自發性通報系統與個案評估

藥害救濟基金會 藥物安全組

全國藥物不良反應通報中心 趙必暉 藥師

Disclaimer

- 財團法人藥害救濟基金會接受衛生福利部食品藥物管理署委託辦理「全國藥物不良反應通報中心」及「104年創新藥品風險管理及輔導」計劃
- 本次演講內容僅代表全國藥物不良反應通報中心之觀點， 凡涉及政策方向及法規解釋與適用，應依衛生主管機關之指示為準。

Agenda

- Post-marketing ADR Reporting System
- Individual case safety report (ICSR)
- ICSR assessment and evaluation

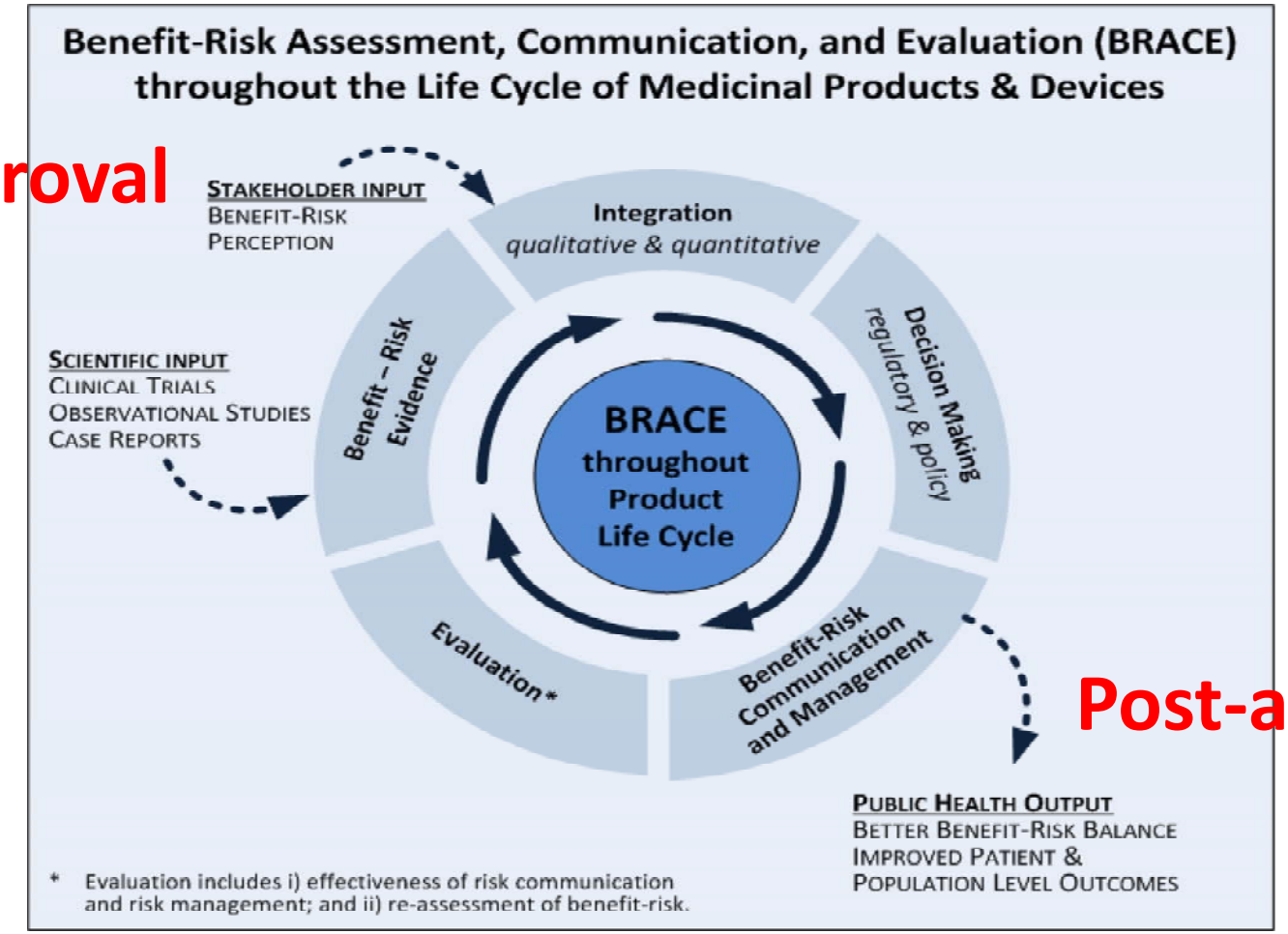
Expectations for Pharmaceutical Company

- From RA, Prescribers, HCPs and Consumers
  - Maintain an appropriate PV system and employ the designated, qualified person responsible for PV.
  - Promptly notify and update any new safety concern and take appropriate action
  - Continually evaluate products and screen potential manufacturing problem

POST-MARKETING ADR REPORTING SYSTEM

Product Life-Cycle Monitoring

Pre-approval



Post-approval

PROTECT:ISPE

Differences Between Trial and Real

Population Size

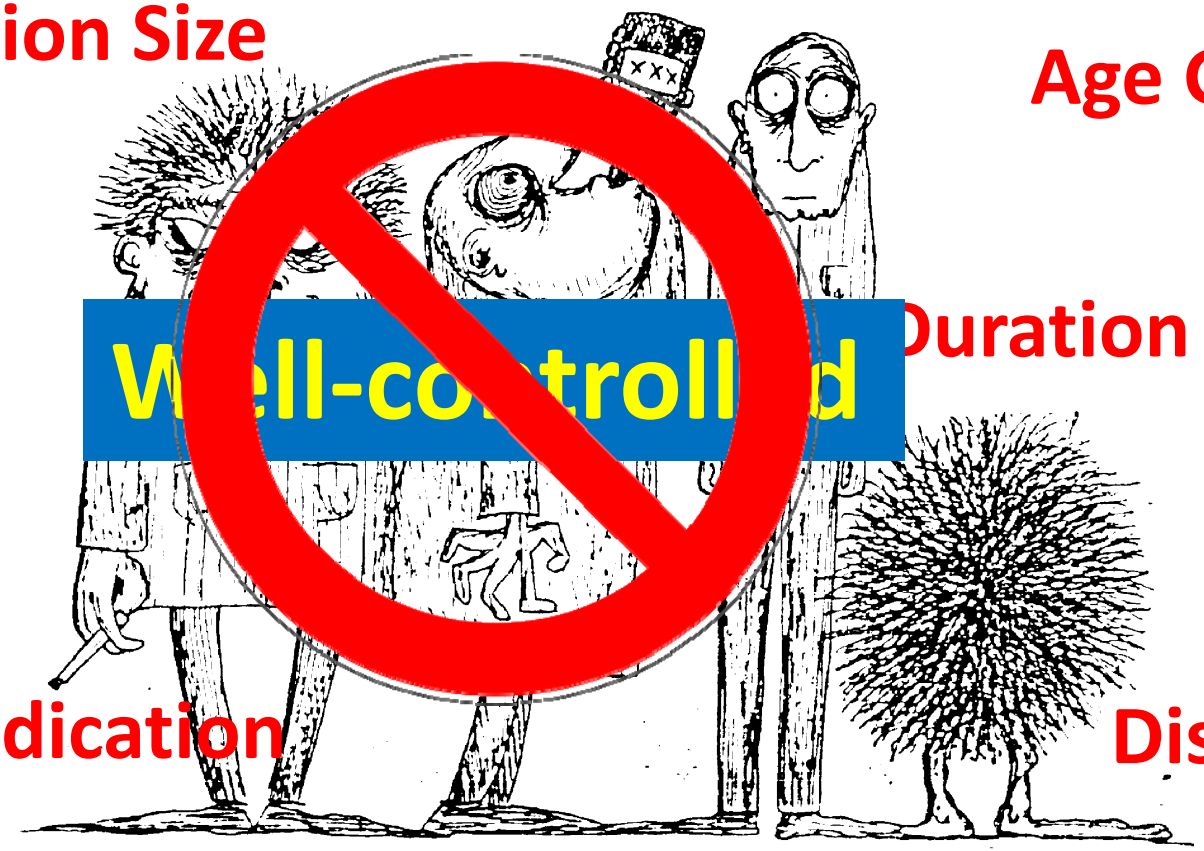
Age Group

Life-style

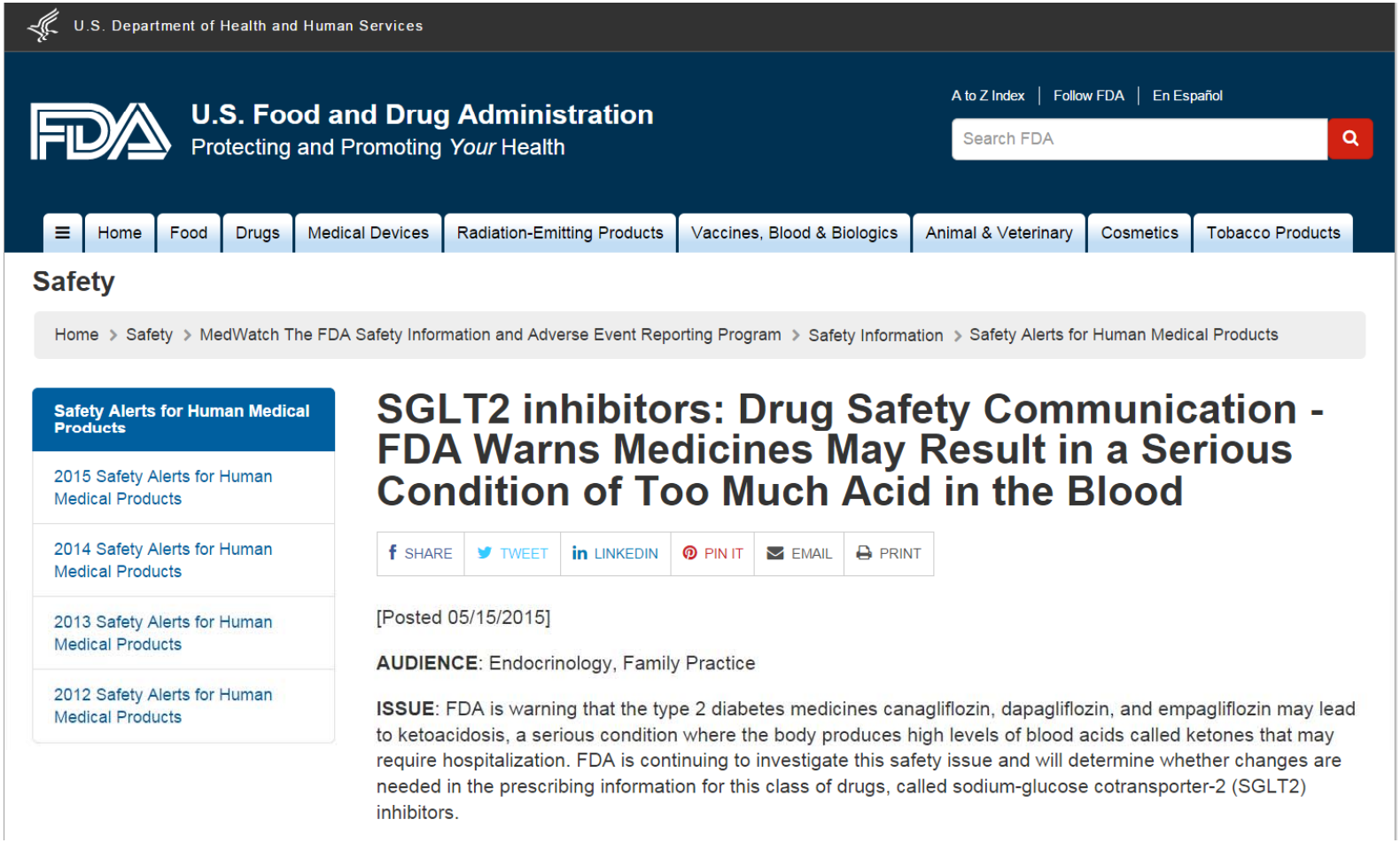
Duration of Use

Clinical Indication

Disease



Example-SGLT2i



U.S. Department of Health and Human Services

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Safety

Home > Safety > MedWatch The FDA Safety Information and Adverse Event Reporting Program > Safety Information > Safety Alerts for Human Medical Products

Safety Alerts for Human Medical Products

- 2015 Safety Alerts for Human Medical Products
- 2014 Safety Alerts for Human Medical Products
- 2013 Safety Alerts for Human Medical Products
- 2012 Safety Alerts for Human Medical Products

SGLT2 inhibitors: Drug Safety Communication - FDA Warns Medicines May Result in a Serious Condition of Too Much Acid in the Blood

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[Posted 05/15/2015]

AUDIENCE: Endocrinology, Family Practice

ISSUE: FDA is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. FDA is continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Data Collection

- **Solicited reports**
  - Reports are those derived from organized data collection systems
  - Clinical trials, registries, patient support program, etc.
- **Unsolicited reports**
  - **Spontaneous reports**
  - Literature
  - Internet, Media, etc.

Spontaneous Reporting

FDA definition

- *The process of reporting of **all unsolicited reports** of adverse events from health care professionals or consumers to the FDA (or any appropriate authority) is called spontaneous reporting*

Ahmad SR, et al. Spontaneous reporting in the United States. Chapter 9. In Strom' s Pharmacoepidemiology, 2005 p. 135-159.

Goals of Spontaneous Reporting

- Identify new (less frequent) ADRs
- Identify drug-drug/food interactions
- Identify risk factors/at-risk populations for known ADRs
- Identify change in reporting of an AE over time
- Identify manufacturing problems
- Reduce the risk of drug toxicity to enhance safe use

Reporting System/Database

- Nationwide (regulatory)
  - FAERS、 Eudravigilance、WHO-vigibase
  - 全國藥物不良反應通報中心
  - From companies, consumers, HCPs, regulatory
- Marketing Authorized holder
  - For the reporting purpose (to regulatory) and responsibility
  - Safety database- To collect, manage and report
  - From consumers, HCPs

Individual case safety report (ICSR)

The format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time.

EMA/873138/2011 Rev 1 Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)

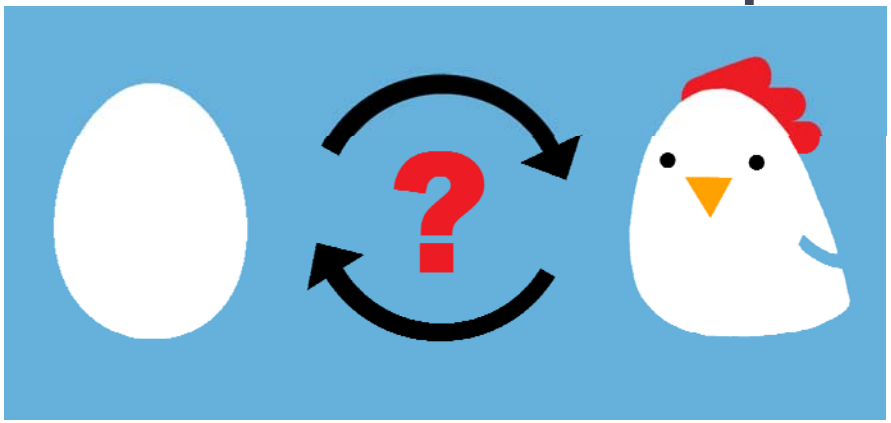
ICSR ASSESSMENT AND EVALUATION

Why individual case assessment?

- For regulatory reporting purpose
  - Report the valid case
- For further evaluation
  - Complete the data as possible
  - Classify reports
  - Identifies reaction characteristics and risk factors

Two types of assessment

- Ensure correct interpretation of medical information
  - Review the report for **quality and completeness** of the medical information
  - Individual case **casual relationship**



Quality and completeness- Key data elements

- Details on **reporter** of an ADR
- Patient details
- Suspected medicinal product(s)
- Other treatment(s)
- Details (all available) of adverse drug reaction(s)
- (Administrative and MAH details)

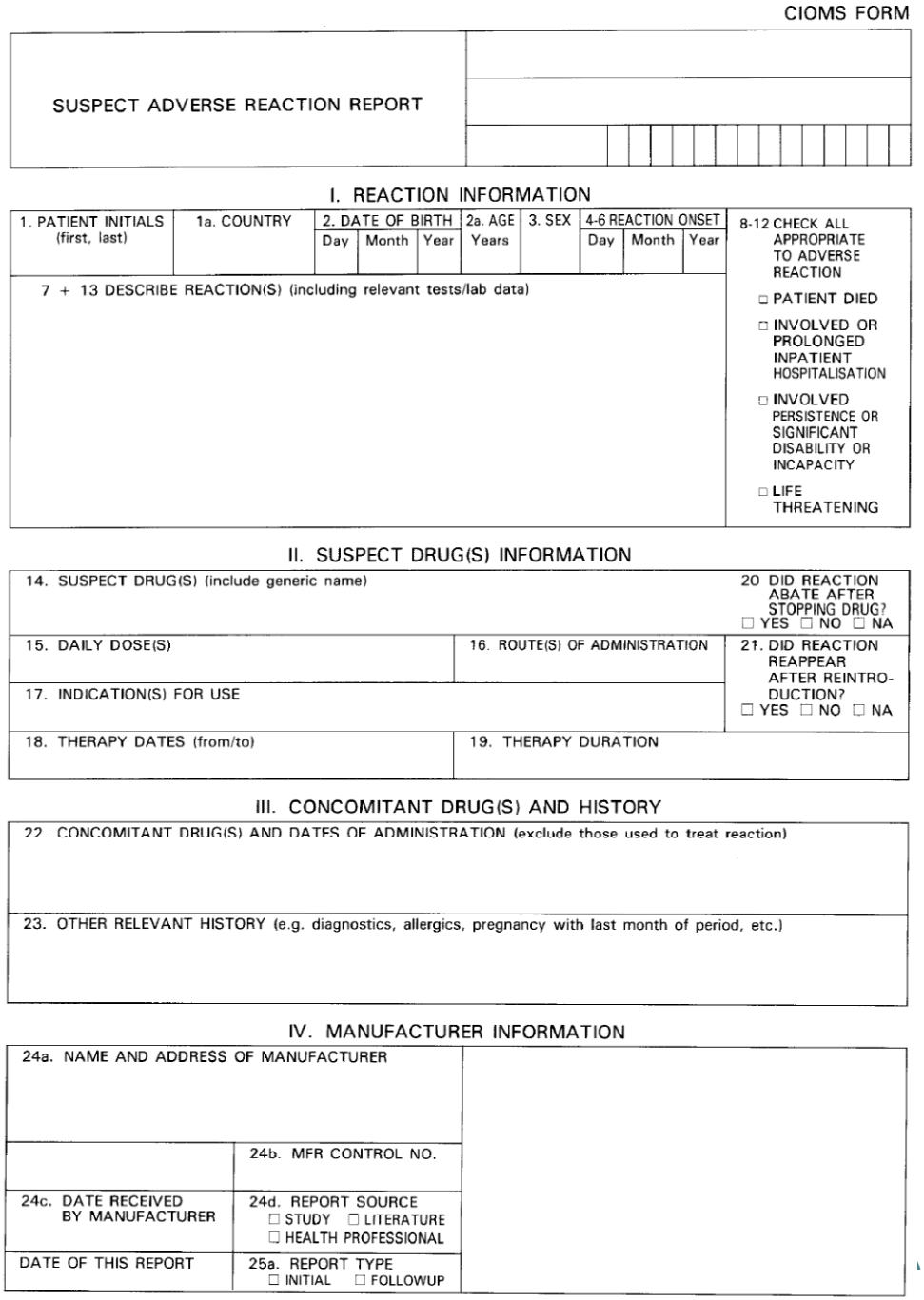
Refer to the ICH E2B/E2D guidelines for detail

CIMOS Form

http://cioms.ch/index.php/cioms-form-i

ICH-E2B

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)

16. ROUTE(S) OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)

19. THERAPY DURATION

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

Quality and completeness-
Patient and reporter identifiability

- Important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases
  - Local data privacy laws
- Verify the existence of an identifiable patient and reporter as possible
  - Age, gender, data of birth, etc.
- All parties supplying case information or approached for case information should be identifiable
  - Including Follow-up

Refer to the ICH E2D guidelines for detail

Quality and completeness- The role of narratives

- Summarize all relevant clinical and related information
  - including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, and ADR(s) including the outcome, laboratory evidence
- Comprehensive, stand-alone “medical story”
  - Should be presented in a logical time sequence
  - New information should be clearly identified in follow-up
  - Abbreviations and acronyms should be avoided

Refer to the ICH E2D guidelines for detail

Quality and completeness- Suspected adverse reaction

- Is a diagnosis possible?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- **What additional information is needed?**
- **The report should include the verbatim term as used by the reporter, or an accurate translation**
  - **Provide an unbiased and unfiltered report**
  - **Coding with MedDRA appropriately**

Refer to the ICH E2D guidelines for detail

Quality and completeness- Follow-up Information

- The information from ADR cases when first received is generally incomplete
- The company should provide specific questions and questionnaire/specific form
- Serious or unexpected or special interest

Quality and completeness-
Minimum Criteria for Reporting(ICH-E2D)

- Only **valid ICSRs** qualify for reporting
  - **Identifiable reporter**
  - One single **identifiable patient**
  - One or more **suspected adverse reaction**
  - One or more **suspected substance/medicinal product**

Quality and completeness-
Minimum Criteria for Reporting

- Identifiable reporter
  - Characterized by qualification, name, contact details
  - Directly contact
- Identifiable patient
  - Initials, patient identification number, date of birth, age, age group or gender
- Suspected medicinal products

Quality and completeness- **Minimum Criteria for Reporting**

- Suspected adverse reaction
  - unspecified adverse reaction
  - Only Outcome (excluding sudden death)
  - Primary source has not indicated a possible causal relationship with the suspected medicinal product
- Invalid cases (incomplete) should not be reported to RA
  - Companies shall keep documenting and completing all invalid cases as possible. (Follow-up)

Casual relationship-
Relationship v.s. Causality

- How close is the relationship between medicine and event?
  - Relationship
- Was the event caused by the medicine?
  - Causality
- Causality for individual reports, even those with a close relationship, can seldom be established beyond doubt and our assessments are based on probability

Casual relationship-
Five Key points

- The timing of the event, relative to the drug exposure
- The presence or absence of other factors which might also cause the event
- The result of withdrawing the drug
- The result of reintroducing the drug
- Other data supporting an association, e.g., previous cases

Casual relationship-
Data elements

- The medicine
  - Date, duration, dose, brand
- The event description
  - Date of onset, duration to onset, the event description
- Outcome of the event
- Patient demographics
- Other factors
  - Concomitant medicine, medical history, Life style influences

Casual relationship-
Data elements

- **Results of dechallenge**
  - Outcome of the event after withdrawal of the medicine
  - Resolved, resolving, resolved with sequela, not resolved, worse, death, unknown

- **Results of rechallenge**
  - Following dechallenge and recovery from the event, the suspect medicine is tried again, under the same conditions as before and the outcome is recorded
  - Recurrence , no recurrence, unknown, no rechallenge

Casual relationship-
Relationship categories

- Practical tools
  - Developed for a structured and harmonised assessment of causality
  - Clinical-pharmacological aspects
- Method
  - Naranjo scored algorithm
  - BARDI (Bayesian Adverse Reaction Diagnostic Instrument)
  - **The WHO-UMC causality assessment system**

Casual relationship-
Relationship categories

WHO-UMC 制訂藥物不良反應(ADR)通報案例之成因相關性(Causality)評估標準表

成因相關性級別	*評估標準
1.確定	a. 此通報反應與藥物的使用有可信的時序性。 b. 且此通報反應無法合理以病人本身的疾病或併用藥物(化學物質)解釋。 c. 且停藥後的反應在藥理或病理上有可信的依據。 d. 且此通報反應須呈現明確之藥理現象或疾病狀態。 e. 如有需要，再投藥即出現類似之反應。
2.極有可能	a. 此通報反應與藥物的使用有合理的時序性。 b. 且此通報反應不太可能以病人本身的疾病或併用藥物(化學物質)解釋。 c. 且可合理解釋停藥後之臨床反應。 d. 再投藥即出現類似的反應，此非必要條件。
3.可能	a. 此通報反應與藥物的使用有合理的時序性。 b. 且此通報反應亦能以病人本身的疾病或併用藥物(化學物質)解釋。 c. 缺乏停藥後該反應變化的相關資訊，或停藥後該反應的變化不明確。
4.存疑	a. 此通報反應與藥物的使用在時序上不太合理(但並非不可能)。 b. 且病人本身的疾病或併用的藥物(化學物質)能更合理的解釋此通報事件。
5.資料不全	a. 此通報反應還需更多必要的資料以作適當評估，或還有其他資料仍在審查當中。
6.無法評估	a. 此通報反應因資訊不充分或矛盾而無法評估。 b. 且無法獲得進一步資料或得到證實而無法評估。

*級別內所有評估點皆須符合

Casual relationship-
Relationship categories

- Certain
  - Event with plausible time relationship
  - No other explanation -disease or drugs
  - Event definitive pharmacologically or phenomenologically
  - Rechallenge satisfactory

Casual relationship-
Relationship categories

- Probable
  - With reasonable time relationship to drug intake
  - Unlikely to be attributed to disease or other drugs
  - Response to withdrawal clinically reasonable
  - Rechallenge not required

Casual relationship-
Relationship categories

- **Possible**
  - With reasonable time relationship to drug intake
  - Could also be explained by disease or other drugs
  - Information on drug withdrawal may be lacking or unclear

Casual relationship-
Relationship categories

- **Unlikely**
  - With a time to drug intake that makes a relationship improbable (but not impossible)
  - Disease or other drugs provide plausible explanations
- Conditional/Unclassified
- Unassessable/Unclassifiable

Casual relationship-
Establishing the relationship

- Objective evaluation
  - Dates of use of all medicine(s)
  - Date of onset of event
  - Response to dechallenge
  - Response to rechallenge
  - Outcome
  - Disease being treated
  - Other diseases

Casual relationship-
Establishing the causality

- Subjective assessment
  - Consider
    - Relationship category
    - Background or past disease
    - Pharmacology
    - Prior knowledge of similar reports with the suspect drug or related drugs

What's Next

- Analyses of the aggregated data
  - Quantitative analysis
- Assessing clinical significance
- Evaluation of benefit and risk
  - Other researches
  - Take an action

Ethics

To know that something is harmful and not report, is unethical, because it is knowledge about a medicine that is lost. Reporting leads to better understanding and the opportunity to prevent similar problems in others.

~~~~ From David Coulter,

WHO Consultant on the Safety of Medicines,

Head of NZ Pharmacovigilance Centre
~~~~

The End ~~ Thank You~~

台北市中正區愛國東路一段22號10樓

ADR專線:(02)23960100；傳真專線:(02)23584100

E-MAIL：ADR窗口- adr@tdrf.org.tw