PV in clinical Trials

Module 9 Topic 2

Need

- Why do we need to know about adverse events
- What importance to they have in clinical trials

Reason for AE Collection and Reporting

- The most important responsibilities of investigators and sponsors of clinical research studies
  - Protection of human subjects
  - Collection of clean and reproducible data
  - Regulatory perspective -- They need to analyze the data and determine
  - Risk/ benefits before giving permission to market

Goals of the Presentation

- Common terms and definitions
- AEs, SAEs, SUSARs
- Assessing the adverse events
- Serious Vs Severe
- Reporting AEs, SAEs, SUSARs
- Formats
- Responsibility of sponsor
- Responsibility of Investigator

ICH Definition– AE (Adverse Event)

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

ICH Definitions

- An adverse event (AE) can be
  - any unfavorable and unintended sign
  - (including an abnormal laboratory finding),
  - symptom, or
  - disease

temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Examples- Unwanted Effects

- Symptoms (headache, nausea)
- Physical findings (elevated BP, lump, pallor, edema)
- Abnormal lab values (increased liver enzymes, decreased hemoglobin)*
- Overdoses

*Important to define what % cut offs to be taken as Adverse events

AE can also be

- Unfavorable deviation from baseline health, which includes:–
  - Worsening of conditions present at onset of the study
  - Patient deterioration due to primary disease
  - Intercurrent illness
  - Events related or possibly related to concomitant medications

Example

- Unfavorable deviation from baseline health, which includes:–
  - Worsening of conditions present at onset of the study
  - Headache present at baseline was mild , now become severe

Example

- Unfavorable deviation from baseline health, which includes:–
  - Patient deterioration due to primary disease
  - BPH study-Patient going into acute retention of urine
  - Antibiotic Study: URTI progressing to LRTI

Example

Intercurrent illness --

In a Hypertensive study

Pt presenting with URTI

Example

Due to concomitant medication --

In a Hypertension trial, a patient comes with Diarrhea. On questioning it is revealed that he had taken antibiotics because of URTI

ICH - Adverse Drug Reaction (ADR)

- In the **pre-approval clinical experience**
- Defined as All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions
- The phrase "responses to a medicinal products" means that a
- Causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out

ICH - Adverse Drug Reaction (ADR)

Regarding marketed medicinal products,

- Adverse drug reaction in the post-marketing setting
- A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function

WHO Technical Report 498 [1972]

ICH – Serious Adverse Event

Serious AE is defined as an AE that:

- Results in death;
- Is life-threatening (see below);
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in a persistent or significant disability or incapacity (see below);
- Results in a congenital anomaly or birth defect.
- Results in cancer;

Also an SAE

Additionally, **important medical events** that may not result in death, be life-threatening, or require hospitalization may be considered serious AE's 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.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or abuse.

Definition SAE

- **Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions.
- If there is any doubt whether the information constitutes a serious AE, the information is treated as a serious AE for the purposes of this policy.

ICH – Unexpected ADRs

- An adverse reaction, the nature of severity of which is not consistent with the applicable product information (package insert or investigator's brochure)

SUSAR: Suspected Unexpected Serious Adverse Reaction

- Serious Unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s)

Assessing AEs

- Seriousness
- Intensity
- Relationship to drug
- Expectedness/ unexpectedness

Seriousness

- 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,
  - Results in persistent or significant disability/incapacity, or
  - Is a congenital anomaly/birth defect.
  - Important Medical events- judged by investigator

NOTE:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

Definition SAE

- **Life-threatening** refers to immediate risk of death as the event occurred, per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death but as it actually occurred did not create an immediate risk of death
- For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal

Life-Threatening

- Any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred
- Does not include a reaction that, had it occurred in a more severe form, might have caused death

21 CFR 312.32 (a)

Examples of Life-Threatening AE

- Pacemaker failure
- Gastrointestinal hemorrhage
- Infusion pump failure
  - Excessive IV fluid dosing
  - Toxic drug levels

Examples of Hospitalization AE

- Diarrhoea needing iv treatment
- Hypoglycemia needing iv dextrose treatment

Disability

- Substantial disruption of person's ability to conduct normal life functions

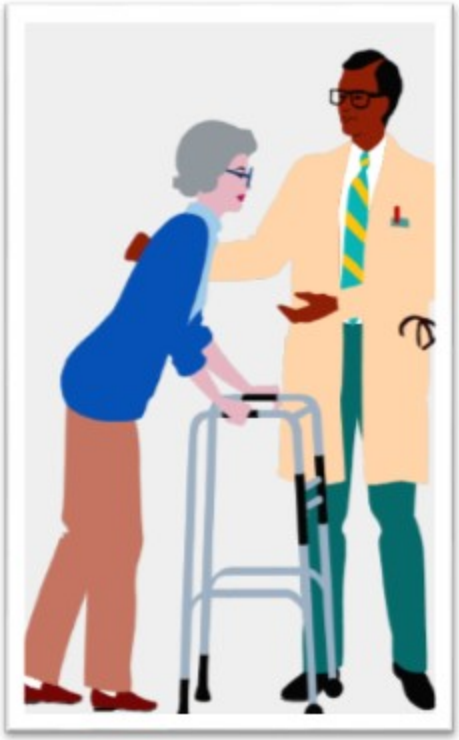
21 CFR 312.32 (a)

- Significant, persistent, or permanent change, impairment, damage or disruption in patient's function, structure, physical activities or quality of life

MedWatch

Examples of Disability

- Stroke
- Loss of limb
- Toxic drugs levels
  - Hearing loss
  - Blindness



Other examples of SAEs

* Important Medical events

- Examples of such events are intensive treatment in an emergency room
- Or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse

Intensity

- Mild
- Moderate
- Severe

Intensity

Severity of the Adverse Event (WHO Classification)

- Mild: Awareness of sign, symptom, or event, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention
- Severe: Incapacitating with inability to do usual activities or Significantly affects clinical status, and warrants intervention required

Serious/ Severe

The term "severe" is often used to describe the intensity (severity) of a specific event **(as in mild, moderate, or severe myocardial infarction)**; the event itself, however, may be of relatively minor medical significance **(such as severe headache)**

This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations

Example

- Dizziness
- Patient feels the symptom, but can go on with routine activities
- Non Serious AE with Mild intensity

Example

- Dizziness
- Patient feels the symptom, needs to lie down, finds it difficult to concentrate on work
- Non Serious AE with Moderate intensity

Example

- Dizziness
- Patient feels the symptom, needs to lie down, finds it difficult to concentrate on
- anything. Unable to get up without getting the symptom. Needs intervention
- Non Serious AE with Severe intensity

Example

- Dizziness
- Patient falls unconscious. BP, Pulse very low. Needs emergency treatment, hospitalization
- Serious AE with severe intensity

Example

- Myocardial infarction
- Affecting only 10% myocardium
- Serious AE, with mild intensity

Example

- Headache
- Causing a person to take leave, not able to work, needs medication.
- Non Serious AE, with severe intensity

Difficulty Assessing Relationship AEs with drug

- Incomplete information: objective criteria
- Multiple drugs taken
- Variability of clinical responses
- Underlying illness mimic AE

Relationship/Causality

- Various definitions
- WHO Definition

Certain

Probable /Likely

Possible

Unlikely

Conditional /Unclassified

Unassessable/Unclassifiable

WHO-UMC Causality Categories

- **Causality term Assessment criteria --- Certain**
- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory

WHO-UMC Causality Categories

Probable /Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, 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

WHO-UMC Causality Categories

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

WHO-UMC Causality Categories

Conditional / Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination
- Unassessable/ unclassifiable

Report suggesting an adverse reaction

- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

Commonly used Adverse Event Relationship to Study Products

Definite

clear, cut temporal association, and no other possible cause

Probable

clear cut temporal association, and a potential alternative etiology is not apparent

Commonly used Adverse Event Relationship to Study Products

Possible

less clear temporal association; other etiologies are also possible

None/Not Related

the AE is completely independent of study product administration; and/or evidence exists that the event is definitely related to another etiology

*Where an event is assessed as possibly related, probably related, definitely related the event is an adverse reaction

Naranjo Algorithm

- Generally used for all serious trial & spontaneous cases, and non-serious, medically confirmed, unexpected events
- Scores of 5 or more, used for upgrades
- For temporal relationship, rule of 5 half lives is used
- For withdrawal reactions, rechallenge & dechallenge interpretation is reversed
- Scoring
  - 9 =definite
  - 5-8= probable;
  - 1-4= possible
  - 0 =unlikely

Naranjo Algorithm

#	Question	Yes	No	Don't Know
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	- 1	0
3	Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0
4	Did the adverse reaction reappear when the drug was re-administered?	+2	- 1	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6	Did the reaction reappear when a placebo was given?	- 1	+1	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0

Example

Antihypertensive study

Drug: Antihypertensive drug

AE: Giddiness,

- Stops on stopping drug
- Restarts if re-challenge given
- No concomitant medication
- Causality: Definitely related

Example

Drug: Antibiotic drug

AE: Giddiness

- Pt known hypertensive, taking antihypertensives
- Does not stop on stopping drug
- Anti hypertensives concomitant medication
- Causality: not related

Example

Drug: Antibiotic drug

AE: Giddiness

- Pt known diabetic
- Stops on stopping drug
- No concomitant medication

Causality: probably related

Example

Drug: antibiotic, URTI

AE: increase in sgot, sgpt

- Pt had normal values at baseline
- Does not stop on stopping drug/ decreasing trend
- NSAIDs were taken ,concomitant medication

Causality: Possibly related

Expectedness

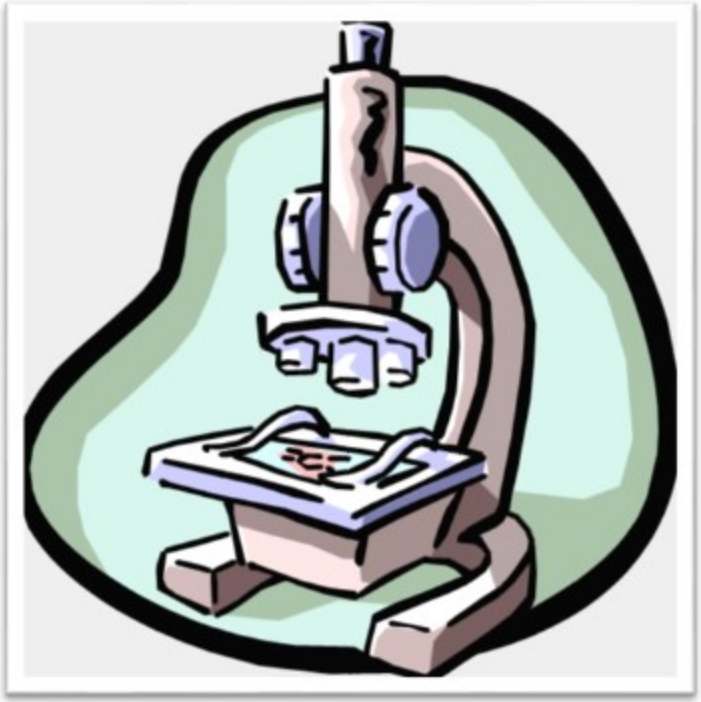
- Expected vs Unexpected AE

- An expected AE is any adverse reaction whose nature and
- severity have been
- previously observed
- and documented for
- the study product.

UnExpectedness

Expected vs Unexpected AE

- An unexpected AE is any adverse reaction not previously observed, whether or not it has been anticipated because of the pharmacological properties of the study



Unexpected AE

- Not previously observed
- Any AE not consistent with protocol, current Investigator's Drug Brochure or general investigational plan
  - Severity, specificity

21 CFR 312.32 (a)

Unexpected AE

- Investigator's Brochure lists
  Elevated hepatic enzymes, hepatitis
- Hepatic necrosis occurs
  - Unexpected AE (UAE)
    - Severity

21 CFR 312.32 (a)

Unexpected AE

Reports which add significant information on **specificity or severity** of a known, already documented serious ADR constitute **unexpected events**

- acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and
- hepatitis with a first report of fulminant hepatitis

Assessing Ex/Unexpectedness

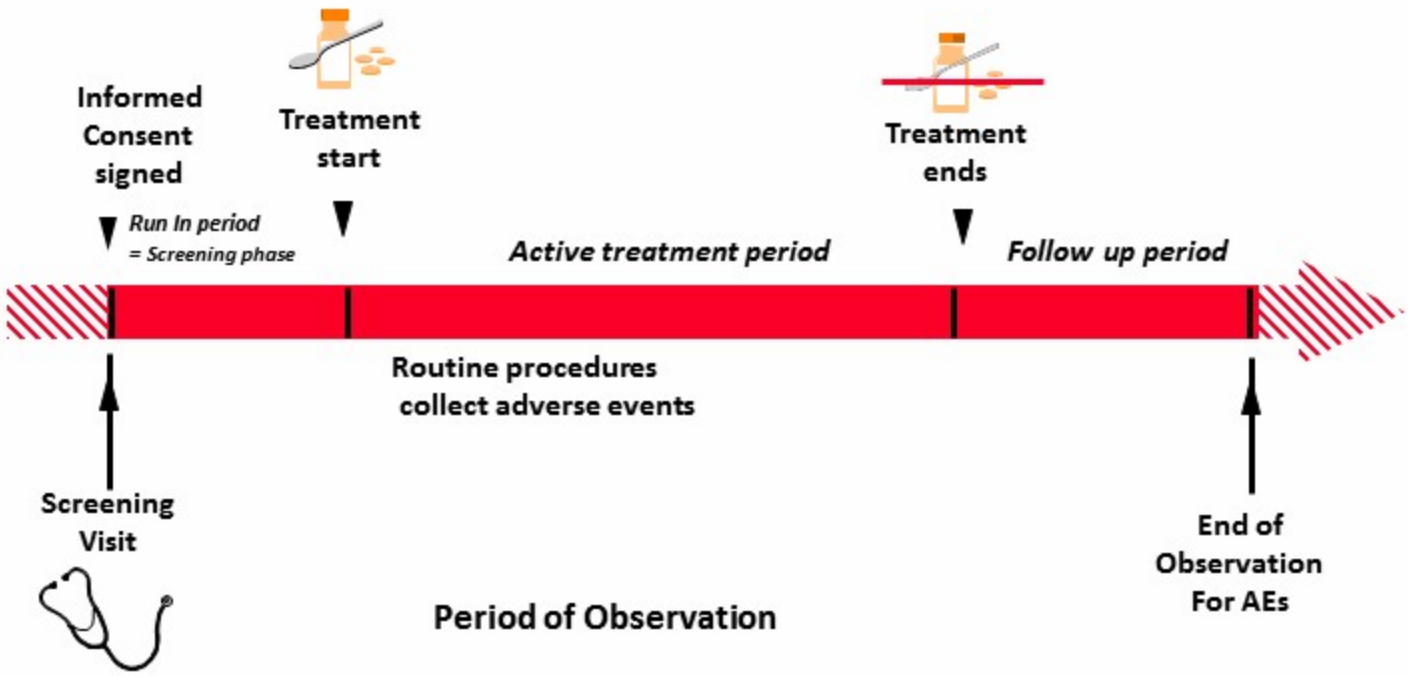
The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

For a medicinal product not yet approved for marketing in a country, a company's **Investigator's Brochure will serve as the source document in that country**

Pharmacovigilance in practice

- All protocols must have a PV section
- Risk to patients varies in the range of clinical trials. Extent of recording and notification of adverse events may vary depending on knowledge of the risks and benefits of drugs under study and aims of the trial.
- Responsibilities and systems to deal with recording, assessment and reporting must be clearly stated.
- Time frames for notification, assessment and reporting are critical
- All the above should be a part of the SOPs of the Site/CRO/Sponsor

Period of Observation



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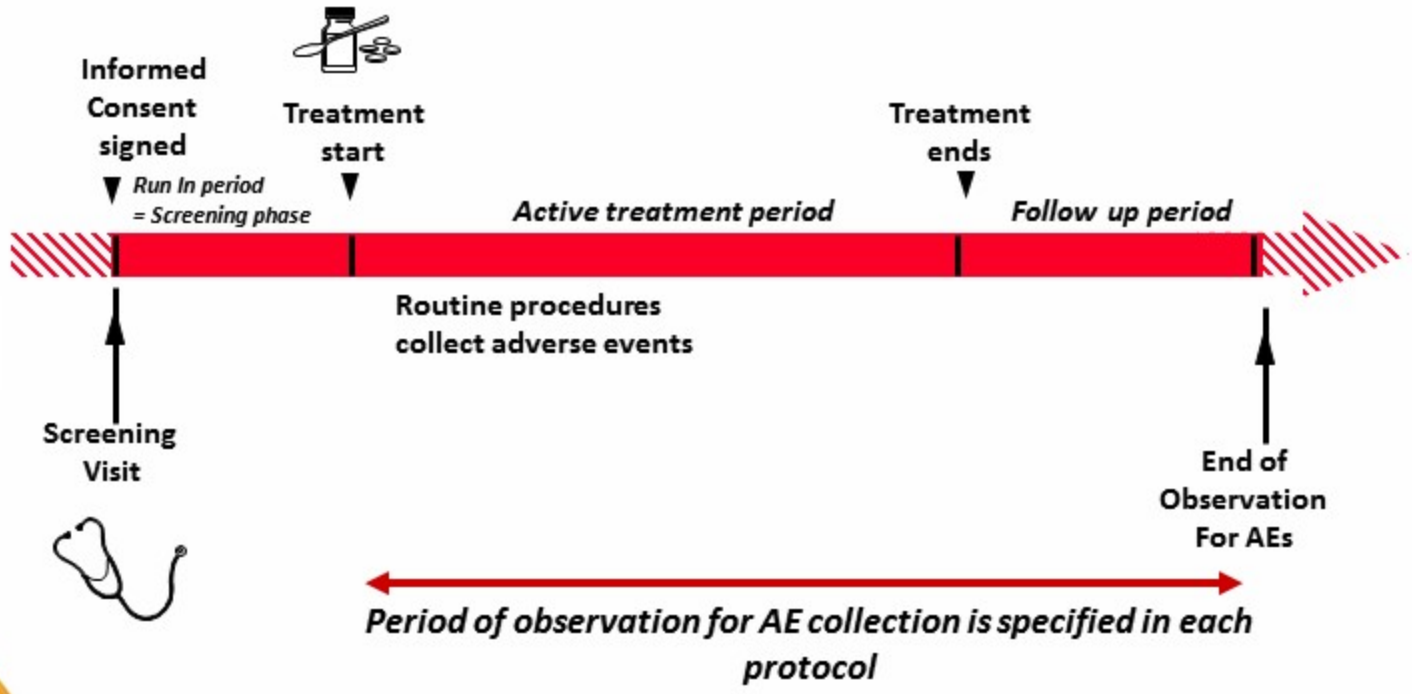


Reporting

- Expedited
- Routine

Reporting

Standards For Expedited Reporting

- What Should be Reported?
- Single Cases of Serious, Unexpected ADRs

All ADRs that are both serious and unexpected are subject to expedited reporting.

Not expedited

What Should Not be Reported?

- Expedited reporting of reactions that are serious but ***expected*** will ordinarily be inappropriate
- Expedited reporting is also inappropriate for serious events from clinical investigations that are considered ***not related*** to study product, whether the event is expected or not
- Similarly, ***nonserious*** adverse reactions, whether expected or not, will ordinarily not be subject to expedited reporting

Others needing expedited reporting

- There are situations in addition to single case reports of “serious” adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation

Others needing expedited reporting

Examples include:

- For an **"expected," serious ADR, an increase in the rate** of occurrence which is judged to be clinically important
- A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease
- c. A major safety finding from a newly completed animal study, (such as carcinogenicity)

Reporting Time Frames to:

- Regulatory
- IRB/ ECs
- Participating investigators

Reporting Time Frames- Serious Unexpected

Fatal or Life-Threatening Unexpected ADRs

- Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting
- Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by within 8 additional calendar days the complete report
- This report should include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products

Reporting Time Frames- Serious Unexpected

All Other Serious, Unexpected ADRs

- Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days
- Case should meet the minimum criteria for expedited reporting

SUSARs

- Until source documents are amended, expedited reporting is required for additional occurrences of the reaction

Reporting Time Frames- Serious Unexpected

India- regulatory

- All Serious, unexpected AEs
- To be reported within 14 calendar days

Reporting to other participating investigators

USFDA & India

- **USFDA**

Sponsor reports all serious, unexpected ADR to other investigators within 15 calendar days

- **India**

Sponsor to report all serious, unexpected AEs to participating investigators within 14 calendar days

Minimum Criteria for Reporting

for regulatory purposes

Initial reports should be submitted within the prescribed time as long as the following minimum criteria are met:

- An identifiable patient;
- A suspect medicinal product;
- An identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, there is a reasonable suspected causal relationship
- Follow-up information, should be actively sought and submitted as it becomes available

Managing Blinded Therapy Cases

In a double-blind study whether to open (break) the code for the specific patient

When a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the Sponsor, even if not broken by investigator

Breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data. Blind be maintained for people responsible for analysis e.g. biometric

Managing Blinded Therapy Cases (contd)

Problems arising by retaining the blind

- Placebo and comparator (usually a marketed product) cases are filed unnecessarily
- When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised
- If the event is serious, new, and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading

Managing Blinded Therapy Cases (contd)

Primary efficacy endpoint- fatal or other "serious" outcome

The integrity of the clinical investigation may be compromised if the blind is broken

Under these and similar circumstances, reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting

Special cases

Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies

Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, no need for expedited reporting

Products with More Than One Presentation or Use

An ADR that qualifies for expedited reporting with one presentation of a product, i.e. one dosage form (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or cross referenced to all regulatory filings across other product presentations and uses, e.g., ADR of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed

Post-study Events

- Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor
- Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required

Sponsor Responsibilities

- In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in accordance with any local regulatory requirements, so as to keep the description of safety information updated

Sponsor Responsibilities (contd)

- Train the study personnel (sponsor personnel & investigator) in
  - Assessing AEs
  - Reporting AEs
- Updating the Investigator Brochure
- Informing Regulatory the expedited and the periodic reports
- Sending the IND safety reports to sites
- Preparing the annual reports
- Final reports with all analysis

Monitor Responsibilities

- Train the site personnel in
  - Assessing AEs- site initiation
  - Reporting AEs with timelines

- Familiarizing them with updated Investigator Brochure wrt expectedness
- Sending the IND safety reports to sites
- Informing Regulatory within timelines

Principal Investigator Responsibilities

- Medical management of the adverse events
- Train the site personnel under him/ her in
  - Assessing AEs
  - Reporting AEs

- Responsibility to IRB
- Informing IRB as per their SOPs
- Inform sponsor & IRB about all SAEs within 24 hours
- All serious adverse events/reactions must be reported to the sponsor within 24 hours
- The only exception to this is where the protocol or Investigator's Brochure identifies the event as not requiring immediate reporting

Principal Investigator Responsibilities- IRB

- Sending the IND safety reports to IRB
- Informing IRB as per their SOPs

- To report all adverse drug reactions (ADRs) that are both serious and unexpected
- New information that may affect adversely the safety of the subjects or the conduct of the trial

Coordinator Responsibilities

- Inform the PI about the adverse events
- Collecting information regarding AEs
- Sending the IND safety reports to IRB
- Informing IRB as per their SOPs

Key data elements for expedited reports

- Inform the PI about the adverse events
- Collecting information regarding AEs
- Sending the IND safety reports to IRB
- Informing IRB as per their SOPs

Key data elements for expedited reports (contd)

Patient Details:

- Initials,
- Other relevant identifier (clinical investigation number, for example),
- Gender,
- Age and/or date of birth,
- Weight,
- Height,

Key data elements for expedited reports (contd)

Suspected Medicinal Product(s):

- Brand name as reported,
- International Non-Proprietary Name (INN),
- Batch number,
- Indication(s) for which suspect medicinal product was prescribed or tested,
- Dosage form and strength,
- Daily dose and regimen (specify units - e.g., mg, mL, mg/kg),

Key data elements for expedited reports (contd)

- Route of administration,
- Starting date and time of day,
- Stopping date and time, or duration of treatment
  Other Treatment(s):

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies

the same information as for the suspected product

Key data elements for expedited reports (contd)

Details of Suspected Adverse Drug Reaction(s):

- Full description of reaction(s) including body site and severity, the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, a specific diagnosis for the reaction. Start date (and time) of onset of reaction, stop date (and time) or duration of reaction, dechallenge and rechallenge information, setting (e.g., hospital, out-patient clinic, home, nursing home), outcome: Information on recovery and any sequel; specific tests and/or treatment may have been required and their results;

Key data elements for expedited reports (contd)

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction

Any autopsy or other post-mortem findings

Other information: anything relevant, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

Key data elements for expedited reports (contd)

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction

Any autopsy or other post-mortem findings

Other information: anything relevant, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

Key data elements for expedited reports (contd)

Details on reporter of event

Name,
Address,
Telephone number,
Profession (specialty)

Administrative and Sponsor/Company Details:

Source of report: - clinical investigation

Date event report was first received by sponsor/manufacturer,

Country in which event occurred,

Type of report filed to authorities: initial or follow-up (first, second, etc.),

Key data elements for expedited reports (contd)

Administrative and Sponsor/Company Details (contd):

Name and address of sponsor/manufacturer/company,

Name, address, telephone number, and FAX number of contact person in reporting company or institution,

Identifying regulatory code or number for marketing authorization dossier or clinical investigation process for the suspected product (e.g. IND or CTX number, NDA number),

Sponsor/manufacturer's identification number for the case (This number should be the same for the initial and follow-up reports on the same

S No.	AE desc	Date started	Date stopped	Intensity (mid/mod/ severe)	Causality (Definitely/ probably/po ssibly/not related)	Treatment

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
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

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	

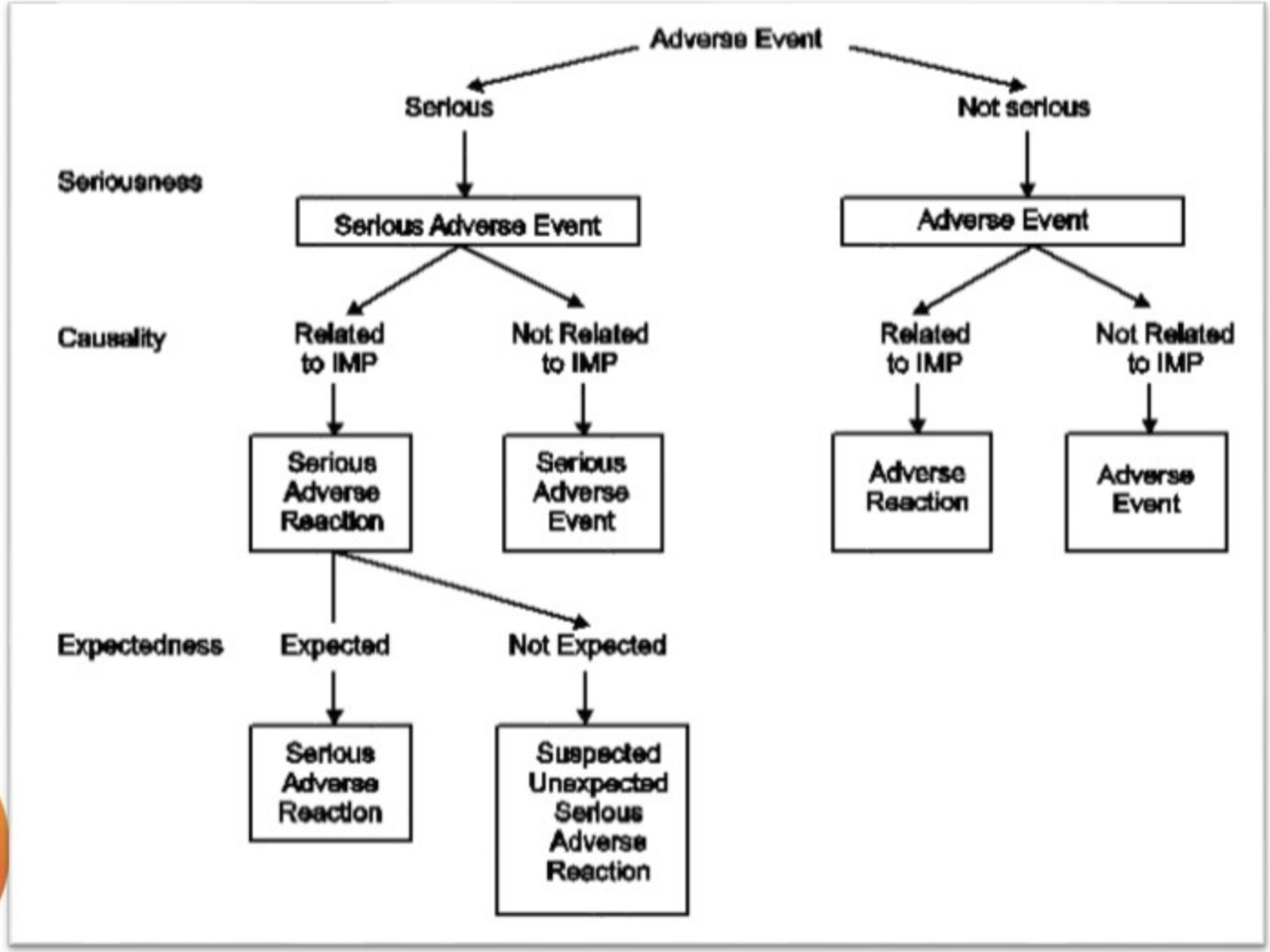
III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, 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	25e. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Decision Chart



Forms

- 500A (Medwatch Form)
- Council for International Organization of Medical Science (CIOMS I Foreign) or other form if approved in advance

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
Nirman Bhawan, New Delhi - 110011
www.cdsco.nic.in

For VOLUNTARY reporting of Adverse Drug Reactions by health care professionals

Report #

To be filled in by Pharmacovigilance centres receiving the form.

A. Patient information

1. Patient identifier initials _____ In confidence

2. Age at time of event: or _____ Date of Birth:

3. Sex ☐ M ☐ F

4. Weight_____Kgs

B. Suspected Adverse Reaction

5. Date of reaction started (dd/mm/yy):

6. Date of recovery (dd/mm/yy):

7. Describe reaction or problem

12. Relevant tests/ laboratory data, including dates

13. Other relevant history, including pre-existing medical conditions (e.g., allergies, race, pregnancy, smoking alcohol use, hepatic/ renal dysfunction, etc.)

14. Seriousness of the reaction

☐ Death (dd/mm/yy)_____
☐ Life threatening
☐ Hospitalization-initial or prolonged
☐ Disability
☐ Congenital anomaly
☐ Required intervention to prevent permanent impairment/ damage
☐ Other (specify)_____

15. Outcomes

☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered ☐ Other (specify)_____

C. Suspected medication(s)

Sl. No.	8. Name (brand and / or generic name)	Manufac-turer (if known)	Batch No. / Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if unknown, give duration)		Reason for Use or prescribed for
								Date started	Date stopped	
i										
ii										
iii										
iv										

Sl. No. As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced, dose
i										
ii										
iii										
iv										

11. Concomitant medical products and therapy dates including self medication and herbal remedies (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address: _____

_____

_____

Pin code: _____ E-mail: _____

Cell No. / Tel. No. with STD Code: _____

Speciality: _____ Signature:

17. Occupation

18. Date of this report (dd/mm/yy)

VACCINE ADVERSE EVENT REPORTING SYSTEM

VAERS

24 Hour Toll Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (____) _____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (____) _____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (____) _____

1. State | 2. County where administered | 3. Date of birth mm / dd / yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm / dd / yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm / dd / yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm / dd / yy AM Time _____ PM

11. Adverse event onset mm / dd / yy AM Time _____ PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions(specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brother and sisters

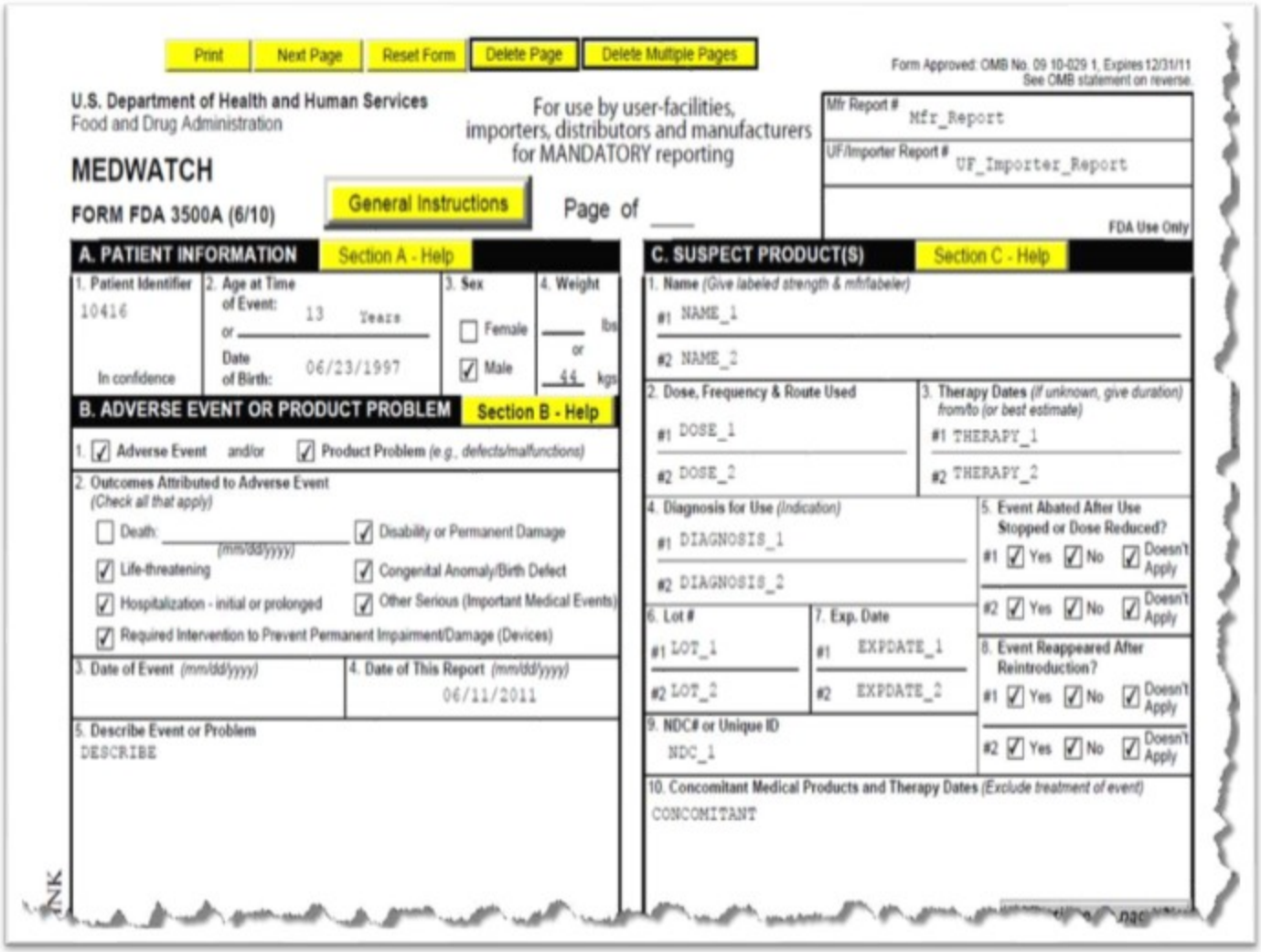
21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./Imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1(rev)



Print | Next Page | Reset Form | Delete Page | Delete Multiple Pages

Form Approved: OMB No. 09 10-029 1, Expires 12/31/11
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Mfr Report # Mfr_Report

UF/Importer Report # UF_Importer_Report

FDA Use Only

MEDWATCH

FORM FDA 3500A (6/10)

General Instructions

Page of ___

A. PATIENT INFORMATION

Section A - Help

1. Patient Identifier: 10416 — In confidence
2. Age at Time of Event: 13 Years — or — Date of Birth: 06/23/1997
3. Sex: ☐ Female ☑ Male
4. Weight: ___ lbs — or — 44 kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

Section B - Help

1. ☑ Adverse Event and/or ☑ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - ☐ Death: ___ (mm/dd/yyyy)
   - ☑ Disability or Permanent Damage
   - ☑ Life-threatening
   - ☑ Congenital Anomaly/Birth Defect
   - ☑ Hospitalization - initial or prolonged
   - ☑ Other Serious (Important Medical Events)
   - ☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (mm/dd/yyyy):
4. Date of This Report (mm/dd/yyyy): 06/11/2011
5. Describe Event or Problem: DESCRIBE

C. SUSPECT PRODUCT(S)

Section C - Help

1. Name (Give labeled strength & mfr/labeler)
   - #1 NAME_1
   - #2 NAME_2
2. Dose, Frequency & Route Used
   - #1 DOSE_1
   - #2 DOSE_2
3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
   - #1 THERAPY_1
   - #2 THERAPY_2
4. Diagnosis for Use (Indication)
   - #1 DIAGNOSIS_1
   - #2 DIAGNOSIS_2
5. Event Abated After Use Stopped or Dose Reduced?
   - #1 ☑ Yes ☑ No ☑ Doesn't Apply
   - #2 ☑ Yes ☑ No ☑ Doesn't Apply
6. Lot #
   - #1 LOT_1
   - #2 LOT_2
7. Exp. Date
   - #1 EXPDATE_1
   - #2 EXPDATE_2
8. Event Reappeared After Reintroduction?
   - #1 ☑ Yes ☑ No ☑ Doesn't Apply
   - #2 ☑ Yes ☑ No ☑ Doesn't Apply
9. NDC# or Unique ID: NDC_1
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event): CONCOMITANT

Wherever possible, adverse events should be described in terms of a change in the status of patient's health, NOT the action taken or outcome

Schedule Y requirement

- Unsuspected adverse event is communicated from
  - Sponsor to regulatory authorities within 14 days
  - Investigator to sponsor within 24 hours
  - Investigator to ethics committee within 7 days

PMS Monitoring in India

- Appendix 11 of Schedule 'Y' provides a form for submission of AE reports to the AE monitoring centers located in AIIMS and 4 regional hospitals
- It is necessary to have this due to the number of doctors, the various systems of medicines being practised, the huge exposure of the product given our massive population
- This would also serve as a trigger to flag presence of spurious drugs in certain areas or existence of some rare adverse events in certain populations of the country.
- The problem in India is that the doctors are not aware of the system of reporting, they do not have the inclination to report and the Government does not have the infrastructure

Deadlines for India

- A PSUR shall be submitted every 6 months for the first 2 years after approval. For the subsequent 2 years, PSURs are submitted annually
- All cases involving serious, unexpected adverse reactions, must be reported to the authorities within 15 days of the initial receipt of information by the applicant

CDSCO Guidance SAEs in CTs

- As per the regulations (Schedule Y of Drugs & Cosmetics Rules), all Unexpected SAEs have to be reported to CDSCO within 14 calendar days
- All the sections of the covering letter should be completed. When some information is not available at the time of report e.g. causality assessment by medical monitor of Sponsor/CRO, compensation provided for study related injury or death, the same has to be provided as a follow-up report

CDSCO Guidance SAEs in CTs (contd)

- Causality assessment by investigator and the medical monitor of Sponsor/CRO. **The assessment report should clearly mention whether the SAE occurred is related or not related (Situations like unlikely, possibly, suspected, doubtful etc. should not be used)**

CDSCO Guidance SAEs in CTs (contd)

- Whether the outcome is fatal
- **Details of compensations provided for injury or death. In case no compensation has been paid, reason for the same should be submitted. It is pertinent to mention that in case of study related injury or death, complete medical care as well as compensation for the injury or death should be provided**
- CDSCO Draft Guidance May 2011