Safety Reporting in Clinical Trials

Supatra Porasuphatana

B. Pharm, PhD. (Pharmacology & Toxicology)

Center for Ethics in Human Research

Khon Kaen University

Drug Development: Regulatory Reviews

Drug discovery and preclinical studies

- Candidate molecules aimed for drug development
- Testing for safety and mechanisms of action

Duration and success rates

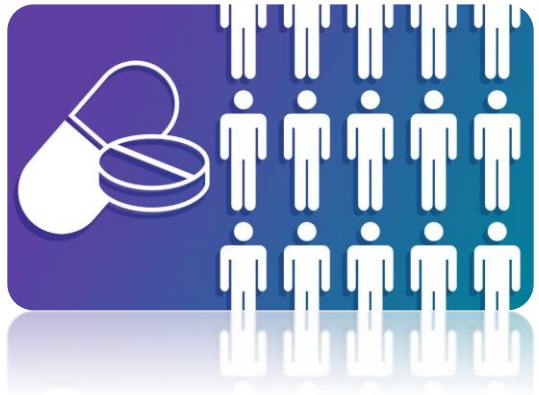
- *30 days for regulatory agency to review*
- *85% are approved*

IND submission

FDA safety review of IND submission

To ensure the avoidance of unnecessary risks to human subjects

Clinical trials



Drug Development: Ethical Reviews

FDA

IND

IRB/EC submission

Ethical review process

To safeguard safety, rights and welfare of human subjects

Clinical trials (FIH/Phase I-III)

- ***Safety?***
- ***Efficacy?***

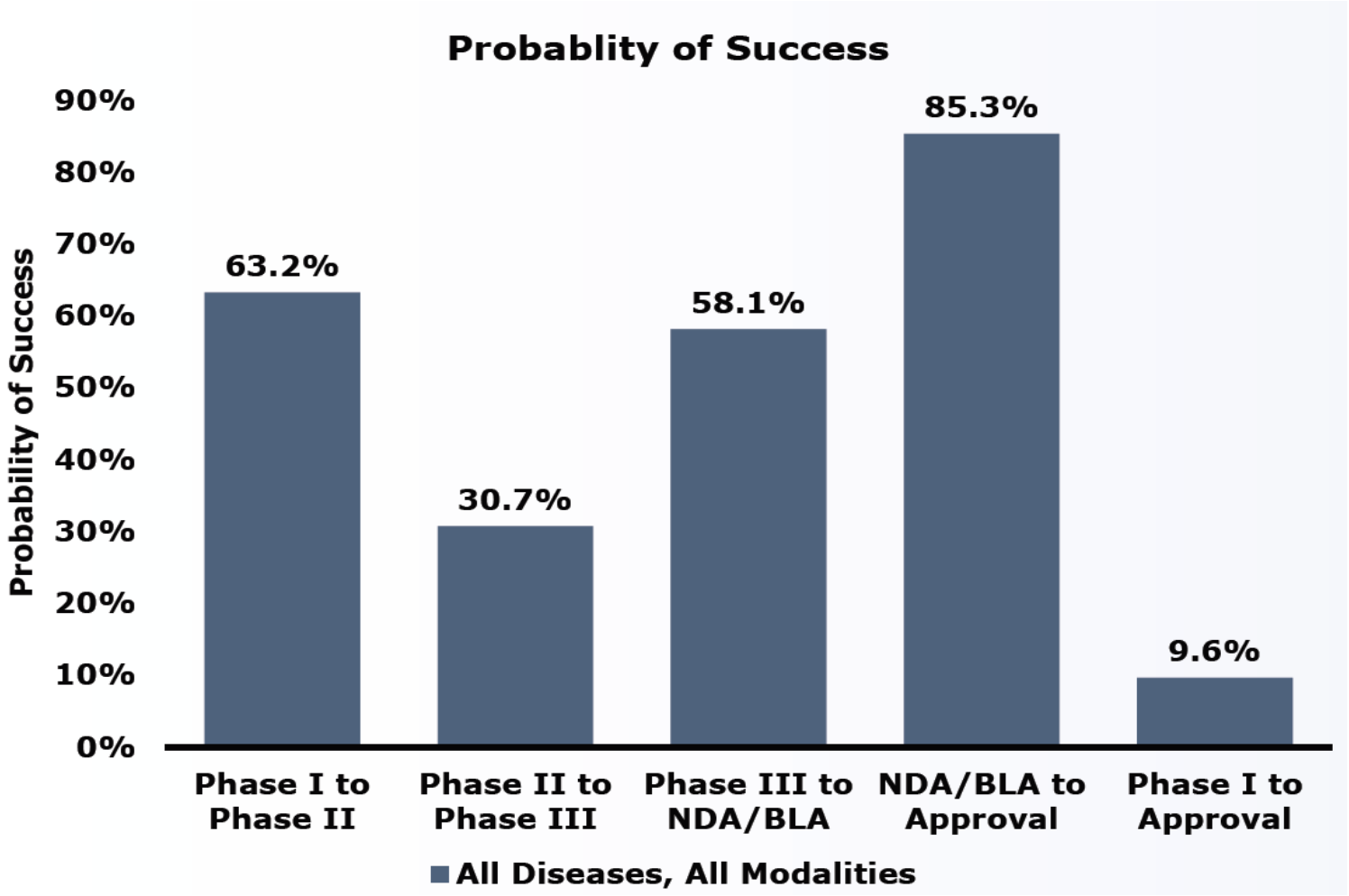
Clinical trials

New Drug Application

FDA APPROVED

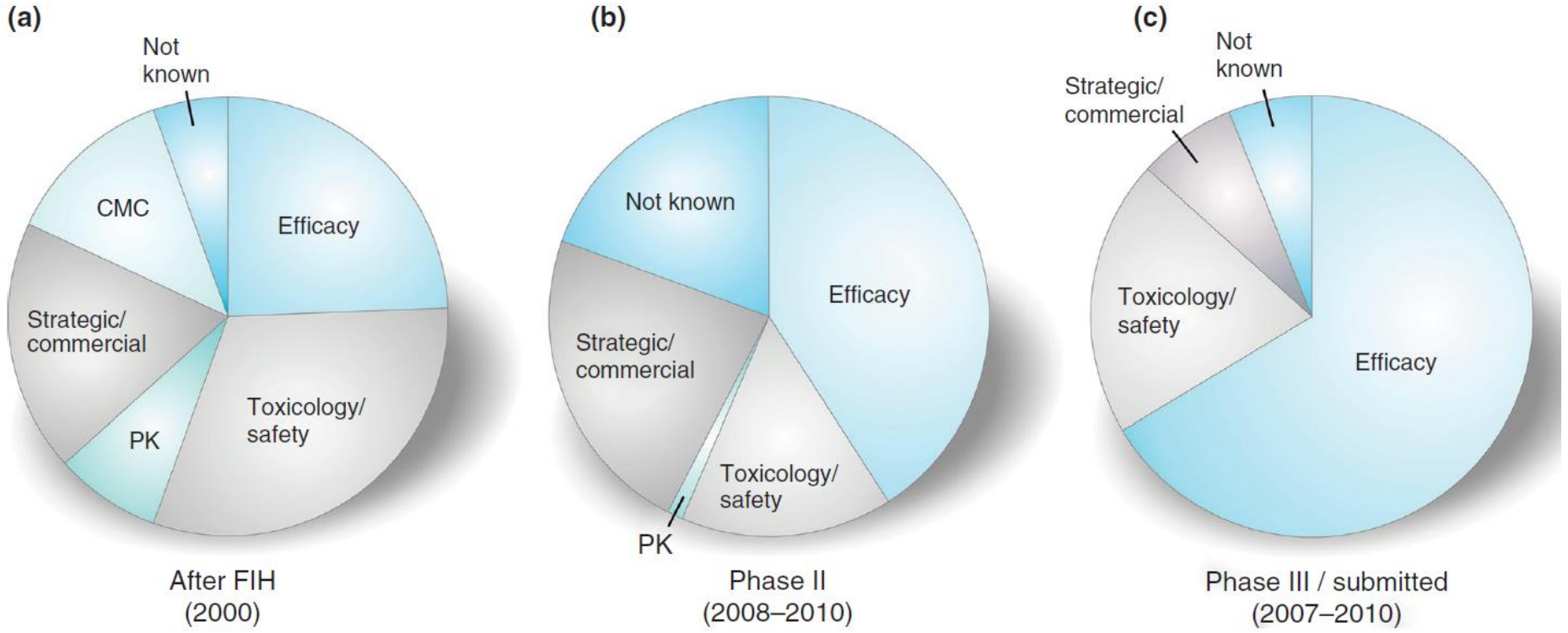
FDA DISAPPROVED

Drug development failure



[Ref. Bioindustry Analysis. Clinical Development Success Rates 2006-2015]

Major reasons for the discontinuation of drug development programs



Major reasons

- Toxicity/Lack of safety
- Lack of efficacy

[Ref. Hornberg, J.J., et al. Drug Discovery Today. 2014;19:1131-1136]

Why 90% of clinical drug development fails? (2010 – 2017)

Possible reasons	Lack of clinical efficacy (40-50%)
	Unmanageable toxicity (30%)
	Poor drug-like properties (10-15%)
	Lack of commercial needs and poor strategic planning (10%)

[Ref. Sun, D., et al. Acta Pharm. Sinica B. 2022;12(7):3049-62]

Safety Monitoring

Why is safety monitoring required in all clinical trials?

To ensure subject safety and study integrity

International Standards for Drug Safety Monitoring: CIOMs and ICH

- **The Council for International Organizations of Medical Sciences (CIOMs) (1949)**
  - Guidelines related to biomedical research in human (CIOMs Guideline)
  - Standards for reporting pharmaceutical manufacturers' adverse ADRs to regulatory authorities by CIOMs I form → model for the ICH Efficiency Guidelines 2A (2EA) and 2B (E2B)
- **International Council for Harmonization (ICH) (1990)**
  - Regulatory agencies and industry associations from Europe, Japan and USA – to harmonize the regulation governing the development and marketing of medicines.
  - ICH - GCP

ICH-GCP: 5.16 Safety information

5.16.1 – The sponsor is responsible for the ongoing safety evaluation of the investigational product(s)

5.16.2 – The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/ favorable opinion to continue the trial.

Safety Reporting: E6(R2)

- All SAEs should be reported immediately to the sponsors
  - Detailed & written reports
  - Immediate & follow-up reports – identify subjects by code numbers
  - Investigator should comply with the regulatory requirement
- AEs and/or laboratory abnormalities identified in the protocol
- For the reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information

Adverse Event (AE)

- Any *untoward or unfavorable medical* occurrence in a human research study participant, *including any abnormal sign* (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that *occurs during the subject's participation in the research*, whether or not it is considered related to the subject's participation in the research.

Serious Adverse Event (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization *or* prolongation of existing hospitalization
- Is a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

(ICH E2A, Final Rule)

Unexpected Adverse Event

21 CFR 312.32 (Sep 2010)

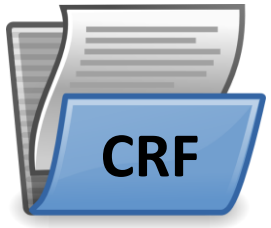
- *Considered unexpected if* ***not listed in the investigator's brochure*** *or is not listed in the specificity or severity that has been observed; … or is not consistent with the risk information described in the general investigational plan…*

SAE

An adverse event (AE) occurs

SAE form

Regulatory safety reporting requirement



FDA

Action

Action

Study database
(Data Management Center)

Safety data flow in clinical trials

SAE Reporting

Relationship/ Causality	1 = Unrelated, 2 = Unlikely, 3 = Possible, 4 = Probable, 5 = Definite
Severity	1 = Death, 2 = Life threatening, 3 = Hospitalization or prolongation of hospitalization, 4 = Persistent or significant disability or incapacity, 5 = Congenital anomaly or birth defect, 6 = Required intervention to prevent permanent impairment, 7 = other significant medical event
Action medication	1 = Continued, 2 = Reduced, 3 = Increased, 4 = Temporary stop, 5 = Permanent stop
Action taken	1 = No action, 2 = Amend consent document, 3 = Amend protocol, 4 = Inform current subjects, 5 = Terminate or suspend protocol, 6 = others
Outcome	1 = Resolved, 2 = Resolved with sequelae, 3 = Improved, 4 = Persistent, 5 = Worsened, 6 = Fatal, 7 = Unknown

Internal SAE Reporting Form (for researcher)

AF/04-06/04.0

แบบรายงานเหตุการณ์ไม่พึงประสงค์ชนิดร้ายแรงที่เกิดแก่อาสาสมัครในสถาบัน (สำหรับผู้วิจัย)

1. เลขที่โครงการ (IRB Protocol's No):	2. ชื่อผู้วิจัยและหน่วยงาน (Investigator's name & Department) ..... เบอร์โทรศัพท์มือถือ .....e-mail	
3.ชื่อโครงการ (Protocol Title):		
4. เลขที่อาสาสมัคร (Subject No):		
5. สถานที่เกิดเหตุการณ์ (Site of SAE): ☐ ใน รพ. ศรีนครินทร์ (Internal) ☐ นอก รพ. ศรีนครินทร์ (External)...(โปรดระบุ).....		
6. ระบุเหตุการณ์ (List of SAE):		
7. วันที่อาสาสมัครเกิดเหตุการณ์ (Date of Occurrence):	8. วันที่ผู้วิจัยรับทราบเหตุการณ์ (Known Date of Occurrence):	9. วันที่รายงานครั้งแรก (Date of Initial Report):
10.ชนิดของรายงาน ☐ รายงานครั้งแรก (initial report) ☐ รายงานติดตาม (follow up report) ครั้งที่... วันที่รายงานติดตาม (Date of follow up report).....		
11. การดำเนินการกับอาสาสมัครที่เกิดเหตุการณ์ (Action taken)		

12. Is adverse event serious?	13. Is adverse event unexpected?
☐ No ☐ Yes, it is ☐ Death ☐ Life threatening conditions (please specify .....) ☐ Inpatient hospitalization ☐ Prolong hospitalization ☐ Persistence or significant disability/ incapacity ☐ Congenital anomaly	☐ No ☐ Yes, it is ☐ Nature is not consistent with protocol* ☐ Severity is not consistent with protocol* ☐ Frequency is not consistent with protocol* (* Protocol or related documents such as Investigator Brochure, inform consent document)

What should the EC review?

- Whether the case is reported to the EC within the timeline
- Details of the case
- ‘Relatedness’, preliminarily determined by the PIs – such as..
  - Previously reported
  - Timeline of the SAEs
  - Challenge/Re-challenge
  - Association between the dosage and degree of SAE
  - Objective evidence showing the causality of the SAE
- Appropriate action taken by the PIs
  - Appropriate action to reduce unnecessary risk to the subjects and to provide sufficient care for the subjects
  - In accordance with the protocol (e.g., withdrawal criteria, risk management)

Guidance for Adverse Event Report

from

"Achieving Guidance in Clinical Trial safety information among stakeholder"

Forum for Ethical Review Committee in Thailand (FERCIT)

Local Serious Adverse Events (Internal SAEs)

Table 1. Guidance for reporting LOCAL Serious adverse events

What must be reported	Reporting time frames	How to report	Who report to whom
Fatal/ Life threatening SAE	Immediately , **no later than 24 hours** after PI acknowledgement	The same form reported to sponsor	1.PI to Sponsor 2.PI to IRB
Non-fatal / Non-life threatening SAE	Immediately , **no later than 7 calendar days** after PI acknowledgement	The same form reported to sponsor	1.PI to Sponsor 2.PI to IRB

Types of Decisions

- No further action required
- Request information
- Recommend further actions

Internal SAE: Common problems

- No safety reporting (PIs do not know, PIs do not report)
- Insufficient safety monitoring following the SAE incidence (PIs did not know when the SAE occurs)
- Delayed safety reporting (according to the FERCIT Guideline)
  - Non-compliance
- Incomplete/insufficient details
- Action taken to the SAE case does not follow the protocol (withdrawal, increased/decreased/temporary suspension, etc.)

Types of Safety Reports

- ***Internal SAE reports (on-site SAEs)***
- ***External SAE reports (off-site SAEs)***
  - Sites in the country
  - Sites in foreign country (periodic reports)
    - CIOMs report
    - Blinded/Unblinded SUSARs Line Listing Report
    - Periodic Safety Summary of SUSARs
    - Clinical Trial Safety Update Report (CTSUR)
    - SAR report
    - Development Safety Update Report (DSUR)
    - IDMC reports

CIOMs

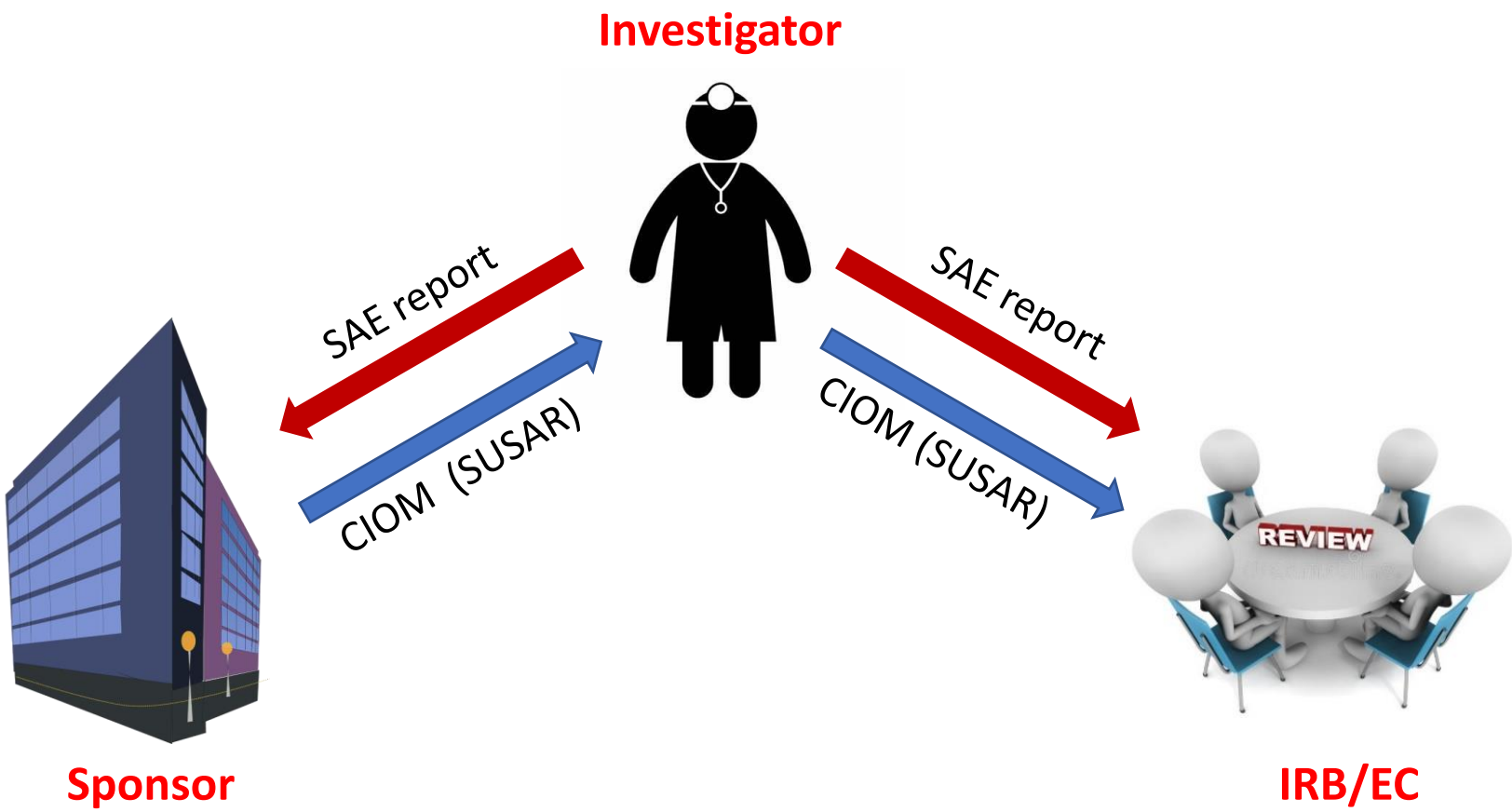
“Council for International Organizations of Medical Sciences”

- Form CIOM-I
  - Provides a standardized format for the reporting of suspected adverse reactions to any particular medical product

Suspected Unexpected Serious Adverse Reactions (SUSARs)

- Aims
  - To keep investigators aware of potential safety issues
  - Enable sponsor to meet global regulatory requirements

CIOMs Reporting



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	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ 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	

Periodic Safety Summary of SUSARs

Contents

- Details of the IMP
- Summary of data and conclusions
- Presentation of the line listing

EC reviews

- No. and period of reporting
- Number of cases (in the country)
- Summary by the sponsor
  - New safety finding/concern
  - New SUSARs/ADRs
  - Benefit/risk balance
  - Risk information in the IB
  - Update of protocols, IB or ICF?

Development Safety Update Report (DSUR)

Contents

- Version, Reporting Period, Release Date
- Details of the IMP
- Summary of the ongoing study and conclusions

EC reviews

- No. and period of reporting
- Summary by the sponsor
  - Update information of the study (no. of subjects, etc.)
  - New safety information
  - Benefit/risk balance

Drug Safety Monitoring Board (DSMB)

An independent group of expert: responsibilities

- *Periodically review and evaluate* the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy

- *Make recommendations to sponsor* concerning the **continuation, modification, or termination of the trial**. Based on study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

THANK YOU