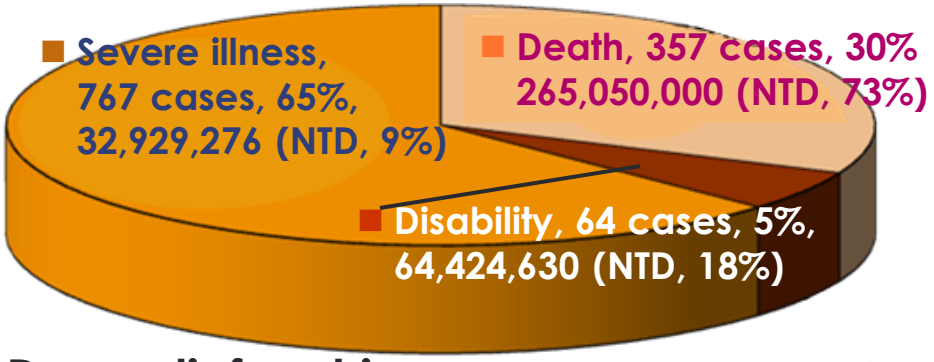
Taiwan Drug Injury Relief System



■Drug relief cases and payment, (since 1999)



■Drug relief ranking, (since 1999)

ranking	Active ingredient	Case no.
1	Allopurinol	178
2	Phenytoin	119
3	Carbamazepine	109
4	Isoniazid/Rifampin/Pyrazinamide	69/68/67
5	Diclofenac	51
6	Co-trimoxazole	36
7	Mefenamic acid	32
8	Lamotrigine	29
9	Cefazolin	28
10	Ibuprofen	27

Direction of International Collaboration

Current Status of International Collaboration

- **Regulation Harmonization**
  - Regulation Convergence, such as **ICH standards**
  - EP* observer、USP* observer
- **Regular participation in international organization/conference**
  - Organization oriented: APEC、ICH、DIA、IGDRP 、FIP、WTO (TRIPS、TBT)、WHO (NRA、ICDRA)
  - Topic oriented: orphan drug、biologics、bridging study、vaccine
- **Active involvement**
  - **APEC GRP roadmap**
  - **MOU**

- **MOU/arrangement/agreement:**
  - **Japan: arrangement**
  - **China: agreement**
  - **Australia: MOU**
  - **UK: confidentiality MOU**
  - **EDQM: confidentiality agreement**

EP: European pharmacopeia
USP: US pharmacopeia

Step in to Taiwan Today
Step out to the World Tomorrow

- China: Cooperation Agreement
- Japan: Arrangement
- Australi… MOU

2013.1.1 PIC/S GMP member
Please expect PICS/GMP talk tomorrow

Future Prospects

Future Prospects

Consumer Protection

Win-Win-Win

Government
Smart Administration

Industry
Competences Enhancement

Thank You for Your Attention

Chiang Kai-shek Memorial Hall

Taipei 101

Yehliu Geopark

Sun Moon Lake

North-East coast of Taiwan

Pingxi Flying Lanterns

Penghu

Night Markets

Temples

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