ADR & Pharmacovigilance in Hospital

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Origin of Pharmacovigilance

- Pharmacovigilance started about 170 years ago, although it was not yet named as such at that time.
- The etymological roots for the word “pharmacovigilance” are: *Pharmakon* (Greek) = medicinal substance, and *Vigilia* (Latin) = to keep watch.
- It is structured activity in the professional health field, with important social and commercial implications aimed at monitoring the risk/benefit ratio of drugs, improving patient’s safety and the quality of life.

Fornasier, G., Francescon, S., Leone, R. and Baldo, P. (2018). An historical overview over Pharmacovigilance. *International Journal of Clinical Pharmacy*, 40(4), pp.744-747.

History of Pharmacovigilance

- The history of Pharmacovigilance started 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anesthetic before removal of an infected toenail. Sir James Simpson had discovered that chloroform was a safer and powerful anesthetic, and he had introduced it in clinical practice. The causes of Hannah's death was investigated to understand what happened to Hannah, but it was impossible to identify what killed her. Probably she died of a lethal arrhythmia or pulmonary aspiration.

- As a result of other deaths and alerts raised by the clinicians and the public about the safety of anesthesia, *The Lancet* Journal established a commission to take on this problem.

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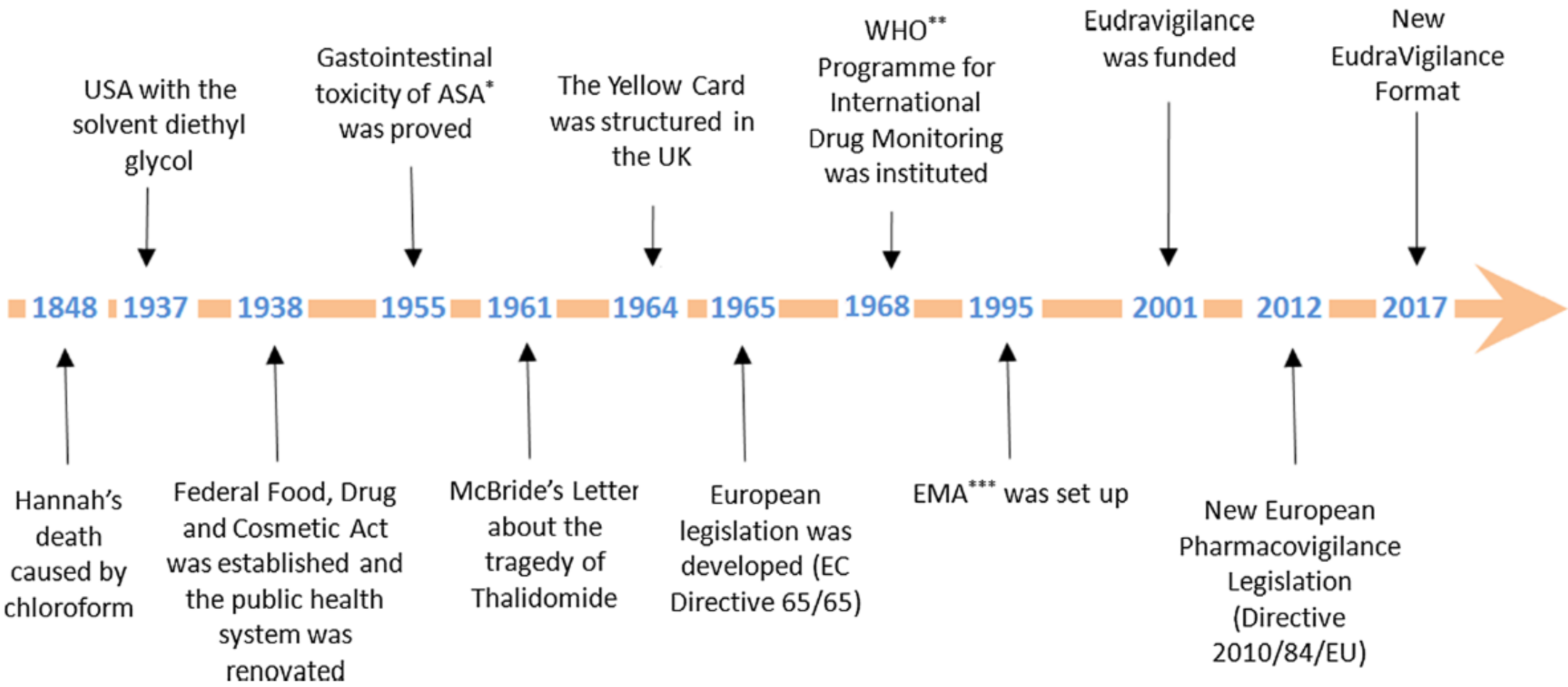


Timeline of the historical evolution of Pharmacovigilance.
*ASA: acetylsalicylic acid;
**WHO: World Health Orgnaisation;
***EMA:
European Medicines Agency

Definitions

Adverse drug reaction (ADR)

- A noxious and unintended response to a medicine that occurs *at normal therapeutic doses* used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
- The word “effect” is used interchangeably with “reaction.”

Side effect

- Any unintended effect of a pharmaceutical product occurring at normal therapeutic doses and is related to its pharmacological properties. Such effects may be well-known and even expected and require little or no change in patient management.

Serious adverse effect

- Any untoward medical occurrence that occurs at any dose and results in death, requires hospital admission or prolonged hospital stay, results in persistent or significant disability, or is life threatening

Definitions

Adverse drug event

- Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment. Adverse drug events include medication errors and overdoses.

Causality

- The probability that a particular medicine is responsible for an isolated effect or ADR.

Signal

- Reported information on a possible causal relationship between and adverse event and a medicine, the relationship being previously unknown or incompletely documented. Usually more than one signal report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

Definitions

Prescribing error

- Incorrect medicine ordering by a prescriber

Medication error

- Administration of a medicine or dose that differs from the written order

Negligence

- Medical decision making or care below the accepted standards of practice

Adverse Drug Reactions

Patient injury caused by a medicine taken in therapeutic doses

- **Type A—Exaggerated pharmacological response**
  - Pharmacodynamic (e.g., bronchospasm from beta-blockers)
  - Toxic (e.g., deafness from aminoglycoside overdose)
- **Type B—Nonpharmacological, often allergic, response**
  - Medicine-induced diseases (e.g., antibiotic-associated colitis)
  - Allergic reactions (e.g., penicillin anaphylaxis)
  - Idiosyncratic reactions (e.g., aplastic anemia with chloramphenicol)

Adverse Drug Reactions

- **Type C—Continuous or long term (time related)**
  - Osteoporosis with oral steroids
- **Type D—Delayed (lag time)**
  - Teratogenic effects with anticonvulsants or lisinopril
- **Type E—Ending of use (withdrawal)**
  - Withdrawal syndrome with benzodiazepines
- **Type F—Failure of efficacy (no response)**
  - Resistance to antimicrobials

Determining Medicine Safety: Identifying and Managing ADRs

- **Premarketing clinical trials**
  - Animal studies, human studies—Phases I, II, III
  - Cannot identify ADRs with incidence < 1%
  - Unproven ADRs listing for legal protection of manufacturer
- **Postmarketing surveillance**
  - Spontaneous reporting
  - Postmarketing clinical trials—Phase IV
  - Other methods—observational studies, meta-analysis, case reports
  - Determining causality
  - Actions taken to manage new ADRs

Post marketing Surveillance of ADRs: Spontaneous Reports

- Best method for detecting new ADRs
- Necessary because many ADRs not detected in pre- or post marketing studies
- Initiated by physicians, pharmacists, nurses, patients
- Problems include underreporting, inaccurate reporting that may not show causality, and high false positive rates

Post marketing Surveillance of ADRs: Clinical Studies

- Post marketing clinical studies
  - Done to determine efficacy and safety (Phase IV trials)
  - Generally poor in detecting ADRs because—
    - RCTs often insufficient for assessing ADRs, so observational cohort and cases control studies are used
    - Nonrepresentative patient selection
    - Narrow medicine indications and dosing structure
    - Limited concomitant medicine use

Post marketing Surveillance: Other Methods

- Observational studies provide limited identification of new ADRs
  - Large databases in the United States and Europe from national health programs, HMOs, health insurance programs can provide data for case control or cohort studies
  - Cohort studies useful for assigning causality
- Published case reports—provide limited information about ADRs
- Meta-analysis of published papers—provide identification of new ADRs by increasing the power of the clinical studies

Determining Causality of an ADR

- Factors in determining causality
  - Strength of the association
  - Consistency of the observed evidence
  - Temporality of the relationship
    - ADR that occurs in association with a medicine does not mean the medicine is responsible
    - Delayed reactions do not rule out the medicine as causing the ADR
  - Dose-response relationship
  - Confounding factors

Classifying Causality of an ADR

- ***Certain causality*—**when a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to medicine administration and cannot be explained by concurrent disease or other medicines or chemicals; re-administration of the medicine causes a similar reaction
- ***Probable or likely causality*—**when a clinical event occurs with a reasonable time sequence to medicine administration and is unlikely to be due to any concurrent disease or other medicine administration
- ***Possible causality*—**when a clinical event occurs with a reasonable time sequence to medicine administration, but which could be explained by concurrent disease or other medicine administration
- ***Unlikely causality*—**when a clinical event (including laboratory test abnormality) occurs in temporal relationship to medicine administration that makes a causal relationship improbable, and when other medicines, chemicals, or underlying disease provide plausible explanations

Classifying Causality of an ADR: Naranjo Algorithm

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected medicine was administered?	+2	-1	0
Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the medicine was re-administered?	+2	-1	0
Are there alternate causes (other than the medicine) that could solely have caused the reaction?	-1	+2	0
Was the medicine detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Managing ADRs

Step 1. Evaluate the nature of the event.

- Obtain a detailed history of the patient.
- Identify and document the clinical reaction. Look up suspected medicines and known ADRs in the literature and match them with the reactions described by the patient
- Classify the severity of the reaction.
  - Severe—fatal or life threatening
  - Moderate—requires antidote, medical procedure, or hospitalization
  - Mild—symptoms require discontinuation of therapy
  - Incidental—mild symptoms; patient can chose whether to discontinue treatment or not

Managing ADRs

Step 2. Establish the cause.

- Use the Naranjo algorithm (or other system) to assess the patient's reaction.
- Evaluate the quality of the medicine.
- Check for a medication error.

Managing ADRs

Step 3. Take corrective and follow-up action.

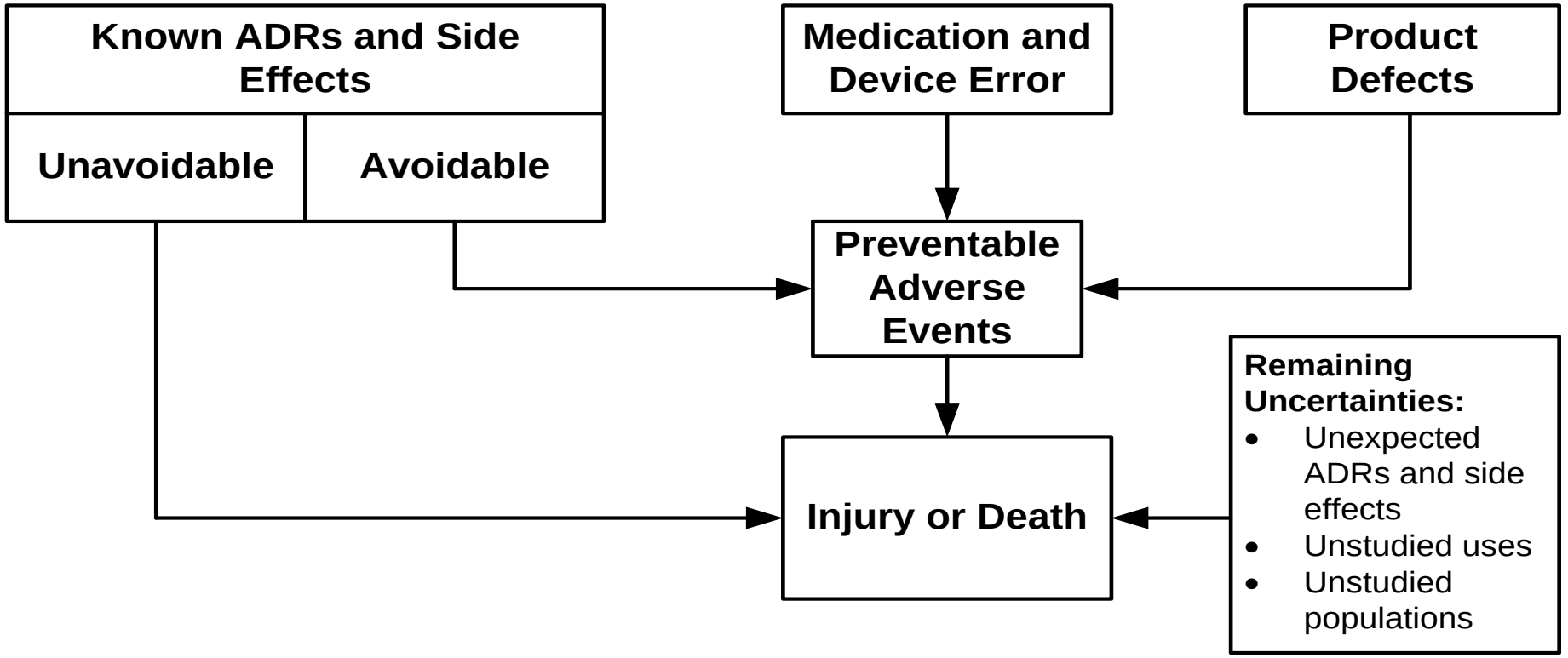
Corrective action will depend on cause and severity

- **Severe ADRs**
  - Educate and monitor prescribers.
  - Change the formulary or standard treatment guideline if necessary to substitute a medicine that is safer or that is easier to use by staff.
  - Modify patient monitoring procedures.
  - Notify drug regulatory authorities and manufacturers.

- **All ADRs**
  - Educate and warn patients.

Prevention of ADRs

Schematic of preventable and unavoidable adverse events



DTC's Role in Preventing ADRs

- Review ADR reports regularly and inform professional staff of the incidence and impact of ADRs in the region.
- Discuss changes in the formulary or standard treatment guidelines for significant or recurring problems with ADRs.
- Educate staff, especially providers, concerning ADRs.
- Identify medicines on the formulary that are “high risk” and should be monitored closely by physicians and pharmacists.
- Identify “high-risk” patient populations, including pregnant women, breast-feeding women, the elderly, children, and patients with renal or liver dysfunction; close monitoring of these patient populations by physicians and pharmacists will help prevent serious adverse reactions.
- Review medication errors and product quality complaints to ensure they are not contributing to the incidence of ADR at the hospital.

Adverse Drug Events

- An adverse drug event is any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment.
- Adverse drug events include medication errors.

Adverse Drug Events

- Record review of 15,000 inpatients in 1992
- Adverse events 2.9% (30% due to negligence)
- 55% adverse events were non-operative; 19% were due to medicines
- 0.56% adverse drug events
- 35% drug adverse events due to negligence
- Primary medicines involved were antibiotics (25%), cardiovascular medicines (17%), analgesics (9%), and anticoagulants (9%)
- Types of medicine use error—
  - Wrong medicine prescribed (21%)
  - Prescribed despite known allergy (6%)
  - Incorrect frequency (5%)
  - Wrong dose (8%)
  - Missed dose (5%)
  - Medicine interaction (3%)

*Thomas, E.J., D.M. Studdert, H.R. Burstin, et al. 2000. Incidence and Types of Adverse Events and Negligent Care in Utah and Colorado. *Medical Care* 38(3):261–271.

Causes of Adverse Drug Events

- Record review of 4,031 inpatients
- 247 (6.1%) adverse drug events; 70 (28%) preventable
- 194 (4.8%) additional errors without patient harm detected
- 264 errors were due to—
  - Physician ordering (39%)
  - Transcription (12%)
  - Nurse administration (38%)
  - Pharmacy dispensing (11%)
- Reasons for error included—
  - Lack of prescriber knowledge (37%)
  - Inadequate checking of medicine identity or dose (15%)
  - Incomplete patient information (14%)
  - Inaccurate transcription (11%)
  - Failure to note medicine allergy information (9%)

*Bates, D.W., D.J. Cullen, N. Laird, et al. 1995. Incidence of Adverse Drug Events and Potential Adverse Drug Events. Implications for Prevention. ADE Prevention Study Group. *JAMA* 274(1):29–34.

Medication Errors

- Administration of medicine or dose that differs from written order
  - Medicine prescribed but not given
  - Administration of a medicine not prescribed
  - Medicine given to the wrong patient
  - Wrong medicine or IV fluid administered
  - Wrong dose or strength given
  - Wrong dosage form given

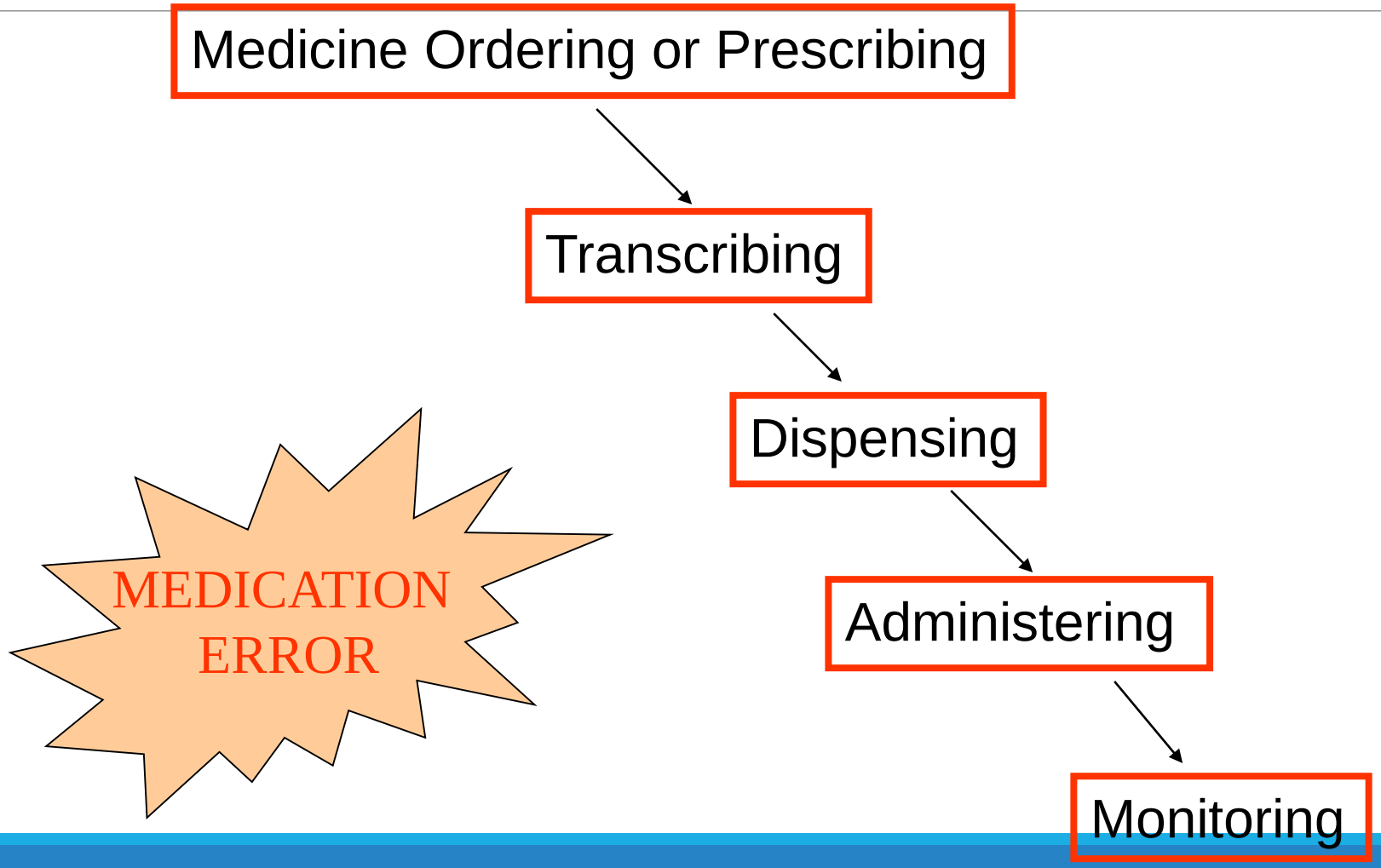
Medication Errors

- Medicine given for wrong duration
- Wrong preparation of a dose (e.g., incorrect dilution)
- Incorrect administration technique (e.g., unsterile injection)
- Medicine given to a patient with known allergy
- Wrong route of administration used
- Wrong time or frequency of administration

Causes of Medication Errors

- Human factors
  - Heavy staff workload and fatigue
  - Inexperience, lack of training, poor handwriting, and oral orders
- Workplace factors
  - Poor lighting, noise, interruptions, excessive workload
- Pharmaceutical factors
  - Excessive prescribing
  - Confusing medicine nomenclature, packaging, or labeling
  - Increased number or quantity of medicines per patient
  - Frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine
  - Lack of effective policies and procedures

When Medication Errors Occur (1)



Preventing Medication Errors

- Establish consensus group of physicians, nurses, and pharmacists to select best practices
- Introduce a punishment-free system to collect and record information about medication-related errors
- Develop written procedures with guidelines and checklists for IV fluids and high-risk medicines (e.g., insulin, heparin, narcotics)

Preventing Medication Errors

- Require legible handwriting and complete spelling of medicine name
- Use standardized notation
  - Doses given in mg, mcg, g
  - Leading zero used for values < 1 and no trailing zero (e.g., 0.2 mg instead .2 mg; 2 mg instead of 2.0 mg)
- Write route of administration on all orders
- Write out directions completely (e.g., “daily” not “QD” or “OD”)

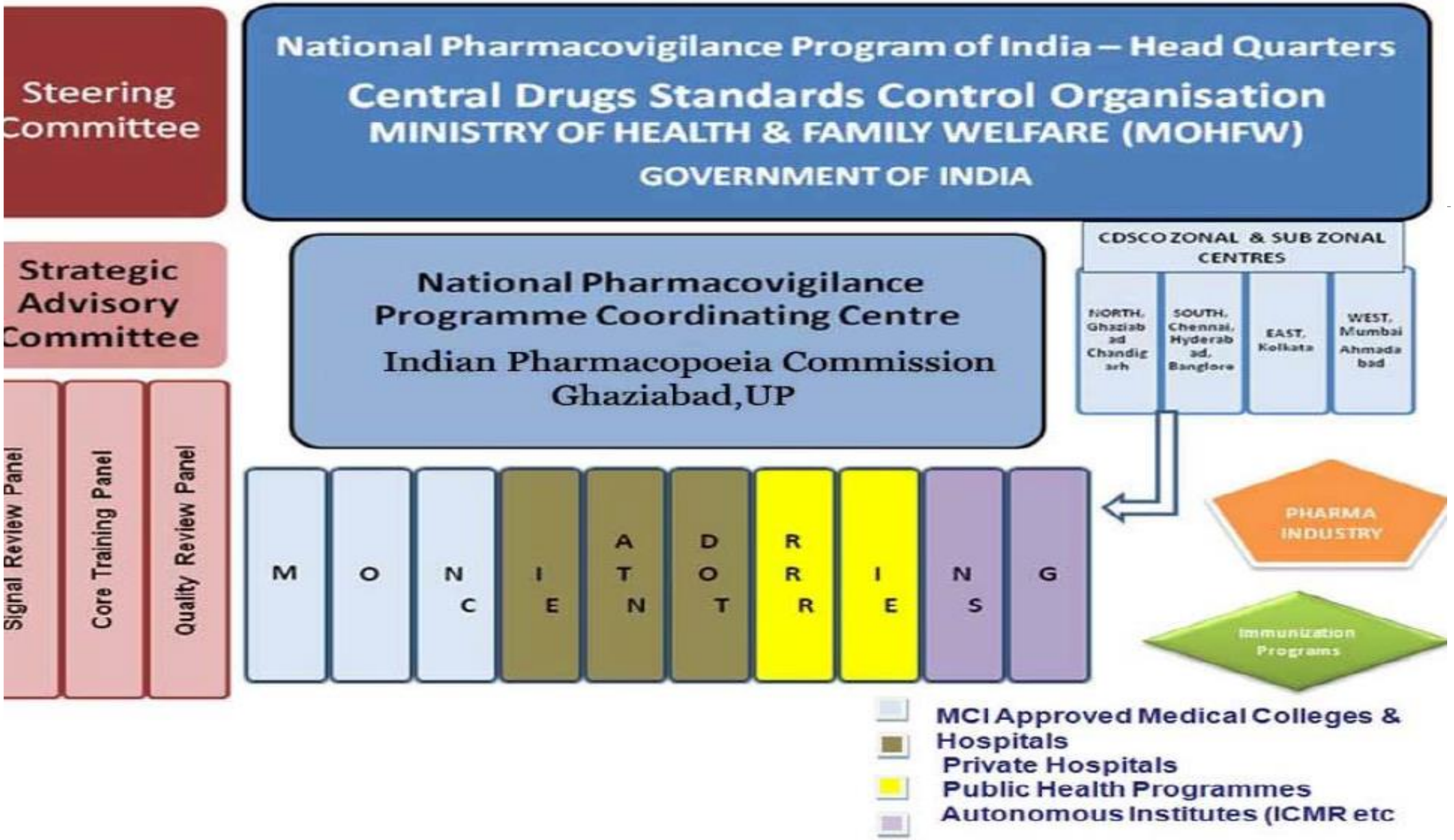
Preventing Medication Errors

- Limit use of telephone and oral orders to emergency situations
- Confirm identity of patients before administering medication
- Use standard administration times for hospitalized patients
- For look alike and sound alike names, establish a policy requiring that prescribers write both brand and generic names
- Use pharmacy staff to help prevent errors

Pharmacovigilance Programme of India(PvPI)

Objectives

- To monitor Adverse Drug Reactions (ADRs) in Indian population
- To create awareness amongst health care professionals about the importance of ADR reporting in India
- To monitor benefit-risk profile of medicines
- Generate independent, evidence based recommendations on the safety of medicines
- Support the CDSCO for formulating safety related regulatory decisions for medicines
- Communicate findings with all key stakeholders
- Create a national center of excellence at par with global drug safety monitoring standards


Steering Committee
National Pharmacovigilance Program of India – Head Quarters
Central Drugs Standards Control Organisation
MINISTRY OF HEALTH & FAMILY WELFARE (MOHFW)
GOVERNMENT OF INDIA
Strategic Advisory Committee
National Pharmacovigilance Programme Coordinating Centre
Indian Pharmacopoeia Commission
Ghaziabad,UP
CDSCO ZONAL & SUB ZONAL CENTRES
NORTH, Ghaziabad Chandigarh
SOUTH, Chennai, Hyderabad, Banglore
EAST, Kolkata
WEST, Mumbai Ahmadabad
Signal Review Panel
Core Training Panel
Quality Review Panel
MONITORING ADR
PHARMA INDUSTRY
Immunization Programs
MCI Approved Medical Colleges & Hospitals
Private Hospitals
Public Health Programmes
Autonomous Institutes (ICMR etc

Case Study

A 67 year old woman with an extensive rash is referred urgently to hospital. The rash started on the backs of her hands and spread very quickly to the arms, trunk, neck, and face. The lesions consist of concentric rings with frank blistering in some areas. Lesions have also started to appear on her lips and inside her mouth.

Her medications include: ramipril 10mg once daily, simvastatin 40mg at night, aspirin 75mg once daily, metformin 1g twice daily, gliclazide 40mg each morning. She was started on aspirin 5 years ago following a stroke. At about the same time, she was diagnosed with type 2 diabetes and has been taking metformin, ramipril, and simvastatin for over 4 years. She was prescribed gliclazide during her annual diabetes review 2 months ago.

The patient denies taking any over-the-counter medicines or herbal remedies. She has not made any significant changes to her diet and there is no history of recent infection.

On admission:

Blood pressure = 127/75 mmHg

Body Mass Index = 26kg/m^2

HbA_{1c} = 8.0% (64mmol/mol)

Her U + Es, renal, and liver function are normal.

Case Study

Q1: Which drug is most likely to be causing erythema multiforme?

Q2: How should this adverse drug reaction (ADR) be managed?

Q3: Should this ADR be reported to PVPI?

Case Study

A1: According to the side-effects under the prescribing notes for sulphonylureas, hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy. They consist mainly of allergic skin reactions which progress rarely to erythema multiforme. The monograph for ramipril, BNF 59, also includes erythema multiforme as a side-effect. The time at which erythema mutiforme occurred in this patient is closely related to the time from when gliclazide was started and characteristic of hypersensitivity reactions with sulphonylureas.

A2: This patient has suffered a major manifestation of erythema multiforme accompanied by mucosal involvement after starting gliclazide. Gliclazide should be stopped and the reaction should be clearly documented in the patient's medical record and allergy history to prevent recurrence. If the reaction does not subside after stopping gliclazide, other causes for the reaction should be considered. Treatment to ameliorate the symptoms of erythema multiforme can be provided as necessary.

A3: ADRs should be reported through the ADR reporting form available from the CDSCO website or by using the android app PVPI.


Thank You