SUSAR與不良事件通報

高純琇

財團法人醫藥品查驗中心 執行長

2012年「人體研究倫理審查會-審查委員教育訓練課程」

大綱

- Introduction to Pharmacovigilance
- SUSAR Reporting in Clinical Trials
- Role of IRB in SAE

Safety Data Generation

Efficacy Proving & Emergent Safety Data Collecting

- ✓Pre-clinical Pharmacology and Toxicology
- ✓Clinical Pharmacology
- ✓Clinical Safety Data

→ **Pre-Marketing Safety Data** → **Product Label**

Thalidomide Tragedy (1957-1961)

- In the late 50s and early 60s, more than 10,000 children in 46 countries were born with deformities such as phocomelia, as a consequence of thalidomide use.
- A sedative-hypnotics, tranquilizer, painkiller, antiemetic (an inhibitory effect on morning sickness)
- At the time of the drug's development it was not thought likely that any drug could pass from the mother across the placental barrier and harm the developing fetus

  It was not promptly reviewed at the time it received market approval in Germany.

Actions after Thalidomide Tragedy

- Much stricter testing being required for drugs and pesticides before they can be licensed.
- In 1962, the United States Congress enacted laws requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S.
- More animal experiments needed before Human trials? Animal experimental model for teratogenecity?

Actions after Thalidomide Tragedy

- "We need to encourage doctors and drug companies to watch for, report and take note of side effects in order to protect patients properly. If proper drug surveillance techniques had been available in the 1960s the thalidomide problem would have been picked up much earlier. We still don't have proper post marketing trials in place."
- There is a need for post-marketing surveillance

Spontaneous ADR Reporting Systems

Yellow Card Scheme in UK

1962 – Committee on Safety of Drug

1964 – A letter sent out to physicians

"to report promptly details of any untoward condition in a patient which might be the result of drug treatment". This spontaneous adverse reaction reporting scheme was based upon such reports through reply-paid yellow cards and became popularly known as the "Yellow Card Scheme".

Up to now, the Yellow Card Scheme is still under operation.

Spontaneous ADR Reporting Systems

MedWatch

a change in focus - 1993 to 2003

- 1993 - MedWatch, The FDA Adverse Event Reporting Program
- 1998- MedWatch, The FDA Medical Products Reporting and Safety Information Program
- 2001 - MedWatch, The FDA Safety Information and Adverse Event Reporting Program

Copied from US FDA website

Spontaneous ADR Reporting Systems

Product Problems

- when there is a concern about the quality, authenticity, performance, or safety of any medication or device. Problems with product quality may occur during manufacturing, shipping, or storage.
- They include:

  suspect counterfeit product; product contamination; defective components; poor packaging or product mix-up; questionable stability; device malfunctions; and labeling concerns.

Limitations in Pre-marketing Trials

- 臨床試驗人數有限

  狹隘的試驗族群 narrow population –

  試驗結果常無法提供特定族群（例如：老人、小孩、婦女）所需資訊
- 狹隘的試驗適應症 narrow indications–

  排除部分疾病狀況
- 試驗期短無法反映慢性長期使用藥品產生的作用

Post Marketing

- 臨床試驗中未確認的低發生率不良反應可能出現
- 高危險群 high risk groups
- 長期作用 long-term effects
- 藥品/藥品、藥品/食物交互作用drug/drug, drug/food interactions
- 已知不良反應的嚴重度 或/和 發生率上升

Safety profile of a drug may have changed

Efficacy Proving & Emergent Safety Data Collecting

Pharmacovigilance

Main system:
A National Spontaneous ADR Reporting System

WHO Definition: is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medicines, biological products, herbals and traditional medicines, with a view to: *identifying new information about hazards, and preventing harm to patients.*

藥品安全監視策略三步驟

發掘藥品使用潛在的安全性問題
策略：透過建立自動性通報系統
(spontaneous reporting system)

⇩

以科學方法驗證前述的藥品安全性問題
(case-control study, cohort study...etc.)

⇩

藥品安全性問題的處理機制
（用藥教育,仿單修改…）

Major Aims of Pharmacovigilance

- Early detection of hitherto unknown adverse reactions and interactions
- Detection of increases in frequency of (known) adverse reactions
- Identification of risk factors and possible mechanisms underlying adverse reactions
- Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation

WHO Program for International Drug Monitoring
in Uppsala Monitor Center

the UPPSALA MONITORING CENTRE

台灣藥物安全監視制度之建構

- 台灣藥物不良反應通報系統
- 藥物安全通報資料庫建置
- 相關法規與規範之建立與推動

台灣藥物安全監視制度之建構

Set-up Period

- ✓ The ADR Reporting System in Taiwan was established in 1998 (a two-year research project was carried out during 1996-1998)
- ✓ Include pharmaceutical products and medical devices
- ✓ The national ADR reporting center is operating inside the Taiwan Drug Relief Foundation (TDRF) since 2002
- ✓ TDRF was founded by Department of Health to assist the implementation of Drug Injury Relief Act.

台灣藥物安全監視制度之建構

- **A web-based reporting system (adr.doh.gov.tw)**
  - ✓ Provide updated information of drug safety and related pharmaceutical regulation issues to the public for the Reporting center and DOH
  - ✓ On-line submission of ADR reports through the web system.

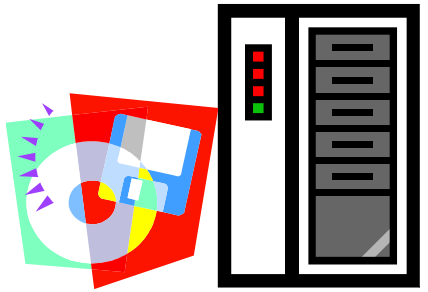
http://adr.doh.gov.tw/default.asp

台灣藥物安全監視制度之建構

ADR Related Databases in the Center

- ✓SAE reports of clinical trials for new drug registration
- ✓Postmarketing ADR reports –

  MedDRA terminology and ATC code adopted since 2005. All the cases in the database were retrospectively coded since then.
- ✓PSUR for new drug under monitoring for five years
- ✓ADE for Medical Devices



台灣藥物安全監視制度之建構

Legislation

- ✓ Amendments of Pharmaceutical Affairs Act on April, 2004.
- ✓ Mandatory reporting for serious ADRs
- ✓ Safety monitoring of new drug at the first five years when they were approved for marketing

Good Pharmacovigilance Practice Guidance

announced in 2008

藥事法

2004.4.21立法院通過修訂藥事法第四十五條第二項及增訂第四十五條之一。

- 第四十五條：（衛生署公告：藥物安全監視管理辦法）

  經核准製造或輸入之藥物，中央衛生主管機關得指定期間，監視其安全性。

  藥商於前項安全監視期間應遵行事項，由中央衛生主管機關定之。

- 第四十五條之一：（衛生署公告：嚴重藥物不良反應通報辦法）

  醫療機構、藥局及藥商對於因藥物所引起之嚴重不良反應，應行通報；其方式、內容及其他應遵行事項之辦法，由中央衛生主管機關定之。

- 第九十二條：

  違反……、第四十五條之一，處新台幣三萬元以上十五萬元以下罰鍰。

嚴重藥物不良反應通報辦法 -1

(2004年 08 月 31 日發布)

- 第3條
  - 因藥物所引起之嚴重藥物不良反應發生時，醫療機構、藥局、藥商應依本 辦法填具通報書，連同相關資料，向中央衛生主管機關或其委託機構通報 。
- 第4條
  - 本辦法所稱之嚴重藥物不良反應，係指因使用藥物致生下列各款情形之一者：
    - 死亡。
    - 危及生命。
    - 造成永久性殘疾。
    - 胎嬰兒先天性畸形。
    - 導致病人住院或延長病人住院時間。
    - 其他可能導致永久性傷害需做處置者。

嚴重藥物不良反應通報辦法 -2

- 第5條
  - 醫療機構及藥局應於得知前條第一款(死亡)及第二款(危及生命)之嚴重藥物不良反應之日起七日內，依第三條規定辦理通報，並副知持有藥物許可證之藥商。 前項通報資料如未檢齊，應於十五日內補齊。 第一項通報資料如需持有藥物許可證之藥商提供產品相關資料，藥商不得拒絕。
- 第6條
  - 持有藥物許可證之藥商於得知嚴重藥物不良反應之日起十五日內，依第三條規定辦理通報。

When-

- 醫療機構及藥局在得知死亡及危及生命案例時，應在7日內通報，並於15日內補齊相關資料，並應副知持有藥物許可證之廠商。
- 藥商應於得知嚴重藥物不良反應起15日內通報。

How-

將通報書及相關資料以郵寄、傳真及網路方式通報。緊急時得以口頭通報，並於期限內完成書面通報。

Where-

全國藥物不良反應通報中心

✖其他

必要時，醫療機構、藥局及藥商需提供嚴重藥物不良反應病人之就醫紀錄、給藥紀錄及產品資料。

藥品臨床試驗之安全控管

時機點

- 臨床試驗計畫書之審查 (Safety concerns, IRB)
- 不定期之個案評估

  Review of individual SUSARs, Protocol Amendments
- 定期回顧

  ASRs, Review of monthly SUSAR listings

  Independent Reviews by Data Monitoring Committees (DMC)

SUSAR: Suspected Unexpected Serious Adverse Reactions

時機點

- ICH E2F: The Development Safety Update Report (DSUR) is required annually for drug under development (including marketed drugs that are under further study) among ICH region.

  Sponsor應定期檢視及回顧試驗藥品之安全性

  Information in DSUR includes:
  - ✓ the status of ongoing individual investigations,
  - ✓ manufacturing changes,
  - ✓ overall development status and plans
  - ✓ safety-related information.
- Annual Report of Investigational drugs

The basis and the most important action is:

臨床試驗之SAE通報

Definition

中文	英文	簡稱
嚴重不良事件	Serious Adverse Event	SAE
藥品不良反應	Adverse Drug Reaction	ADR
嚴重藥品不良反應	Serious Adverse Drug Reaction	SADR
未預期嚴重藥品不良反應	Suspected Unexpected Serious Adverse Reactions	SUSARs

不良事件：受試者參加試驗後所發生之任何不良情況。
此項不良情況與試驗藥品間不以具有因果關係為必要。

Good Clinical Practice (GCP)

藥品優良臨床試驗規範

1996/11/20 第一次公告

藥品優良臨床試驗準則

2002/09改公告

2010/07/19 修正第106條

藥品優良臨床試驗準則(GCP)

第七章　臨床試驗之進行 第三節紀錄與報告

第一０四條 主管機關得要求試驗主持人向其所屬機構提出書面報告，說明臨床試驗進度。

試驗主持人及試驗機構每年應將臨床試驗進度向人體試驗委員會提出定期摘要報告。必要時，人體試驗委員會得要求縮短定期摘要報告之間隔期間。

第一０五條 發生重大影響臨床試驗執行或增加受試者風險之情形，試驗主持人應立即向試驗委託者、人體試驗委員會及主管機關提出書面報告。

藥品優良臨床試驗準則

第七章　臨床試驗之進行 第三節紀錄與報告

第一０六條 （2010/07/19 公告修正）

◆受試者發生任何嚴重不良事件，試驗主持人應立即通知試驗委託者，並儘快提供詳細書面報告。發生未預期之嚴重藥品不良反應，試驗主持人應立即通知人體試驗委員會。但若試驗計畫書或其他文件明確排除者，不在此限。

- 試驗委託者獲知未預期之死亡或危及生命之嚴重藥品不良反應，應於獲知日起七日內通報主管機關或其委託機構，並在獲知日起十五日內提供詳細書面資料。

參考ICH E6 Guidance for Industry (E6 Good Clinical Practice: Consolidated Guidance)修正

藥品優良臨床試驗準則

第七章　臨床試驗之進行 第三節紀錄與報告

第一０六條 （2010/07/19公告修正）cont.

- 試驗委託者獲知未預期之死亡或危及生命以外之嚴重藥品不良反應，應於獲知日起十五日內通報主管機關或其委託機構，並提供詳細書面資料。
- 第一項之口頭及書面報告，應以受試者代碼代表受試者之身分，不得顯示受試者之姓名、身分證統一編號、住址或其他可辨認受試者身分之資訊。
- 嚴重不良事件及嚴重藥品不良反應之項目由主管機關公告之。

藥品優良臨床試驗準則

第七章　臨床試驗之進行 第三節紀錄與報告

第一０七條 發生與試驗藥品安全性評估相關之不良反應或異常實驗室檢查值時，試驗主持人應於試驗計畫書規定之時間內向試驗委託者提出書面報告。

第一０八條 發生死亡病例時，試驗委託者、人體試驗委員會與主管機關得要求試驗主持人提出驗屍報告、最終醫療紀錄及其他任何額外資訊。

何謂“但若試驗計畫書或其他文件明確排除者，不在此限。”（依ICH 4.11.1新增）

舉例：

- Trial endpoint 觀察mortalities or morbidities，計畫書強調屬於endpoint之SAE將不會快速通報。
- 計畫書強調某些Hospitalization (如：scheduled hospitalization)等將不會快速通報。
- 計畫書強調和Disease progression有關之Death將不會快速通報。

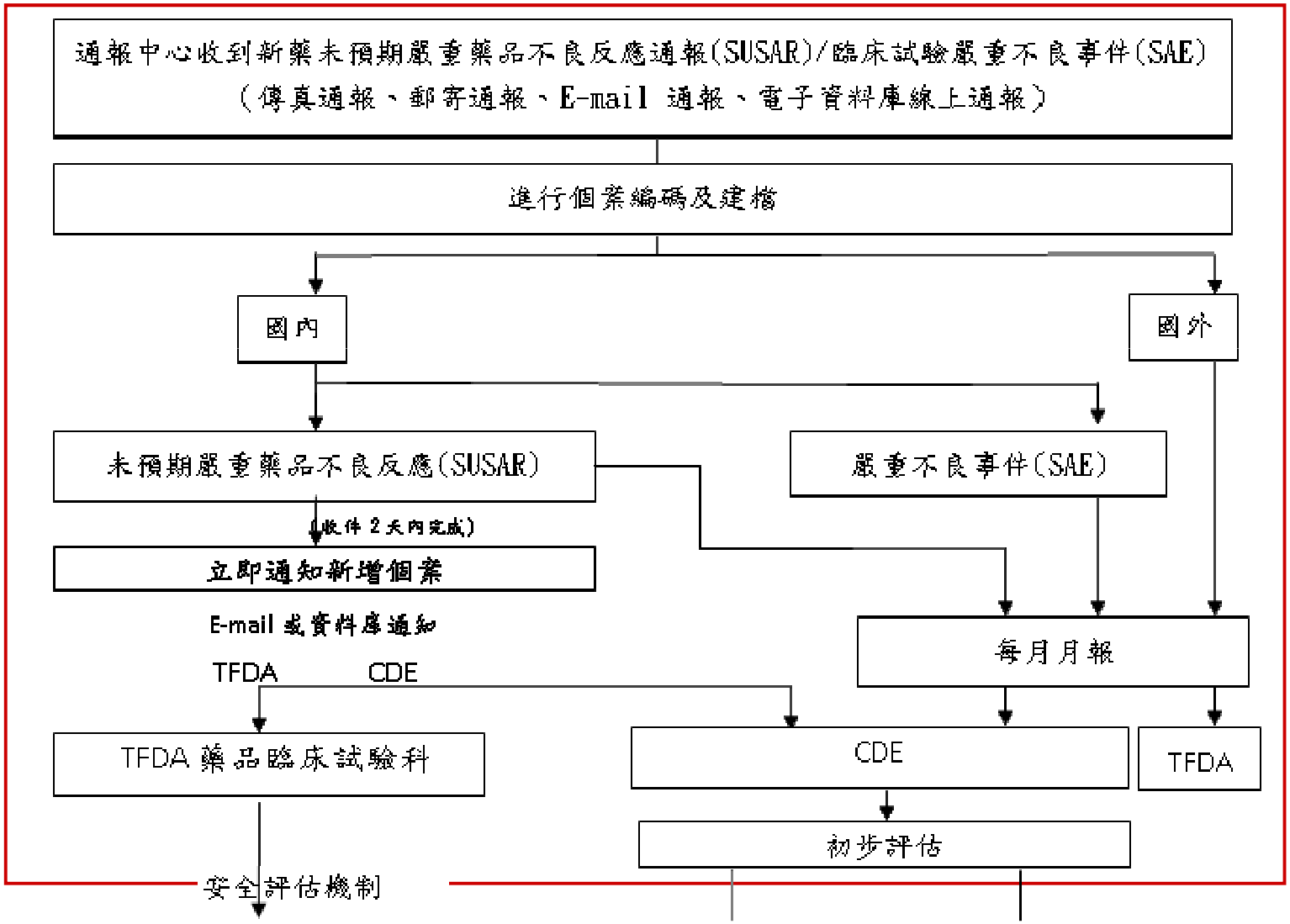
Expedited Reporting in Taiwan

2010.07.19

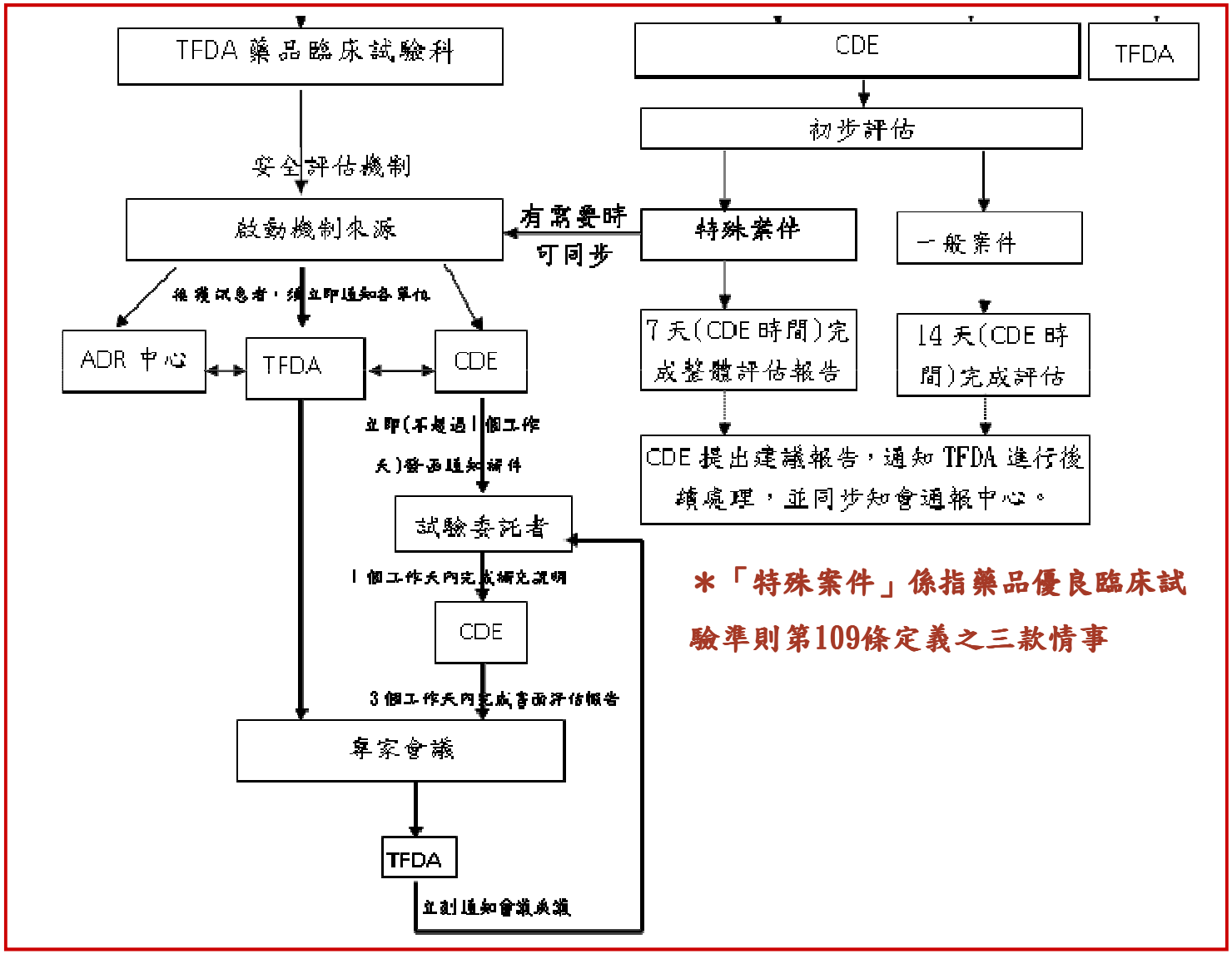
Apply to all Local and Global Clinical Trials

新藥臨床試驗未預期嚴重藥品不良反應（SUSAR）通報作業流程

2010.11.30修訂



新藥臨床試驗未預期嚴重藥品不良反應（SUSAR）通報作業流程　2010.11.30修訂



＊「特殊案件」係指藥品優良臨床試驗準則第109條定義之三款情事

藥品優良臨床試驗準則

第七章　臨床試驗之進行 第三節紀錄與報告

第一０九條　以下情形發生時，試驗委託者應立刻通知試驗主持人、試驗機構及主管機關：

一. 可能危害受試者安全之新發現。

二. 影響試驗執行之新發現。

三. 影響人體試驗委員會同意試驗繼續進行之新發現。

第一一０條 試驗委託者應向主管機關提出最新安全性報告。

SUSAR vs SAE

Expectedness of the ADR?

- **According to ICH E2A**
  - Expected/unexpected event is defined from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

  - **Unexpected ADR:**
    1. The experience that has not been previously observed.
    2. The nature or severity of which is not consistent with information in the relevant source document(s), e.g., a company's Investigator's Brochure.

未預期藥品不良反應

係指此藥品不良反應未曾於藥品資訊文件上記載，或雖有記載但此不良反應的本質或嚴重程度有所改變時。前開藥品資訊文件，若在未核准藥品，可為主持人手冊（Investigator's Brochure, IB）；已核准藥品則可為仿單或包裝盒內附之說明書。

Good Expedited Safety Report Should

- help regulatory agency to figure out
  (1) reasonable causal relationship between the SAE and the study drug
  (2) expectedness of the SAE (ADR)

Beginning

- Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with clinical study procedures.

- Important following information should be captured for all SAEs: onset, duration, intensity, seriousness, relationship to investigational product, and action taken.

個案編號（由通報中心填寫）：

藥品不良反應通報表格(02)
（此表為臨床試驗通報用）

藥物不良反應通報表
行政院衛生署

電話：(02) 2396-0100
傳真：(02) 2358-4100
台北郵政 84-664 號信箱
網址：http://adr.doh.gov.tw
電子信箱：adr@doh.gov.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
姓名:
電話:
電子郵件信箱：
服務機構：
地址：
屬性：□醫療人員，職稱:_____
□廠商

5.案例來源：□ 國外，_____(國家)
□ 國內，試驗醫院:_____
試驗醫師:_____

6.報告類別：□ 初始報告
□ 追蹤報告，第_____次

7. 試驗名稱：

8. 衛生署核准函文號：_____　□查驗登記用 □學術研究用

9. 廠商試驗編號：

I. 病人基本資料

10. 識別代號：
（供通報者辨識用）

11. 性別：□男□女

12. 出生日期：　　年　　月　　日 或年齡：_____

13. 體重：_____公斤

14. 身高：_____公分

15.是否為其他單位副知：□是（原通報單位識別代號：_____）□否

II.不良事件有關資料

16. 不良事件後果

□ A.死亡，日期：　　年　　月　　日，死亡原因：_____

□ B.危及生命　　□ C.導致病人住院

□ D.造成永久性殘疾　　□ E.延長病人住院時間

□ F.需作處置以防永久性傷害　　□ G.先天性畸形

□ H.非嚴重不良事件（請敘述）_____

17. 通報案件之描述（請依案件發生前後時序填寫，應包括不良事件發生之日期、部位、症狀、嚴重程度及處置）

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

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

☐ D.造成永久性殘疾　☐ E.延長病人住院時間 ☐ F.需作處置以防永久性傷害　☐ G.先天性畸形 ☐ H.非嚴重不良事件（請敘述）_____	
17. 通報案件之描述（請依案件發生前後時序填寫，應包括不良事件發生之日期、部位、症狀、嚴重程度及處置）	19. 其他相關資料（例如：診斷、過敏、懷孕、吸菸、喝酒、習慣、其他疾病、肝/腎功能不全...等）

III. 懷疑藥品（包括西藥及中草藥）

20.用藥情形	☐ 試驗組 _____ ☐ 對照組_____ ☐ 安慰劑組_____ ☐ 尚未用藥　☐ 無法得知 （☐ 尚未解碼 ☐ 其他_____）							
21.可疑藥品	學名/商品名	含量/劑型	給藥途徑	劑量/頻率	起迄日期	適應症	廠牌/批號	效期
	#1 #2							
22.併用藥品	#1 #2							

23. 曾使用同類藥品之經驗　☐是☐否 ☐無法得知 藥品：_____不良反應：_____ 24. 停藥後不良反應是否減輕 ☐是 ☐否☐無法得知	25. 再投藥是否出現同樣反應☐是 ☐否 ☐無法得知 26. 同時使用 ☐中草藥* ☐西藥* ☐健康食品 ☐其他: _____ *若有同時使用，請將所用品項填入併用藥品內

IV. 試驗醫師評估藥品與 SAE 之因果關係

27. ☐ 確定相關 (certain)， ☐ 很可能相關 (probable/likely)， ☐ 可能相關 (possible)， ☐ 不太可能相關 (unlikely)，
☐ 不相關 (unrelated)

2008.11

To clarify reasonable causal relationship between the SAE and the study drug

- Usage of study drug before onset of SAE
  - ✓Not yet started (SAE occurred prior to first dose)
  - ✓Permanently discoutinued (follow-up period); Duration of discontinuation
  - ✓Yes (Study group or Control group or Placebo group or Unknown (Undecoded or others)
- Therapy duration until onset of first signs/ symptoms of SAE.
- The location, syndrome, severity, and management of the event following the time sequence

To clarify reasonable causal relationship between the SAE and the study drug

- **Action taken with the drug due to event?**
  - None,
  - Dose adjustment,
  - Temporary stop,
  - Permanent stop
- **Alternative explanation for SAE?**
  - Concomitant disease?
  - Concomitant drug?
  - Intercurrent disease?
  - Related to study procedure?
  - Progression of Underlying illness?

Causality Assessment By PI

- **Reasonable** causal relationship between the event and the study drug (i.e., the relationship cannot be ruled out)
  - ✓Certain, Probable/Likely, Possible
- **No reasonable** causal relationship between the event and the study drug
  - ✓Unlikely, Unrelated

Assessment of Causality-1

- **Certainly (definitely):**
  - Follows a reasonable temporal sequence from study drug administration.
  - Abates upon discontinuation of the study product (Dechallenge)
  - Is confirmed by reappearance of the reaction on repeat exposure (Rechallenge)

Assessment of Causality-2

- **Probably/Likely related:**
  - Follows a reasonable temporal sequence from study drug administration.
  - Abates upon discontinuation of the study product (Dechallenge)
  - Cannot be reasonable explained by the known characteristics of the subject's clinical state.

Assessment of Causality-3

- **Possibly related:**
  - Follows a reasonable temporal sequence from study drug administration.
  - Could have been produced by the subject's state or by other modes of therapy administered to the subject.

    Concomitant disease? Concomitant drug?
    Intercurrent disease? Related to study procedure?
    Progression of Underlying illness?

Assessment of Causality-4

- **Unlikely related:**
  - The temporal sequence between the AE and the study product administration is such that the drug is not likely to have had any reasonable association with the observed event.
  - The AE could have been produced by the subject's clinical condition or by other modes of therapy administered to the subject.

Concomitant disease? Concomitant drug? Intercurrent disease?
Related to study procedure Progression of Underlying illness?

Assessment of Causality-5

- **Un-related:**
  - There is not a temporal relationship to investigational product administration

    Too early, or late, or investigational product not taken.
  - The AE is definitely produced by the subject's clinical condition or by other modes of therapy administered to the subject.

    Concomitant disease? Concomitant drug? Intercurrent disease? Related to study procedure? Progression of Underlying illness?

According to ICH E2A

All cases judged by either the reporting health care professional (PI) or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.

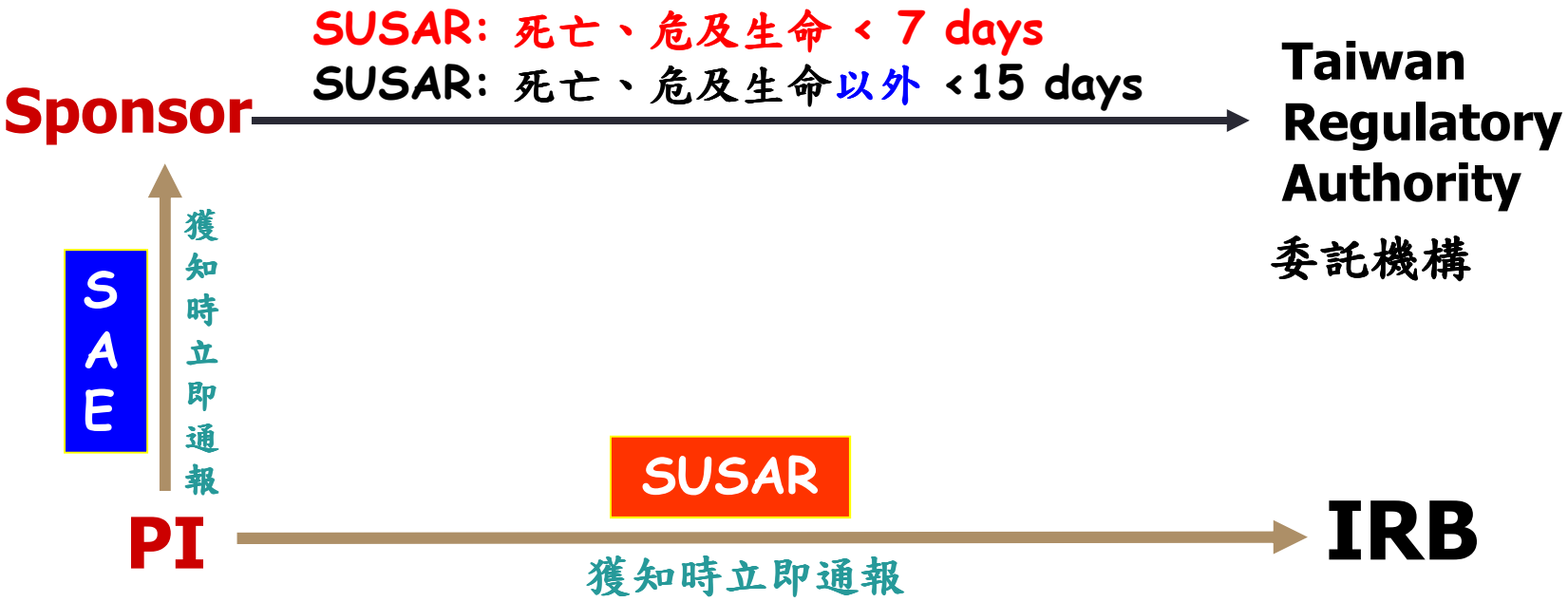
Final Reminder

- The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions.

- For ensuring that studies are stopped as soon as it becomes clear that the trail intervention is harmful.

- To protect the safety of trial participants

SUSAR vs SAE


SUSAR: 死亡、危及生命 < 7 days
SUSAR: 死亡、危及生命以外 <15 days
Sponsor
Taiwan Regulatory Authority
委託機構
SAE
獲知時立即通報
SUSAR
PI
IRB
獲知時立即通報

Question

National Reporting Center for Adverse Drug Reactions in Taiwan

Tel: +886-2-2396-0100;

Fax: +886-2-2358-4100

E-mail: adr@tdrf.org.tw

http://adr.doh.gov.tw

ADR Reporting System

全國藥物不良反應通報系統