Adverse Drug Reaction Reporting and Pharmacovigilance in Taiwan

--Current Status and Policy Direction

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Taiwan Drug Relief Foundation

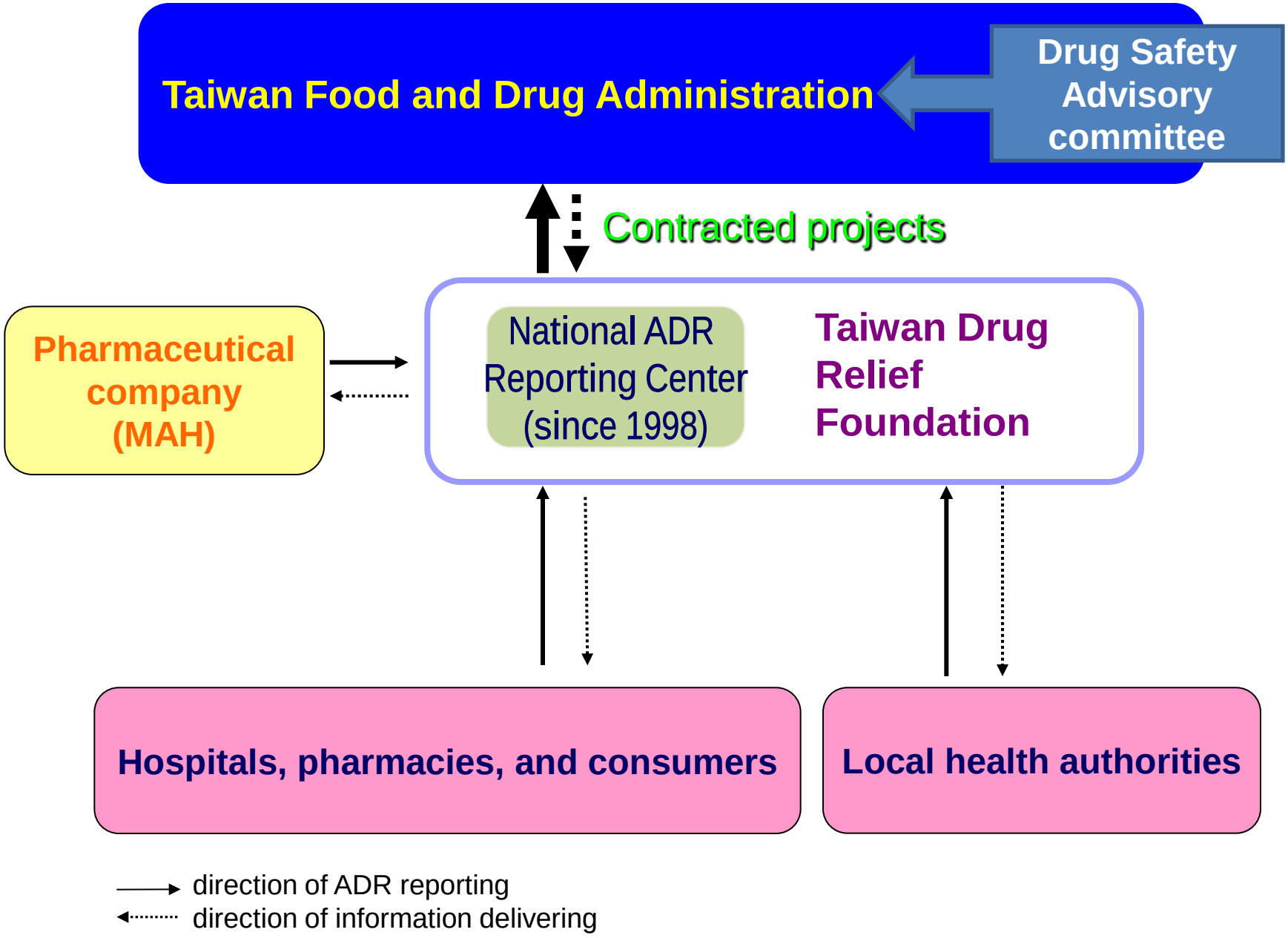
Outline

- Current legislation and policy
- Current status of Taiwan ADR reporting system
- From ADR reporting to Signal management
- Our achievement
- Future perspectives

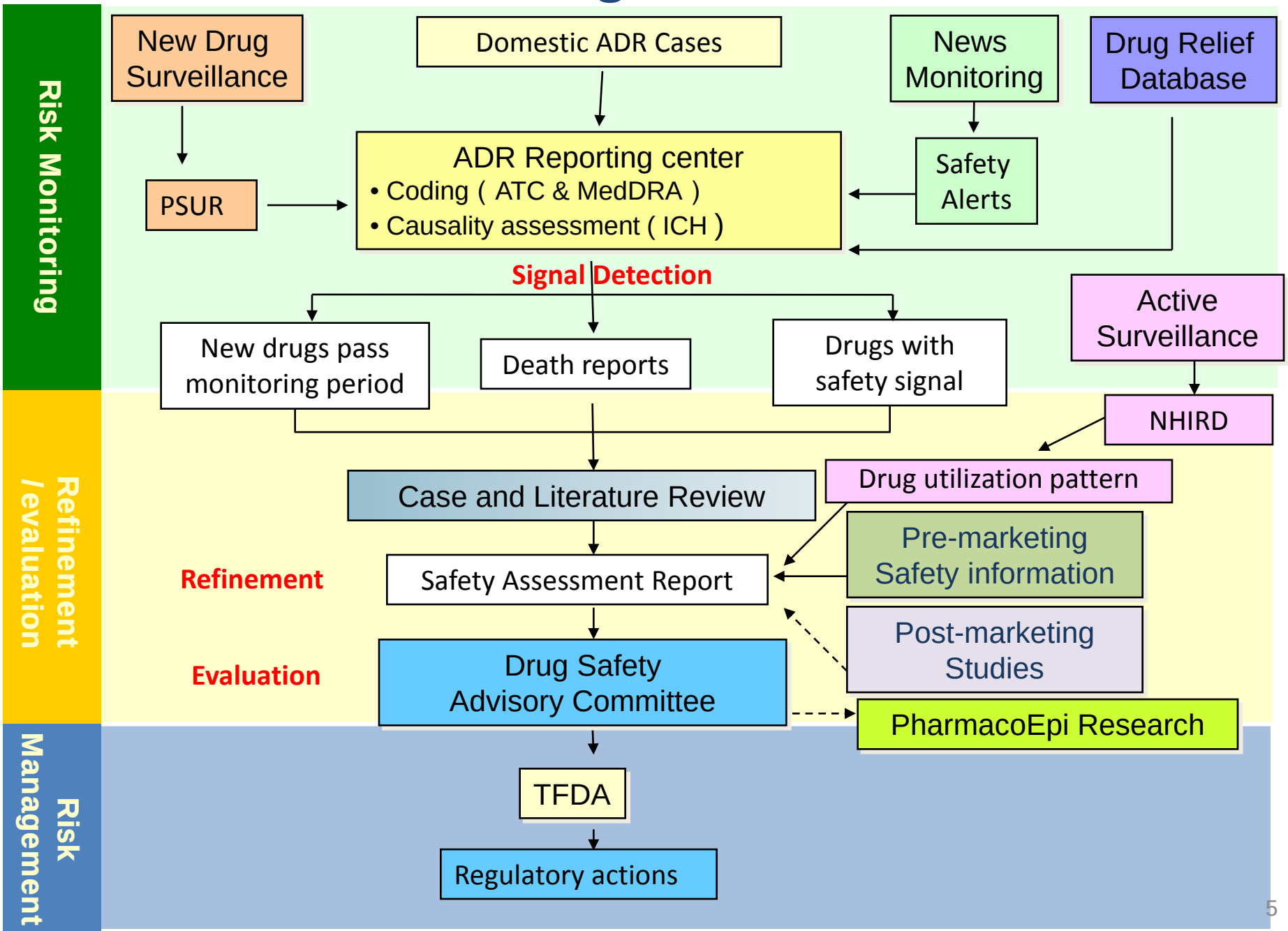
Current scope of post-marketing drug safety surveillance

Pharmacovigilance related legislation in Taiwan

CURRENT LEGISLATION AND POLICY


Taiwan Food and Drug Administration
Drug Safety Advisory committee
Contracted projects
Pharmaceutical company (MAH)
National ADR Reporting Center (since 1998)
Taiwan Drug Relief Foundation
Hospitals, pharmacies, and consumers
Local health authorities
direction of ADR reporting
direction of information delivering

Pharmacovigilance in Taiwan



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.

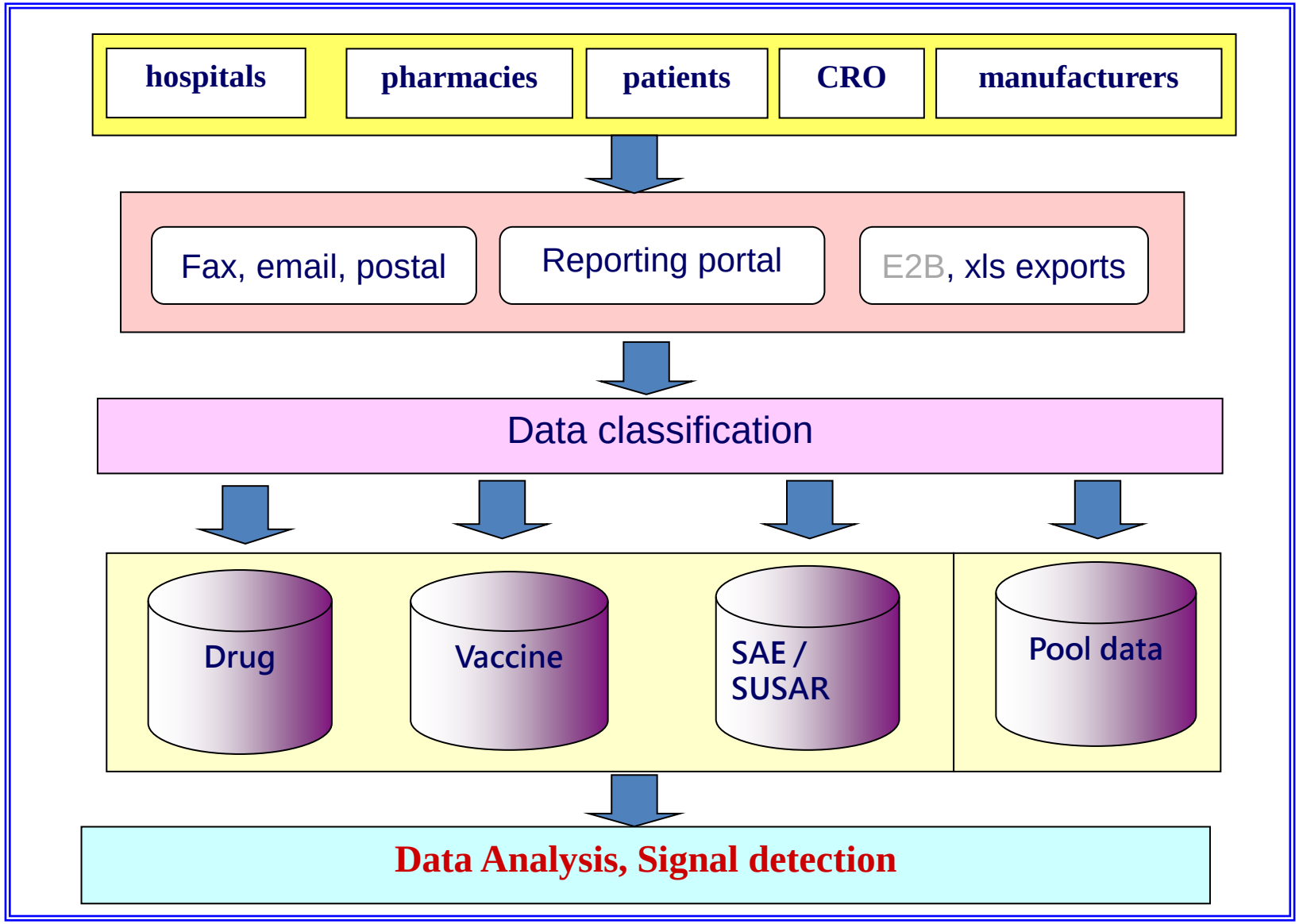
Taiwan ADR Reporting System

- 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



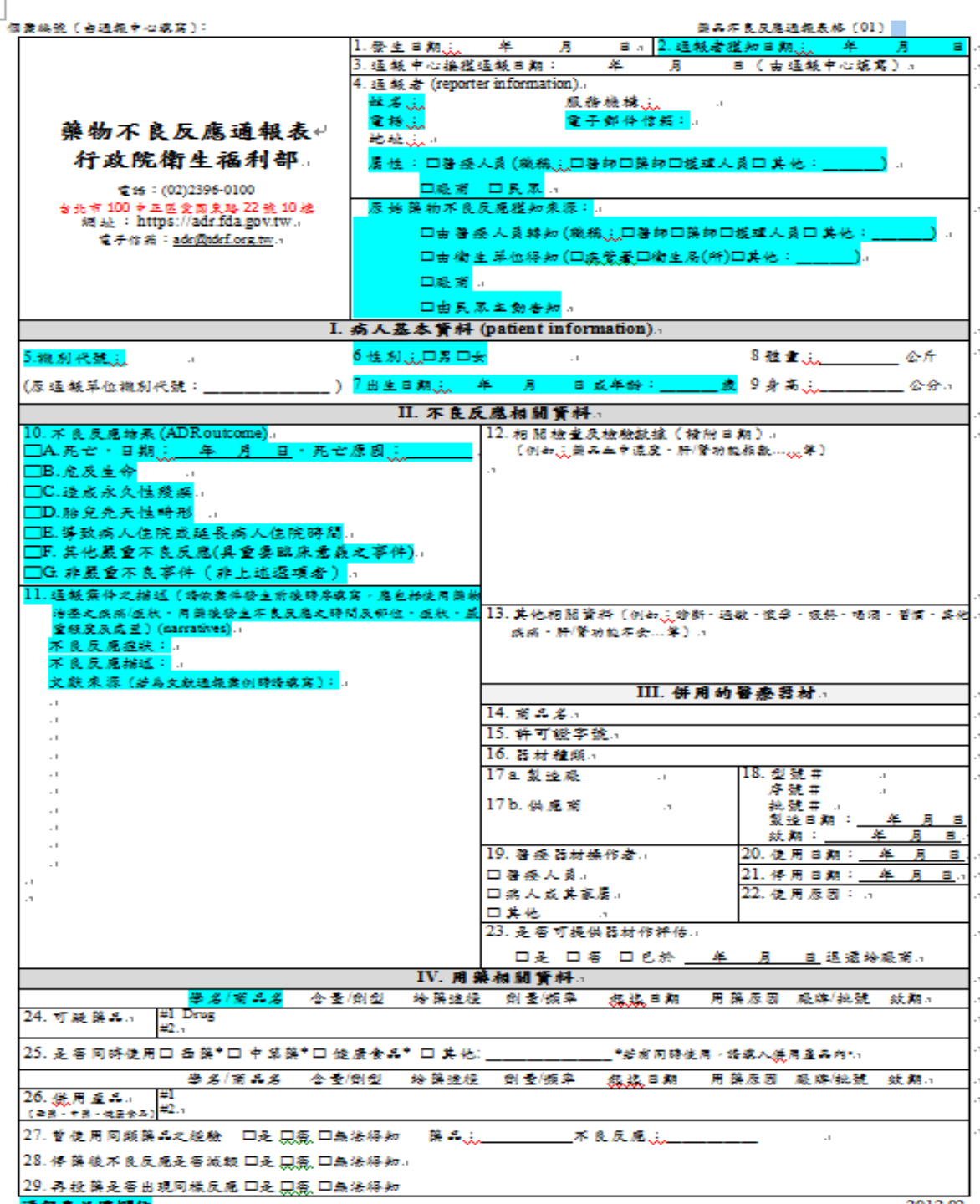
Features of
New ADR Reporting System in Taiwan

- 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



個案編號（由通報中心填寫）：

藥品不良反應通報表格（01）

藥物不良反應通報表
行政院衛生福利部

電話：(02)2396-0100
台北市 100 中正區愛國東路 22 號 10 樓
網址：https://adr.fda.gov.tw
電子信箱：adr@tdrf.org.tw

1. 發生日期：　年　月　日
2. 通報者獲知日期：　年　月　日
3. 通報中心接獲通報日期：　年　月　日（由通報中心填寫）
4. 通報者 (reporter information)
姓名：　服務機構：
電話：　電子郵件信箱：
地址：
屬性：□醫療人員（職稱：□醫師□藥師□護理人員□其他：_____）
□藥商　□民眾

原始藥物不良反應獲知來源：
□由醫療人員轉知（職稱：□醫師□藥師□護理人員□其他：_____）
□由衛生單位得知（□疾管署□衛生局(所)□其他：_____）
□藥商
□由民眾主動告知

I. 病人基本資料 (patient information)

5.識別代號：
（原通報單位識別代號：_____）
6 性別：□男 □女
7 出生日期：　年　月　日 或年齡：_____歲
8 體重：_____公斤
9 身高：_____公分

II. 不良反應相關資料

10. 不良反應結果(ADRoutcome)
□A.死亡，日期：　年　月　日，死亡原因：_____
□B.危及生命
□C.造成永久性損傷
□D.胎兒先天性畸形
□E.導致病人住院或延長病人住院時間
□F.其他嚴重不良反應(具重要臨床意義之事件)
□G.非嚴重不良事件（非上述選項者）

11. 通報案件之描述（請依案件發生前後時序填寫，應包括使用藥物治療之疾病/症狀、用藥後發生不良反應之時間及部位、症狀、嚴重程度及處置）(narratives)
不良反應症狀：
不良反應描述：
文獻來源（若為文獻通報案例時請填寫）：

12. 相關檢查及檢驗數據（請附日期）
（例如：請填血中濃度、肝/腎功能指數…等）

13. 其他相關資料（例如：診斷、過敏、懷孕、疫苗、通用、習慣、其他疾病、肝/腎功能不全…等）

III. 併用的醫療器材

14. 商品名
15. 許可證字號
16. 器材種類
17a. 製造廠
17b. 供應商
18. 型號 #
序號 #
批號 #
製造日期：　年　月　日
效期：　年　月　日
19. 醫療器材操作者
□醫療人員
□病人或其家屬
□其他
20. 使用日期：　年　月　日
21. 停用日期：　年　月　日
22. 使用原因：
23. 是否可提供器材作評估
□是　□否　□已於　年　月　日退還給廠商

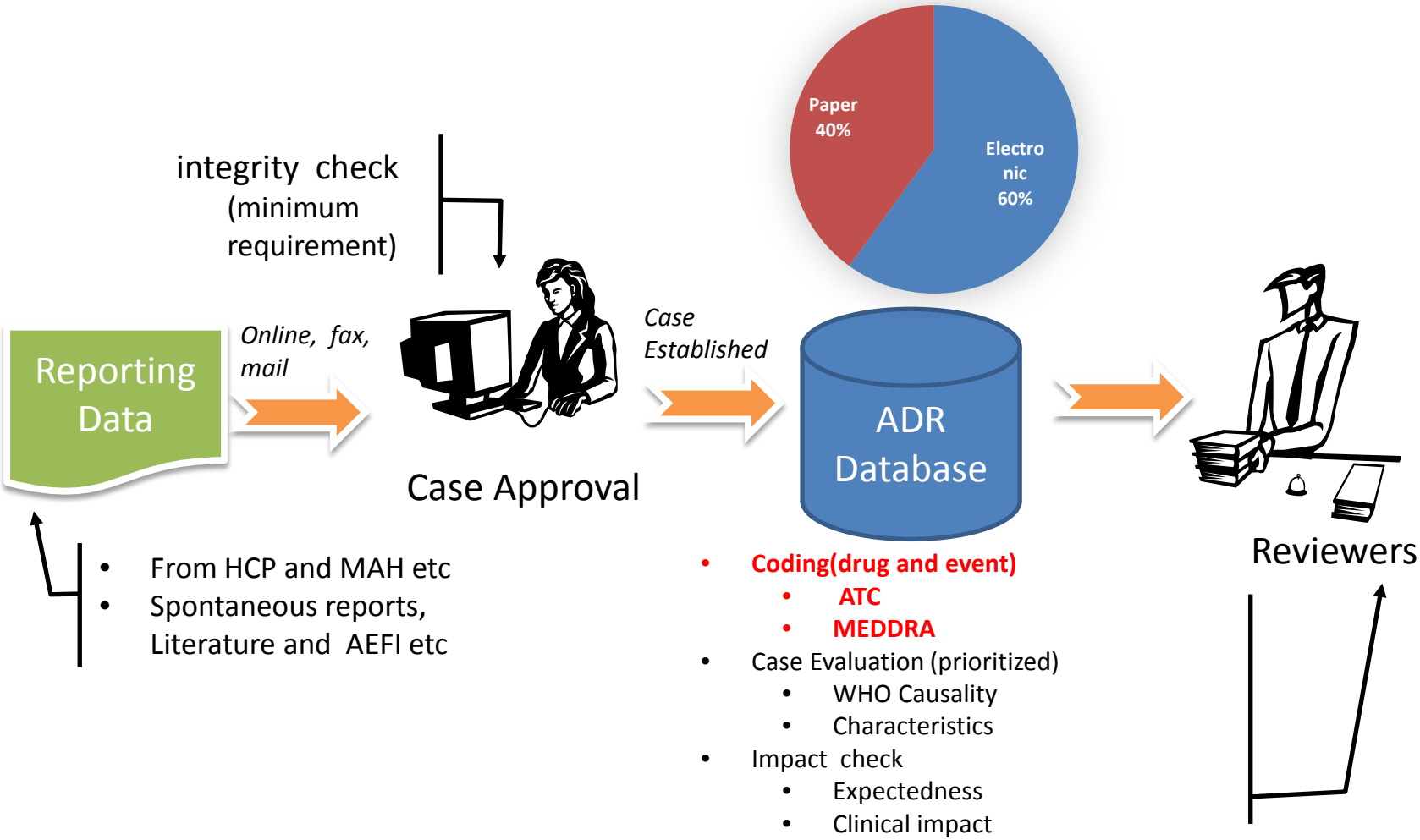
IV. 用藥相關資料

	學名/商品名	含量/劑型	給藥途徑	劑量/頻率	起始日期	用藥原因	廠牌/批號	效期
24. 可疑藥品	#1 Drug #2.							
25. 是否同時使用□西藥*□中草藥*□健康食品* □其他：_____*若有同時使用，請填入使用藥品內*								
26. 併用藥品（西藥、中藥、健康食品）	#1 #2.							

27. 曾使用同類藥品之經驗　□是 □否 □無法得知　藥品：_____不良反應：_____
28. 停藥後不良反應是否減輕 □是 □否 □無法得知
29. 再投藥是否出現同樣反應 □是 □否 □無法得知

2013.03

ADR Data Collection and Management



Report Integrity Check

Field item	Score Fair/poor	Score Good
Onset time		
Suspect drug		
Narratives (how ADR is occurred)		
ADR Outcome		
Drug dose, frequency		
Duration of drug therapy		
ADR term		
Narratives (ADR intervetion and reactions after)		
Age		
Narratives (past history)		
sex		
Height /wieght		
Indication		
Patient ID code		
Concurrent drug info		

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

	Drug Event Combination	Score
Annual accumulation counts	1-5	15
	6-20	19
	21-25	13
	26-30	8
	31-35	5
	36-40	3
	>=41	1
	Content quality	
	GOOD	1.5
	FAIR	0
	POOR	-1.5
	Causality	
	Unlikely, possible, probable, certain	1.5
	Unclassified	-1.5
	Seriousness	
	Serious case	1.5
	Non serious case	-1.5
	Weight	
	DME & New Drugs	5
	DME or New Drugs	3
	Electronically submitted	3
	None of above	0

Report Quality Scoring Parameters

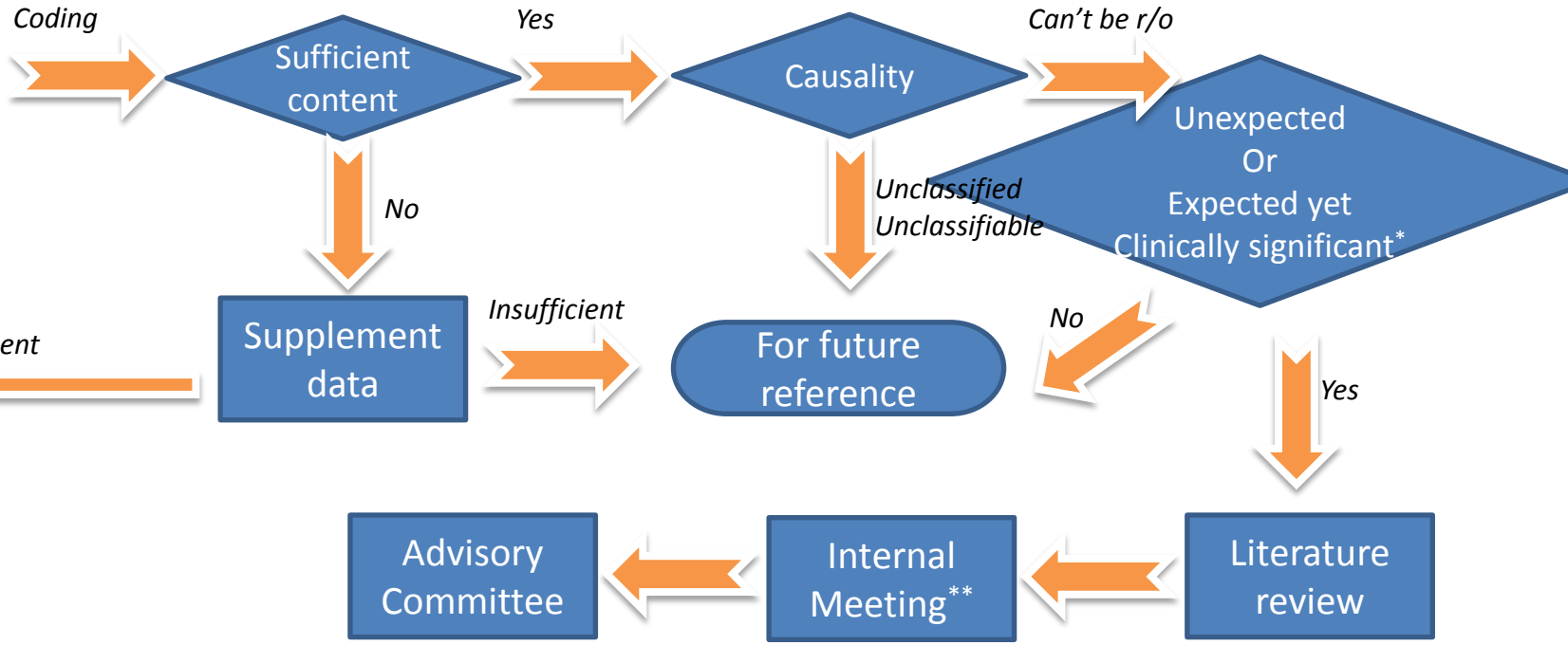
- DEC Annual accumulation
  - Local phenomenon
    - Hospital ADR surveillance mechanism is required for Hospital Accreditation→ report huge amount of cases of specific DEC ONLY!!
  - Suppress over-reporting on certain DECs
- Extra weight:
  - DME
  - Drugs under surveillance
  - others

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

Reviewers



*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.

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

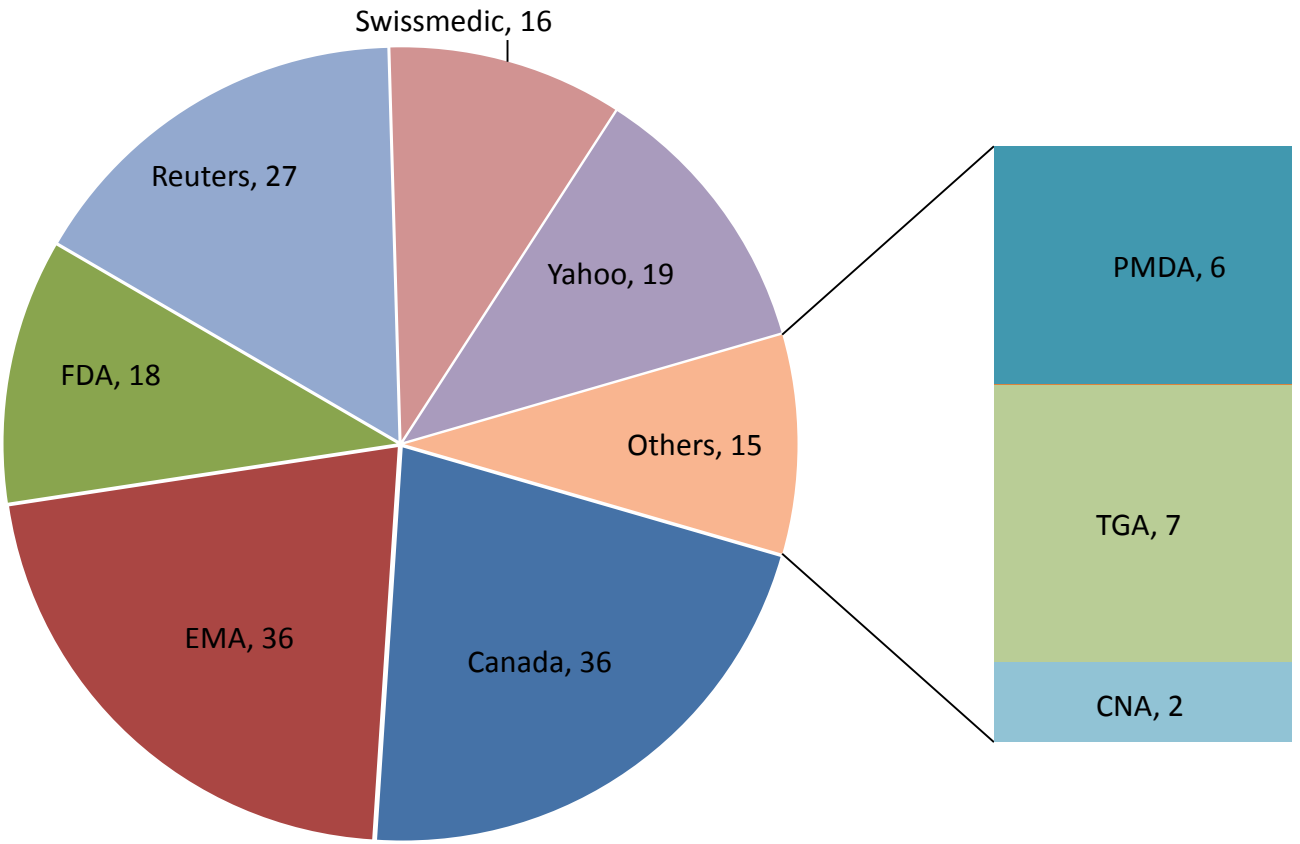
Comprehensive monitoring

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)

Review Team Communication

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

CDE Team

ADR Team

- Join pre-conference meeting
- Review drug-relief material(summary of medical records)

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

- Proactively forward drug relief case series with concern.

Relief Team

Timely assessment

SIGNAL REFINEMENT AND EVALUATION

Timely Assessment

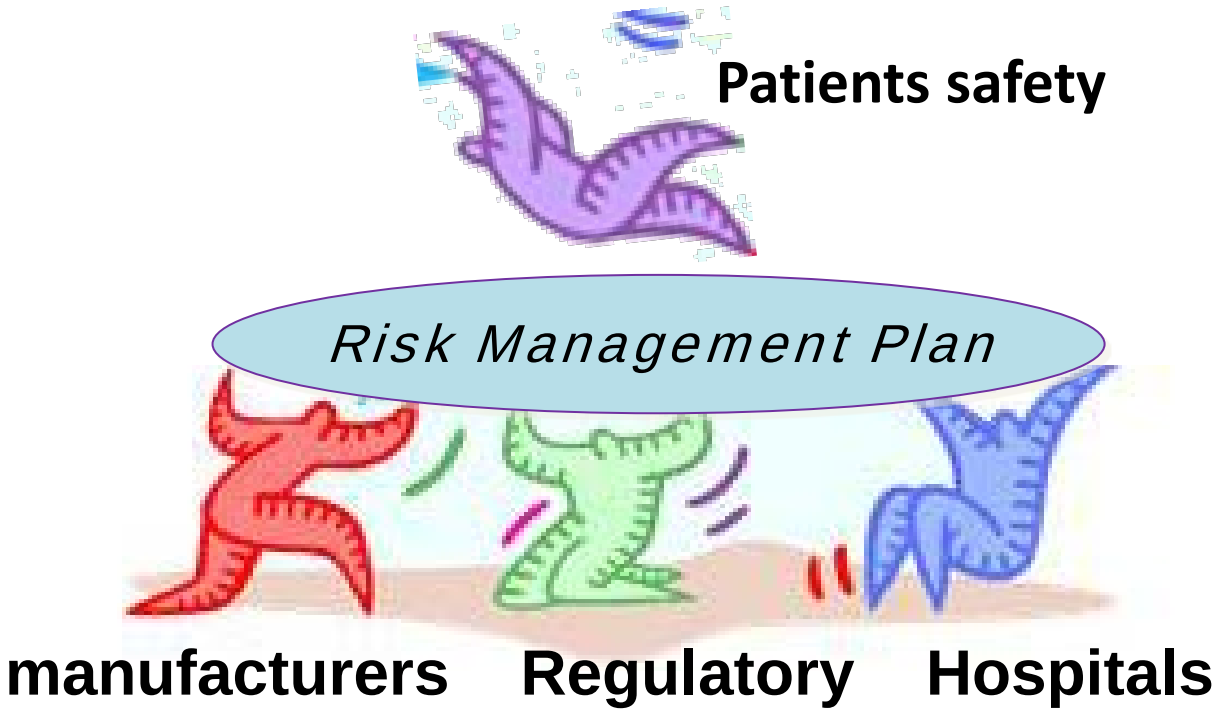
- Signal prioritization
  - Intensity of signals
  - Known knowledge
  - Possibility to study in NHIDB
  - Degree of impact
  - Others
- Signal refinement
  - Case series review
  - Literature review
  - Drug utilization review
- Signal evaluation
  - Pharmacoepidemiology studies
  - Risk/benefit evaluation

Strategy for minimizing risks

Methods for cooperation

RISK MANAGEMENT AND COMMUNICATION

Ensure that the benefits outweigh the risks



Risk Management Plan
Format and Contents

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)

壹、計畫目的(可有多個)

貳、方法(視需要而定，單複選均可)

一、病患用藥說明書(Medication Guide)

1. 採用理由:說明為何選此方法，可以降低哪種風險。
2. 執行面:具體描述如何讓病患取得病患用藥說明書(例如:廠商隨藥品配送、或提供電子檔供下載)、何處交付及何人發送此病患用藥說明書、是否附回條供收受者簽收....等)。
3. 說明書內容:應用文件請檢附所擬之病患用藥說明書。

二、醫療人員通知(Communication Plan)

1. 採用理由:說明為何選此方法，可以降低哪種風險。
2. 執行面:具體描述如何執行(例如:郵寄通知那些醫療相關人員、或擬於專業期刊登載/透過那些學會舉辦講座宣導等等、領證多久內執行....等)。
3. 通知內容:應用文件請檢附所擬寄送或刊載之文件內容。

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，確定驗孕結果為陰性後，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:視個案需求請自行增列。

參、藥品風險管理計畫追綜報告

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、指標為何、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)

請將前述病患說明書等內容編號檢附。

Risk communication letter

Active Pharmaceutical Ingredients

Drug trade name and permit license number

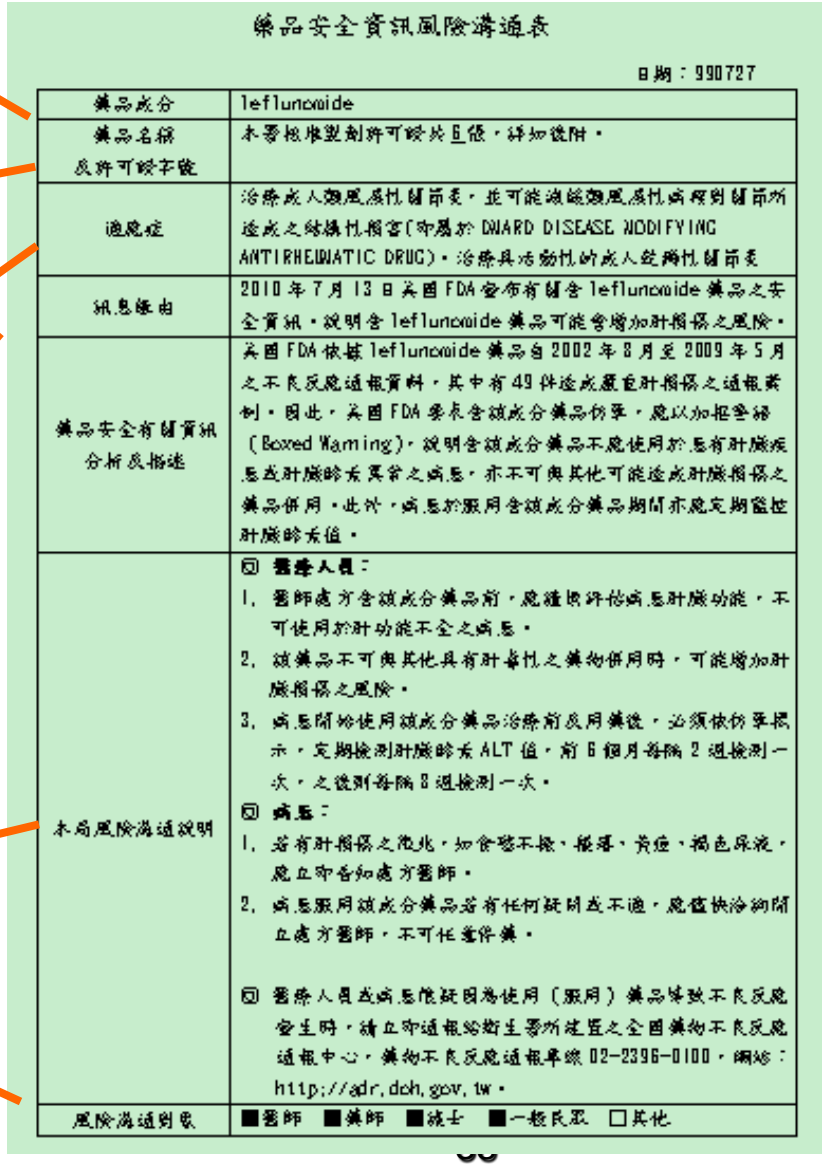
Indications

News origin

News content

Information for risk communication

communication parties



藥品安全資訊風險溝通表

日期：990727

藥品成分	leflunomide
藥品名稱及許可證字號	本署核准並許可證共6張，詳如後附。
適應症	治療成人類風濕性關節炎，並可能減緩類風濕性病程對關節所造成之結構性損害(即屬於 DMARD DISEASE MODIFYING ANTIRHEUMATIC DRUG)。治療具活動性的成人乾癬性關節炎
訊息緣由	2010年7月13日美國FDA發布有關含 leflunomide 藥品之安全資訊，說明含 leflunomide 藥品可能會增加肝損傷之風險。
藥品安全有關資訊分析及描述	美國FDA依據 leflunomide 藥品自2002年3月至2009年5月之不良反應通報資料，其中有49件造成嚴重肝損傷之通報案例。因此，美國FDA要求含該成分藥品仿單，應以加框警語(Boxed Warning)，說明含該成分藥品不應使用於患有肝臟疾患或肝臟酵素異常之病患，亦不可與其他可能造成肝臟損傷之藥品併用，此外，病患於服用含該成分藥品期間亦應定期監控肝臟酵素值。
本局風險溝通說明	☑ 醫療人員： 1. 醫師處方含該成分藥品前，應確認評估病患肝臟功能，不可使用於肝功能不全之病患。 2. 該藥品不可與其他具有肝毒性之藥物併用時，可能增加肝臟損傷之風險。 3. 病患開始使用該成分藥品治療前及用藥後，必須依仿單揭示，定期檢測肝臟酵素 ALT 值，前6個月每隔2週檢測一次，之後則每隔8週檢測一次。 ☑ 病患： 1. 若有肝損傷之徵兆，如食慾不振、腹瀉、黃疸、褐色尿液，應立即告知處方醫師。 2. 病患服用該成分藥品若有任何疑問或不適，應儘快洽詢開立處方醫師，不可任意停藥。 ☑ 醫療人員或病患懷疑因為使用（服用）藥品導致不良反應發生時，請立即通報發生當所建置之全國藥物不良反應通報中心，藥物不良反應通報專線 02-2396-0100，網站：http://adr.doh.gov.tw。
風險溝通對象	■醫師 ■藥師 ■護士 ■一般民眾 □其他

Official real-time drug safety information sharing networks

Local health authorities ← fax — **Drug safety warnings**

- Press release
- Risk Communication Letter

Consumer protection center

Drug info website

https://consumer.fda.gov.tw

E-paper

Real time

Subscribers: HCP and the public

Drug Relief Foundation

Drug safety monitoring website

http://medwatch.fda.gov.tw/

http://recall.fda.gov.tw

email

- **Hospitals and MAH ADR contact points**
- **Subscribers**

TFDA website

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

Related associations

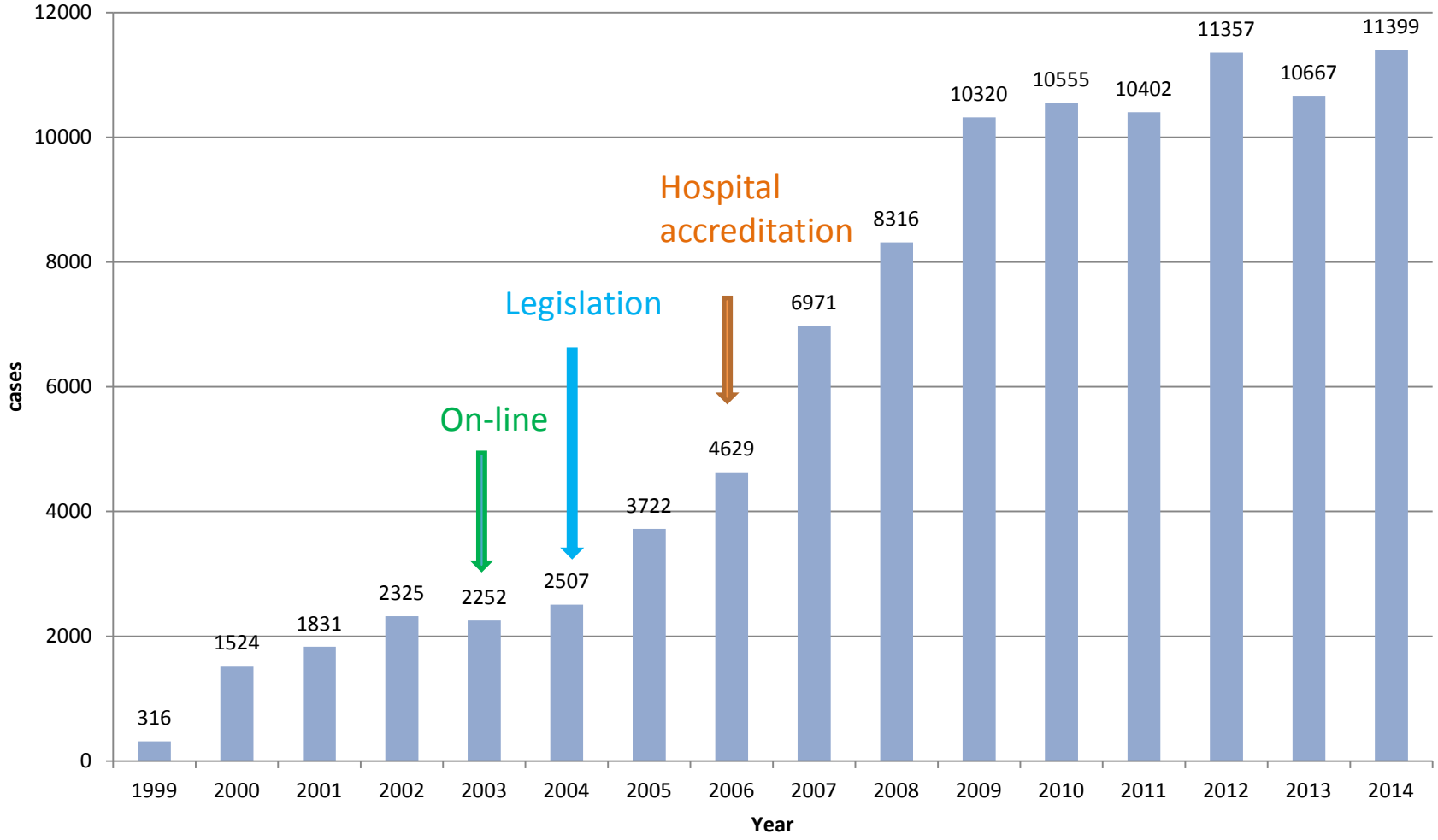
members

Statistics of reports

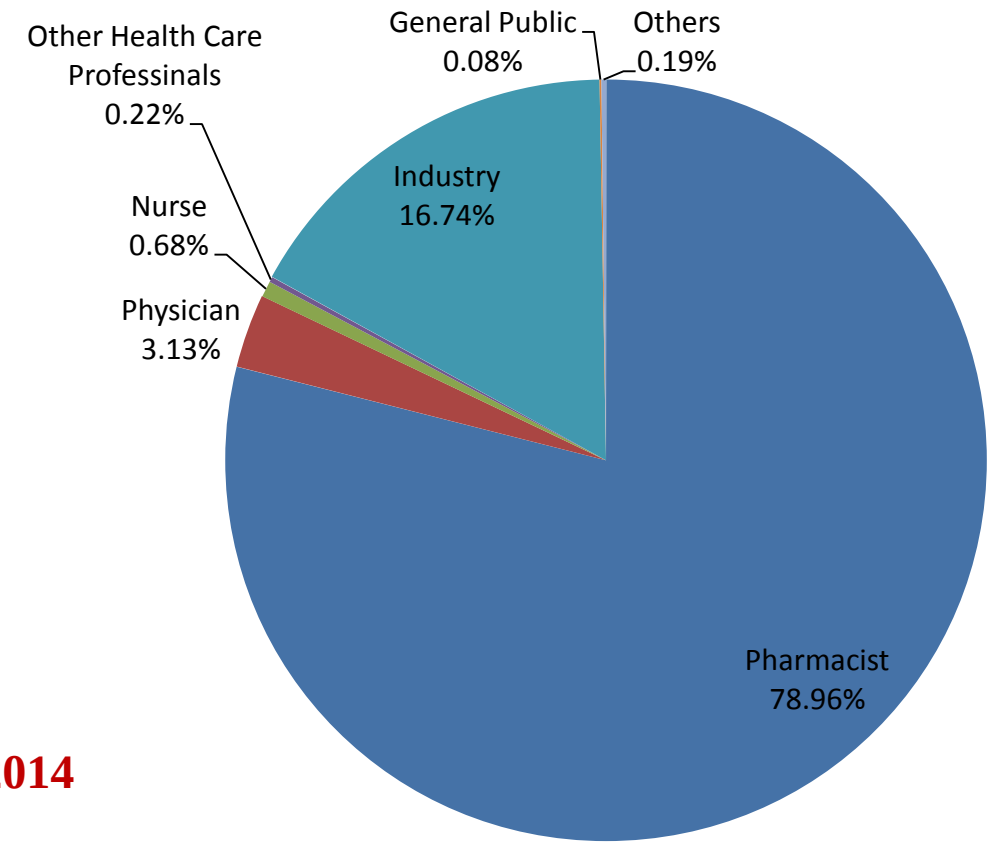
Examples of signal management

OUR ACHIEVEMENT

Annual ADR Reports in TW

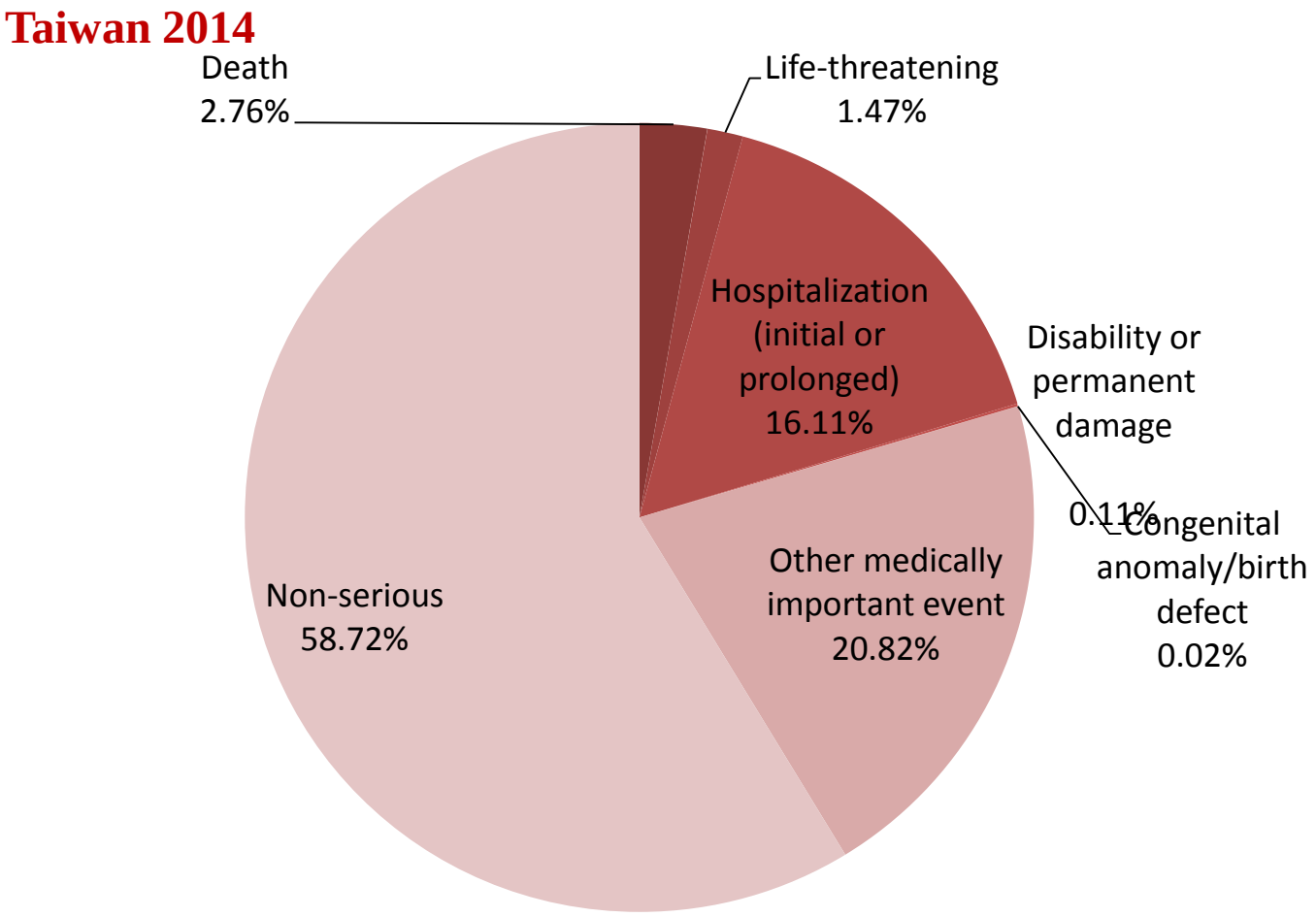


ADR Reporting Source



Taiwan 2014

Characteristic of Reports-Seriousness



ATC Classification of Suspected Drugs

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

Year 2014

System Organ Class of Reported ADR

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

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
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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