Adverse Drug Reaction Reporting and Pharmacovigilance in Taiwan
--Current Status and Policy Direction

Wen Chen, Pharm. D
Taiwan Drug Relief Foundation
Outline

• Current legislation and policy
• Current status of Taiwan ADR reporting system
• From ADR reporting to Signal management
• Our achievement
• Future perspectives
Current scope of post-marketing drug safety surveillance
Pharmacovigilance related legislation in Taiwan

CURRENT LEGISLATION AND POLICY
Pharmacovigilance in Taiwan

Risk Monitoring

- New Drug Surveillance
  - PSUR
- Domestic ADR Cases
  - ADR Reporting center
    - Coding (ATC & MedDRA)
    - Causality assessment (ICH)
- News Monitoring
  - Safety Alerts

Refinement / evaluation

- New drugs pass monitoring period
- Death reports
- Drugs with safety signal
- Case and Literature Review
  - Safety Assessment Report
- Drug Safety Advisory Committee
- TFDA
  - Regulatory actions

Evaluation

- Drug utilization pattern
  - Pre-marketing Safety information
  - Post-marketing Studies

Management

- Active Surveillance
  - NHIRD
- Drug Relief Database
- PharmacoEpi Research

Risk Management
PV LEGISLATION IN TAIWAN
Legislation

• Article 45 & 45-1, Pharmaceutical Affairs Act
• Announced in Aug 2004
• Medical institutions, pharmacies, and pharmaceutical companies should report all suspected serious adverse drug reactions (mandatory to report).
• Article 92: Violators of any of the provisions shall be imposed on a fine between NT$30,000 ~ NT$150,000.
Serious Adverse Drug Reaction

- Death
- Life-threatening
- Permanent disability/incapacity
- Congenital anomaly/birth defect
- Result in hospitalization or prolongation of an existing hospitalization
- Require further management to avoid from possible permanent injuries
Filial Law of
Article 45-1, Pharmaceutical Affairs Act
(Reporting Time Frame)

• Fatal or life-threatening serious ADRs
  – Medical institutions and pharmacies should report within 7 days and a supplementary follow-up report should be completed and submitted within additional 8 days.
  – Pharmaceutical companies should report within 15 days

• Other serious ADRs
  – Pharmaceutical companies should report within 15 days

• Non-serious ADRs
  – To report at anytime voluntarily
Filial Law of
Article 45, Pharmaceutical Affairs Act

• During drug safety monitoring periods (5 years for drugs and 3 years for medical devices), pharmaceutical license-holders shall actively collect worldwide safety information and submit PSUR in announced format.

• Pharmaceutical license-holders shall submit follow-up reports of risk management plan within the appointed timeframe.
Guidance for Good Pharmacovigilance Practice

• **Introduction**

• **Adverse Drug Reaction Reporting and Requirements**
  – Spontaneous Reporting
  – Periodic Safety Update Reports
  – Expedited Reporting

• **Risk Management**
  – Health Authority
  – Healthcare Providers and Pharmacies
  – Pharmaceutical Companies
  – Risk Management Tools

• **Training and Education**
  – Health Authority
  – Healthcare Providers and Pharmacies
  – Pharmaceutical Companies

• **Pharmacovigilance Inspection**
  – Routine Inspection
  – Target Inspection
  – Inspection Report
  – Continuous Follow-ups
ADR data collection and management
Features of new ADR database
Utilization and analysis of reports

CURRENT STATUS OF TAIWAN ADR REPORTING SYSTEM
Drug Safety Reporting System in Taiwan

- Adverse Drug Reaction reporting system
- Food, Medicinal Product and Cosmetics Product Defect Reporting System
  - Drug defect and therapeutic in-equivalence
  - Medical device adverse reaction and product defect
  - Dietary supplement unexpected reaction
  - Cosmetics adverse reaction and product defect
- Patient Safety Reporting System
  - Medication errors
Taiwan National ADR Reporting System
Definition of ADR

Based on evidence and possible causal relationship, a noxious and unintended response to a drug used at any doses.
Taiwan ADR Reporting System

• First set up in July 1998
• Collects
  – Pre-marketing:
    • SAE: prior to July, 2010
    • SUSAR: from July, 2010
  – Post-marketing
    • Spontaneous ADR report: mainly from HCP and MAH
    • Literature, phase IV trial

♦ MedDRA terminology and ATC code adopted in 2006
Launched in April 2013

NEW ADR REPORTING SYSTEM IN TAIWAN
Structure of New ADR Reporting System

- **hospitals**
- **pharmacies**
- **patients**
- **CRO**
- **manufacturers**

- Fax, email, postal
- Reporting portal
- E2B, xls exports

**Data classification**

- Drug
- Vaccine
- SAE / SUSAR
- Pool data

**Data Analysis, Signal detection**
Features of **New ADR Reporting System in Taiwan**

- Facilitate electronic submission
- Computer-aid data collection & standardization
  - Logic checking throughout e-sub fill-out procedure
  - Duplicate check
  - Pre-defined library of domestic medical product license registry, company/hospital registry information, etc.
  - On-line case management for reporters
Features of New System

• Coding Dictionary
  – ATC, MedDRA
  – Auto coding

• Case life-cycle management
  – case process flow: Quality checking → Triage → Specialist reviewing

• Case communication/follow up information

• Compatible with ICH E2B(R2) standards
  – New data entry/storage will comply with E2B standard
  – Old data converted may only be partially compatible with E2B standard
Reporting form
ADR Data Collection and Management

**Reporting Data**
- From HCP and MAH etc
- Spontaneous reports, Literature and AEFI etc

- **Case Approval**
- **Case Established**
- **Integrity check** (minimum requirement)

**ADR Database**
- **Coding** (drug and event)
  - ATC
  - MEDDRA
- Case Evaluation (prioritized)
  - WHO Causality
  - Characteristics
- Impact check
  - Expectedness
  - Clinical impact

**Reviewers**

ICPE 2014, Taipei, Taiwan  Cliff Ke
<table>
<thead>
<tr>
<th>Field item</th>
<th>Score Fair/poor</th>
<th>Score Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspect drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narratives (how ADR is occurred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug dose, frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of drug therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narratives (ADR intervention and reactions after)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narratives (past history)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height /weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient ID code</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent drug info</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Orange: mandatory field
Poor report: any of the green missing
Fair report: at least fulfill all green
Good report: at least fulfill all red
## Report Quality Scoring Parameters

### DEC Annual accumulation
- Local phenomenon
- Hospital ADR surveillance mechanism is required for Hospital Accreditation → report huge amount of cases of specific DEC ONLY!!
- Suppress over-reporting on certain DECs

#### Extra weight:
- DME
- Drugs under surveillance
- others

### Drug Event Combination Score

<table>
<thead>
<tr>
<th>Annual accumulation counts</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>15</td>
</tr>
<tr>
<td>6-20</td>
<td>19</td>
</tr>
<tr>
<td>21-25</td>
<td>13</td>
</tr>
<tr>
<td>26-30</td>
<td>8</td>
</tr>
<tr>
<td>31-35</td>
<td>5</td>
</tr>
<tr>
<td>36-40</td>
<td>3</td>
</tr>
<tr>
<td>&gt;=41</td>
<td>1</td>
</tr>
</tbody>
</table>

### Content quality

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOOD</td>
<td>1.5</td>
</tr>
<tr>
<td>FAIR</td>
<td>0</td>
</tr>
<tr>
<td>POOR</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

### Causality

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely, possible, probable, certain</td>
<td>1.5</td>
</tr>
<tr>
<td>Unclassified</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

### Seriousness

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious case</td>
<td>1.5</td>
</tr>
<tr>
<td>Non serious case</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

### Weight

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DME &amp; New Drugs</td>
<td>5</td>
</tr>
<tr>
<td>DME or New Drugs</td>
<td>3</td>
</tr>
<tr>
<td>Electronically submitted</td>
<td>3</td>
</tr>
<tr>
<td>None of above</td>
<td>0</td>
</tr>
</tbody>
</table>
Utilization of Reports

• Drug Re-evaluation Mechanism
  ✓ Drug Alerts with new safety concerns
  ✓ ADR death reports
  ✓ High frequency (pattern changes) of ADR reporting
  ✓ High alert drugs in the Drug Injury Relief application
  ✓ Drugs pass surveillance period

• Drug Safety Newsletter
  – Published quarterly

• Signal Detection
Death Case Evaluation Process

*Expected:
1. Documented on CCIS or package insert
2. Well-known ADR by HCP
3. Pharmacologically explainable
4. Complication from ADR

Clinical meaningful:
- Signals identified should be communicated with HCP.

---

1. Documented on CCIS or package insert
2. Well-known ADR by HCP
3. Pharmacologically explainable
4. Complication from ADR
Drug Safety Newsletter

- Published quarterly
- Electronic downloading available
- A circulation of 3,000 copies
- Subscriber
  - Medical Professionals
  - MAH
- Contents
  - articles on drug safety news
  - reviews of ADRs
  - analysis of cases applied for Drug Injury Relief
  - news of activities and others
Signal generation
Signal refinement and evaluation
Risk management and communication

FROM ADR REPORTING TO SIGNAL MANAGEMENT
Comprehensive monitoring

SIGNAL GENERATION
Comprehensive Monitoring

- ADR reporting system
- Safety news monitoring
- High Alerts
  - Safety concerns of NEW drugs
  - Drug Relief applications
Drug Safety Alert Monitoring

- Total of 167 safety news
- 23 news were released through "Risk Communication Letter"
- 5 drugs(classes) were followed by re-evaluation process (b-agonists, nicardipine, domperidone, RAS, OC)

Year 2014

- Canada, 36
- EMA, 36
- FDA, 18
- Reuters, 27
- Yahoo, 19
- Swissmedic, 16
- Others, 15
- PMDA, 6
- TGA, 7
- CNA, 2
Review Team Communication

1. Daily drug safety news summary
2. Join NDA filing and review meeting

1. Proactively forward NDA application with safety issues
2. Response to safety information if the drug is under review

- Join pre-conference meeting
- Review drug-relief material (summary of medical records)
- Proactively forward drug relief case series with concern.

ADR Team

CDE Team

Relief Team
Timely assessment

SIGNAL REFINEMENT AND EVALUATION
Timely Assessment

• Signal prioritization
  – Intensity of signals
  – Known knowledge
  – Possibility to study in NHIDB
  – Degree of impact
  – Others

• Signal refinement
  – Case series review
  – Literature review
  – Drug utilization review

• Signal evaluation
  – Pharmacoepidemiology studies
  – Risk/benefit evaluation
RISK MANAGEMENT AND COMMUNICATION

Strategy for minimizing risks
Methods for cooperation
Ensure that the benefits outweigh the risks

Risk Management Plan

Patients safety

manufacturers  Regulatory  Hospitals
Risk Management Plan
Format and Contents

一、藥品風險管理計畫(格式及內容說明)

藥品基本資料
（中英文藥名）
（劑型）
（劑量）
（廠商名）

三、特殊風險預防措施( Element to Assure Safety Use)

特殊風險預防措施實施面詳述: 例如有致畸胎性時，使用藥品之女性病患需
每個月進行驗孕，確診驗孕結果為陰性後，醫師方可開立處方，藥師必需於
看到符合規定期限內的陰性驗孕報告方可給藥等。

四、其他: 請個案需求請自行彙報。

參、藥品風險管理計畫追蹤報告

一、實施方法說明: 說明如何評估藥品風險管理計畫的效果(由何人執行、指導為
何、如何比較等等)

二、檢送時間: 原則上為滿二年及滿五年時，可依個案情形調整並提出說明。

肆、應用文件( Supporting Documents)

請將前述病患風險說明書等內容編號檢附。
### Risk communication letter

<table>
<thead>
<tr>
<th>Active Pharmaceutical Ingredients</th>
<th>Drug trade name and permit license number</th>
<th>Indications</th>
<th>News origin</th>
<th>News content</th>
<th>Information for risk communication</th>
<th>communication parties</th>
</tr>
</thead>
</table>

#### Drug Safety Information

<table>
<thead>
<tr>
<th>Date: 980727</th>
</tr>
</thead>
</table>

#### Active Pharmaceutical Ingredients

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Leflunomide</th>
</tr>
</thead>
</table>

#### News Origin

2010年7月13日 美國FDA公布有關leflunomide藥品之安全資訊。說明leflunomide藥品可增加肝損害之風險。

#### News Content

<table>
<thead>
<tr>
<th>醫療人員：</th>
</tr>
</thead>
</table>
| 1. 應重點提醒使用該藥品前，應確診輕併發症及肝功能不良，不可使用於肝功能不良之患。
| 2. 使用該藥品不可與其他具有肝毒性之藥物併用，可能增加肝損害之風險。
| 3. 副作用使用該藥品治療前後均應做定期檢查，定時檢測肝臟之AST ALT 值。前6個月每2週檢測一次，之後則每4週檢測一次。

<table>
<thead>
<tr>
<th>病患：</th>
</tr>
</thead>
</table>
| 1. 若有肝損害之徵兆，如食慾不振、煩憂、黃疸、腹部脹氣，應立即通知處方醫師。
| 2. 病患服用藥品有任何疑問或不舒服，應盡快洽詢處方 ...

#### Communication Parties

| 醫師 | 藥師 | 護士 | 一般民眾 | 其他 |
Official real-time drug safety information sharing networks

Local health authorities

Drug safety warnings

Press release

Risk Communication Letter

Related associations

Consumer protection center

Drug info website https://consumer.fda.gov.tw

Drug Relief Foundation


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

E-paper

Real time

Subscribers: HCP and the public

• Hospitals and MAH
• ADR contact points
• Subscribers

members

Letter
Statistics of reports
Examples of signal management

OUR ACHIEVEMENT
Annual ADR Reports in TW

Year | Cases
--- | ---
1999 | 316
2000 | 1524
2001 | 1831
2002 | 2325
2003 | 2252
2004 | 2507
2005 | 3722
2006 | 4629
2007 | 6971
2008 | 8316
2009 | 10320
2010 | 10555
2011 | 10402
2012 | 11357
2013 | 10667
2014 | 11399

Legislation
On-line
Hospital accreditation
ADR Reporting Source

Taiwan 2014

- Pharmacist: 78.96%
- Physician: 3.13%
- Nurse: 0.68%
- Other Health Care Professionals: 0.22%
- Industry: 16.74%
- General Public: 0.08%
- Others: 0.19%
- General Public: 0.08%
- Others: 0.19%

Pharmacist: 78.96%
Characteristic of Reports-Seriousnessness

Taiwan 2014

- Death: 2.76%
- Life-threatening: 1.47%
- Hospitalization (initial or prolonged): 16.11%
- Disability or permanent damage: 0.11%
- Congenital anomaly/birth defect: 0.02%
- Other medically important event: 20.82%
- Non-serious: 58.72%
## ATC Classification of Suspected Drugs

### Year 2014

<table>
<thead>
<tr>
<th>ATC Classification</th>
<th>No. of suspected drugs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimentary tract and metabolism</td>
<td>1139</td>
<td>5.84%</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
<td>3929</td>
<td>20.13%</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents</td>
<td>4641</td>
<td>23.78%</td>
</tr>
<tr>
<td>Antiparasitic products, insecticides and repellents</td>
<td>66</td>
<td>0.34%</td>
</tr>
<tr>
<td>Blood and blood forming organs</td>
<td>854</td>
<td>4.38%</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>1421</td>
<td>7.28%</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>88</td>
<td>0.45%</td>
</tr>
<tr>
<td>Genito urinary system and sex hormones</td>
<td>342</td>
<td>1.75%</td>
</tr>
<tr>
<td>Musculo-skeletal system</td>
<td>2266</td>
<td>11.61%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>2662</td>
<td>13.64%</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>458</td>
<td>2.35%</td>
</tr>
<tr>
<td>Sensory organs</td>
<td>174</td>
<td>0.89%</td>
</tr>
<tr>
<td>Systemic hormonal preparations, excl. Sex hormones and insulins</td>
<td>375</td>
<td>1.92%</td>
</tr>
<tr>
<td>Various</td>
<td>1104</td>
<td>5.66%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19519</strong></td>
<td><strong>100.00%</strong></td>
</tr>
</tbody>
</table>
## System Organ Class of Reported ADR

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>No. of reported reactions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>5341</td>
<td>29.8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1886</td>
<td>10.5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1782</td>
<td>9.9</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1383</td>
<td>7.7</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1249</td>
<td>7.0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>819</td>
<td>4.6</td>
</tr>
<tr>
<td>Investigations</td>
<td>743</td>
<td>4.1</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>682</td>
<td>3.8</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>585</td>
<td>3.3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>520</td>
<td>2.9</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>423</td>
<td>2.4</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>391</td>
<td>2.2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>383</td>
<td>2.1</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>320</td>
<td>1.8</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>317</td>
<td>1.8</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>312</td>
<td>1.7</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>240</td>
<td>1.3</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>218</td>
<td>1.2</td>
</tr>
<tr>
<td>Others</td>
<td>343</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>17937</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Year 2014
Report Content Quality Analysis

Poor data: data is insufficient to perform the basic evaluation of the case
Fair data: data is sufficient to perform the basic evaluation of the case
Good data: data contains detailed information to perform more advanced evaluation
Future Perspectives

墾丁鵝鑾鼻燈塔
Kenting, Taiwan
Goal

• To protect and enhance the public health through systematic PV system
• Turn ADR reporting to be a Routine Clinical Practice
• Continue ADR reporting quality promotion
• Carry out Good Pharmacovigilance Practice Inspection
• Establish Signal Management Standard Operating Procedure
• Strengthen feedback mechanism
Thank you for attention