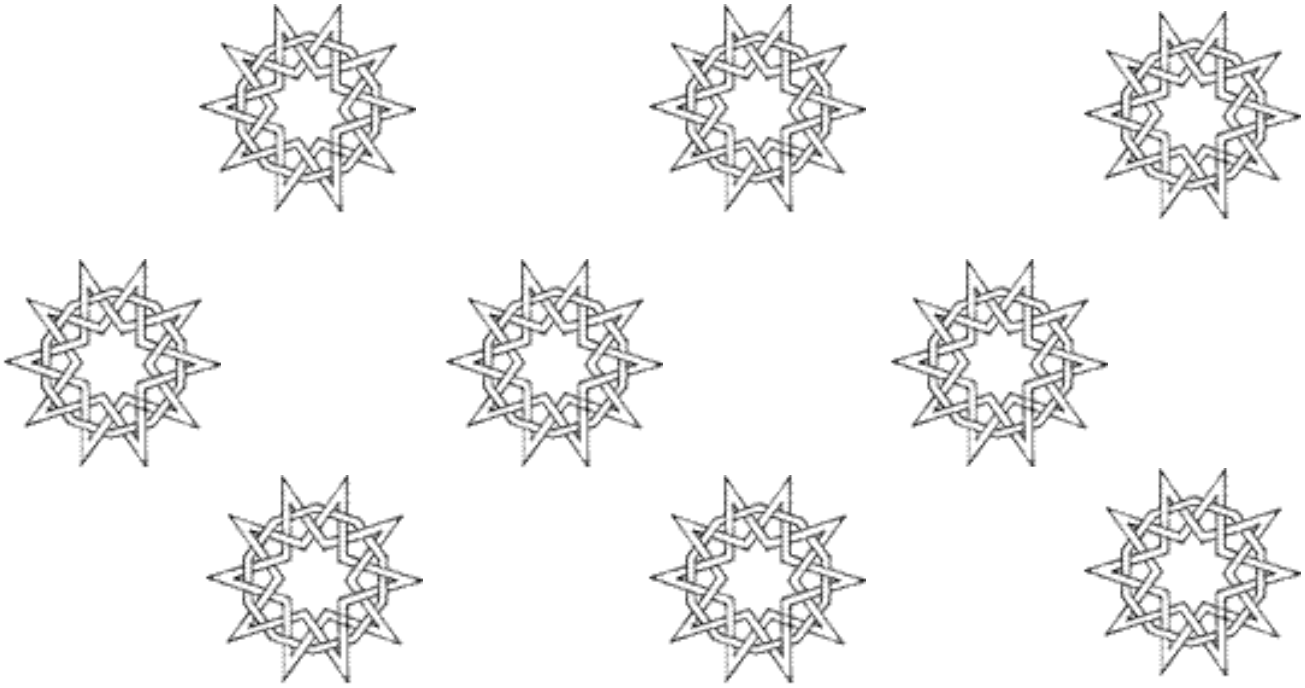
Guidelines for Detecting & Reporting Adverse Drug Reactions



Individual Case Safety Reports
For Healthcare professionals

Central Administration of Pharmaceutical Affairs (CAPA)

Egyptian Pharmacovigilance Center (EPVC)

2010

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Individual Case Safety Reports
For Healthcare professionals

This Guideline for the Egyptian Pharmacovigilance System has been developed to complement and support the efforts of orienting all healthcare professionals on the important concept of Pharmacovigilance. It gives an overview of what Pharmacovigilance is, how to detect and classify ADR's. It also describes the reporting system to the Egyptian Pharmacovigilance Centre in the context of the Individual Case Safety Reports (ICSR). The reporting requirements stated in this guideline are based mainly on the guidelines of International Conference for Harmonization (ICH), the European Medicine Evaluation Agency (EMEA) and the United States Food and Drug Administration (FDA).

Its ultimate goal is to enhance efforts in ensuring that safe, efficacious, and quality medicines are made available for all Egyptians.

All healthcare professionals are encouraged to actively participate in Pharmacovigilance and to report all suspected adverse drug reactions to help safeguard the patients' health.

Contributors

Dr. Rehab O. Deghedy
P.A. of Assistant Minister of Pharmaceutical Affairs

Dr. Hadir M. Ahmed
Team leader of The Egyptian Pharmacovigilance center

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Abbreviations

ADR	Adverse Drug Reaction
CAPA	Central Administration of Pharmaceutical Affairs
CIOMs	Council for International Organizations of Medical Sciences
EDA	Egyptian Drug Authority
EPVC	Egyptian Pharmacovigilance Centre
ICSR	Individual Case Safety Report
MAH	Marketing Authorization Holder
MOH	Ministry of Health
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
SPC	Summary of Product Characteristics
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

What is Pharmacovigilance?

According to the WHO, Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Adverse drug reaction (ADR) Vs. Adverse Events

Adverse drug reaction is a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Adverse Event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this medicinal product.

An adverse drug reaction, is distinguished from the adverse event by; the former has a suspicion of a causal relationship between the medicinal product and the reaction, i.e. judged as being at least possibly related to the reaction by the reporting or the reviewing health professional, while the adverse event does not necessarily have such causal relationship.

Importance of Pharmacovigilance

The information collected during the pre-marketing phase is incomplete with regard to adverse drug reactions and this is mainly because:

- Patients used in clinical trials are limited in number and are not representative to the public at large. In addition, the conditions of use of medicines differ from those in clinical practice and the duration is limited.
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete. Therefore, post-marketing surveillance is important to permit detection of less common but sometimes very serious ADRs

Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.
Therefore health professionals worldwide should report on ADRs as it can save lives of their patients and others.

Objectives of Pharmacovigilance

- To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions.
- To improve public health and safety in relation to the use of medicines.

- To Detect problems related to the use of medicines and communicate the findings in a timely manner,
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- Encourage the safe, rational and more effective (including cost effective) use of medicines,
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

WHO Programme for International Drug Monitoring

As a means of pooling existing data on ADRs, WHO's Programme for International Drug Monitoring was started in 1968. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed national Pharmacovigilance centers for the recording of ADRs. Currently, many countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden (UMC). The collaborating centre is responsible for maintaining the global ADR database, Vigibase.
The WHO Collaborating Centre analyses the reports in the database to:

- Identify early warning signals of serious adverse reactions to medicines;
- Evaluate the hazard;
- Undertake research into the mechanisms of action to aid the development of safer and more effective medicines.

Through an advisory committee, WHO plays an important role in the provision of expert advice on all matters relating to the safety of medicines. The Committee also exists to facilitate consistent policies and action among member countries and to advise those who may be concerned about action taken in another country.

Types of Adverse Drug Reactions

- **Type A effects**

  Augmented pharmacologic effects - dose dependent and predictable (medicine actions) are those which are due to (exaggerated) pharmacological effects. Type A effects tend to be fairly common, dose related (i.e. more frequent or severe with higher doses) and may often be avoided by using doses which are appropriate to the individual patient. Such effects can usually be reproduced and studied experimentally and are often already identified before marketing.

- **Type B effects**

  Bizarre effects (or idiosyncratic) - dose independent and unpredictable (Patient reactions) characteristically occur in only a minority of patients and display little or no dose relationship. They are generally rare and unpredictable, and may be serious and are notoriously difficult to study. Type B effects are either immunological or non-immunological and occur only in patients, with - often unknown - predisposing conditions. Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Also non-immunological Type B

effects occur in a minority of predisposed, intolerant, patients, e.g. because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or accumulation of a toxic metabolite. Examples are chloramphenicol aplastic anaemia and isoniazid hepatitis.

- **Type C effects**

  Chronic effects refer to situations where the use of a medicine, often for unknown reasons, increases the frequency of a "spontaneous" disease. Type C effects may be both serious and common (and include malignant tumours) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove.

- **Type D effects**

  Delayed effects (dose independent)
  Carcinogenicity (e.g., immunosuppressants)
  Teratogenicity (e.g., fetal hydantoin syndrome)

- **Type E effects**

  End-of-treatment effects

- **Type F effects**

  Failure of therapy

Introduction to the Egyptian Pharmacovigilance system

An Egyptian Pharmacovigilance Center (EPVC) has been established in the central administration of pharmaceutical affairs (CAPA), Ministry of Health to be responsible for the **collection** and **evaluation** of information on pharmaceutical products marketed in Egypt with particular reference to adverse reactions. Furthermore, EPVC is taking all appropriate measures to:

a) Encourage physicians and other healthcare professionals to report the suspected adverse reactions to EPVC and

b) Oblige marketing authorization holders to systematically collect information on risks related to their medical products and to transmit them to EPVC.

c) Provide information to end-users through adverse drug reaction news bulletins, drug alerts and seminars.

EPVC is handling these pharmacovigilance data in a way, which is compatible with the procedures undertaken by WHO Collaborating Center for International Drug Monitoring in order that pertinent data may be transferred between EPVC and WHO center.

The following summarize the spontaneous reporting system procedure:

- A healthcare professional or marketing authorization holder reports a suspected adverse drug reaction related to one or more pharmaceutical products, to The Egyptian pharmacovigilance center (EPVC). Reports are made in writing (e.g. using report forms), electronically, or by any other approved way.
- Reports are collected, collated, and validated by the pharmacovigilance centre and are usually entered into a database. Serious reactions are handled with the highest priority.
- The database is used to identify potential signals and analyze data in order to clarify risk factors, apparent changes in reporting profiles etc.

Spontaneous reporting of Adverse Drug Reactions

The Spontaneous reporting structure is the **voluntary** and the most common way through which the regulatory bodies collect ADR information for medicines once they are on the market.

In Egypt the Yellow Card (a reporting form described below) is used by EPVC to collect information on ADRs from healthcare professionals and members of the public. Each yellow card concerns an Individual Case experienced ADRs, thus it is also called Individual Case Safety Report (ICSR).

Individual Case Safety Report (ICSR)

A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary reporter to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time.

Who should report

Healthcare Professionals are the preferred source of information in pharmacovigilance, for example physicians, family practitioners, medical specialists, and dentists.

Nurses and other health workers may also administer medicines and should report relevant adverse drug reactions experienced by the patients.

Pharmacists can play an important role in the stimulation of reporting and in the provision of additional information (for example, on co-medication and previous medicine use).

Patients & their relatives can also report their experienced adverse drug reactions directly to EPVC, or through their healthcare professionals. In this case seek the patient permission to contact their healthcare professionals for additional information and data verification.

Marketing authorization holder (MAH), being primarily responsible for the safety of their products, they are obligated to report **serious** adverse drug reactions they receive about their products to EPVC. While the Non-serious ADRs should be included in the periodic safety update report (PSURs).

It is important to appreciate

Firstly, that EPVC database for ICSRs can detect duplicate reports. Therefore, if a doctor deems it necessary to submit a report they should do so even if there is a possibility that someone else might have done the same.

Secondly, different people will include different information when they complete a Yellow Card, all of which is useful in creating a full picture of the reaction that has taken place.

The Yellow Card and the Online Reporting

For the suspected adverse drug reaction to be reported; a unified form should be used to facilitate the reporting and to insure that the required information is included; therefore EPVC has developed this unified reporting form (attached), it was adapted from the international Yellow Card.

This yellow card is to be used by the healthcare professionals and the patients while the Marketing authorization holders (MAH) should report the ICSRs using the International CIOMs form.

In addition, for most reporting convenience, a web-based dynamic reporting module was established for the easy report completion and online submission.

Characteristics of good case report

The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse reactions, thus good case reports include the following elements:

1. Description of the adverse reaction or disease experience, including time to onset of signs or symptoms and the seriousness of the reaction/s;

2. **Suspected** and **concomitant** medicines details (i.e., Name, concentration, dose, dosage form, rout of administration, indication for use, duration of use& batch number especially for vaccines), including over-the-counter medications, dietary supplements, and recently discontinued medications;
3. Patient characteristics, including the name or initials, age, sex, weight, and baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
4. Documentation of the diagnosis of the reactions, including methods used to make the diagnosis;
5. Clinical course of the reaction and patient outcomes (e.g., hospitalization or death);
6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
7. Information about response to dechallenge and rechallenge; and
8. Any other relevant information (e.g., other details relating to the reaction or information on benefits received by the patient, if important to the assessment of the reaction).

The reporting form should be obtained from EPVC, and at least **four sections** should be completed to have a **valid report**. In other words these four sections are the minimum information which allows the case report to be **valid** subsequently to be entered onto the national ADR database and become available for signal generation in order to facilitate evaluation of cases.

When one or more of these information are missing, the case should be followed up in order to validate the report and complete its processing as described above.

The **four sections** to validate the individual case report (ICSR) are as follow:

An identifiable patient

At least 1 of the following:
- Patient initials
- Sex
- Weight
- Age at time of reaction or date of birth

An identifiable reporter

- Name, initials
- Address
- Contact details
- Qualification (if healthcare professional)

Suspected medicine

- Name (INN and brand name)
- Strength (concentration)
- Dose, Frequency
- Dosage form
- Route of administration
- Indication for use
- Duration of use, date started, date stopped
- Batch number (especially for vaccines)

Suspected adverse reaction

- Description of the reaction
- Expectedness of the reaction (in accordance with the approved product information)
- Seriousness of the reaction
- Date the reaction started, stopped
- Outcomes attributed to adverse reaction
- Relevant tests/laboratory data (if available)

What should be reported

If it is suspected that a patient has experienced an ADR it should be reported using a Yellow Card. ADRs resulting from prescription medicines, herbal remedies, and OTC medications can all be reported.. Causality does not need to have been established.

- For **new medicines** report all the suspected reactions, including minor ones. (medicines are still considered "new" up to five years after marketing authorization)
- For established medicines or well-known medicines report **all serious** or unusual unexpected suspected adverse reactions, (see definition of a serious reaction, expectedness of reactions).
- Report if an **increased frequency** of a given reaction is suspected.
- Report all suspected ADRs associated with drug-drug, drug food or drug-food supplements (including herbal and complementary products) **interactions**.
- Report when suspected ADRs are associated with medicine withdrawals.
- Report ADRs occurring from overdose or **medication error**.
- Report ADRs in special fields of interest such as medicine abuse and medicine use in **pregnancy** (teratogenicity) and during lactation.
- In **children** under the age of 18, all suspected ADRs occurring, should be reported regardless of whether the medicine is licensed for use in children. Children are often not exposed to medicines during clinical trials and many medicines are used in children even if they are not licensed for this purpose. This means that monitoring of medicine safety is particularly important for this age group.

As soon as possible
Reports on all suspected adverse reactions
- known or not, serious or not –
are welcome and useful
If there is any doubt about whether or not it is an ADR; always it is best practice to submit a report

How to recognize ADRs in patients

ADRs are difficult and sometimes impossible to distinguish from the disease being treated since they may act through the same physiological and pathological pathways. However, the following approach is helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised.

2. Take a proper history and do a proper examination of patient

- A full medicine and medical history should be taken
- An ADR should be your first differential diagnosis at all times

- Ask if this adverse reaction can be explained by any other cause e.g. patient's underlying disease, other medicines including over-the-counter medicines or traditional medicines, toxins or foods
- It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is.
- A medicine-related cause must be considered, especially when other causes do not explain the patient's condition

3. Establish time relationships by answering the following question: *Did the ADR occur immediately following the medicine administration?*

Some reactions occur immediately after the medicine has been given while others take time to develop. The time from start of therapy to the time of onset of the suspected reaction must be logical.

4. Carry out a thorough physical examination with appropriate laboratory investigations if necessary:

- Remember: only a few medicines produce distinctive physical signs
- Exceptions include fixed medicine eruptions, steroid-induced dermal atrophy, acute extra-pyramidal reactions
- Laboratory tests are important if the medicine is considered essential in improving patient care or if the laboratory tests results will improve management of the patient.
- Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis

5. Effect of Dechallenge and Rechallenge should be determined

- Dechallenge (withdrawal of the suspected medicine):

  Positive dechallenge is the improvement / resolution of ADR when the suspected medicine is withdrawn in a strong, though not conclusive indication of medicine-induced reaction.

- Rechallenge (re-introducing the suspected medicine after a dechallenge)

  Rechallenge is only justifiable when the benefit of reintroducing the suspected medicine to the patient overweighs the risk of recurrence of the reaction, which is rare. In some cases the reaction may be more severe on repeated exposure. Rechallenge requires serious ethical considerations**.**

6. Check the known pharmacology of the medicine

- Check if the reaction is known to occur with the particular suspected medicine as stated in the package insert or other reference.
- Remember: if the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular suspected medicine.

7. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the Egyptian Pharmacovigilance Centre

Most commonly reported ADRs
Rash
Vomiting
Nausea
Abdominal pain
Headache
Renal failure
Hypertension
Fever
Tinnitus
Death

Drug Classes Commonly Reported with ADRs
Non- steroidal anti-inflammatory drugs
Ant -depressants is
Antibiotics
Anti- epileptics
Analgesics and antipyretics
Bronchodilators
Immunosuppressant
Anti malarial
Anti emetics
Anti diabetics

Seriousness of Adverse drug reactions

A serious adverse event or reaction is any untoward medical occurrence associated with the use of a medical product in a patient that at any dose, the patient outcome is one of the following See Annex III for Examples of serious ADRs:

1. **Death**

   Report if the patient's death is suspected as being a direct outcome of the adverse reaction.

2. **Life-Threatening**

   Report if the patient was at substantial risk of dying at the time of the adverse reaction or it is suspected that the use or continued use of the product would result in the patient's death.

   Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive medicine dosing.

   NOTE

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

3. **Hospitalization (initial or prolonged)**

   Report if admission to the hospital or prolongation of a hospital stay results because of the suspected adverse reaction.

   Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing/ prolonging the existing hospitalization.

4. **Disability**

   Report if the adverse reaction resulted in a significant, persistent, or permanent disability/ incapacity; (change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life).

   Examples: Cerebrovascular accident due to medicine-induced hypercoagulability; toxicity; peripheral neuropathy.

5. Congenital Anomaly

Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child (birth defect).

Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

6. Medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might NOT be immediately life-threatening or result in death or hospitalization but might cause danger to the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Examples:

- Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage;
- Burns from radiation equipment requiring medicine therapy;
- Breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.
- **Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction**.
- Intensive treatment in an emergency room or at home for allergic bronchospasm,
- Convulsions that do not result in hospitalization,
- Development of medicine dependency or medicine abuse

Expectedness of the adverse drug reaction

The expectedness of the reaction is assessed in accordance with the approved product information; the reaction is **defined as expected** if it is included in package insert or the summary of product characteristics (SPC).

On the other hand the **unexpectedness** of the reaction includes the following:

- The reaction is not included in the package insert or the summary of product characteristics (SPC).
- The reaction is included in the package insert or the summary of product characteristics (SPC) but showed changes in its known frequency
- The reaction is included in the package insert or the summary of product characteristics (SPC) but showed changes in its known severity i.e. the change in the severity of a known adverse drug reaction is considered as unexpected to that medicine.

What are the benefits of these reports for the patients and the health care providers?

The reporting by the healthcare provider and patient is completely voluntarily, they will stand to benefit as:

- Improvement on the quality of care offered to patients

- Reduction of medicine related problems leading to better treatment outcome
- Improved patient confidence in professional practice, hence professional growth
- Improved knowledge
- Access to feedback information on medicine related problems reported within the country and internationally
- Satisfaction for the fulfillment of a moral and professional obligation

Will reporting have any negative consequences on the reporter?

- The adverse drug reaction report does not constitute an admission that the reporter or any other health professional or the medicine contributed to or caused the reaction in any way.
- The outcome of the report, together with any important or relevant information relating to the reported reaction, will be communicated to the reporter as appropriate.
- The details of the report are stored in a **confidential database** at the EPVC and the analyzed report will be sent to the Uppsala Monitoring Center (UMC).
- The names of the reporters or any other health professionals named on the report and the patient will be removed before any details about a specific adverse drug reaction is used or communicated to others.
- The information obtained from the report will not be used for commercial purposes. It is only meant to improve our understanding and use of medicines in Egypt.

How to obtain the reporting form

A web based dynamic reporting module is available at EPVC website to be completed and submitted online. (www.epvc.gov.eg)

In addition, the reporting forms (yellow cards) are available on the **EPVC web site** for health care professional & patients to be downloaded.

At each hospital a Pharmacovigilance coordinator is assigned (preferred to be the clinical pharmacist, or the medicine information specialist), the reporting forms (yellow cards) are available at the hospital Pharmacovigilance coordinator for the hospital health care professional.

Special stand for yellow cards is to be available in the community pharmacies (mainly for patients, community pharmacists & may be for the nearby private clinics).

How to submit ADR report

After filling the ADR reporting form; All ADR reports can be sent to the EPVC by:

- **Submit on-line**: through the EPVC website, a web based dynamic reporting module is available for completion online.
- **Fax**: special number for the ADR reporting

- **Postal mail** (regular letters)
- **E-mail** : special account for ADR reporting, pv.center@eda.mohealth.gov.eg
- By **Hand:** contact person in hospitals, by pharmaceutical distribution companies….

There is collaboration between EPVC and some pharmaceutical distribution companies to participate in collecting the filled ICSR then forward them to EPVC.

Serious reports should be submitted in expedited manner i.e as soon as possible & no later than 15 calendar days

Thus they best submitted:

Online **Email** **Fax**

While other reports can be submitted on regular basis (every month) by any of the above means.

Frequency of reports submission

Reporter	Serious ICSRs	Other ICSRs
Hospitals	**Expedited;** **as soon as possible** **& no later than** **15 calendar days**	▪ Collected & submitted every month by the hospital Pharmacovigilance coordinator using **any** of the above means
Community pharmacies		▪ Collected & submitted every month by the collaborating pharmaceutical distribution company, ▪ May also on individual report basis.
Private clinics		▪ Submitted by the physician on individual report basis, ▪ Also can be delivered to the nearby community pharmacy to be submitted every month by collaborating pharmaceutical distribution company.
Patients		▪ Any report should be submitted as soon as he experienced the reaction, ▪ Or delivered to the nearby community pharmacy to be submitted every month by the collaborating pharmaceutical distribution company
Marketing authorization holders	**Expedited;** **as soon as possible** **& no later than** **15 calendar days** **Using the CIOM form or online**	Included in the PSURs and submitted as follow: ▪ every 6 month for the first 2 years of its international marketing, ▪ then annually for the subsequent 2 years ▪ then every 3 years thereafter

Remember: the Basic principles of efficient reporting

- **In-time reporting**
  - Report the suspected adverse drug reaction as soon as it occurs- the report involves less work and is more accurate.
  - Send the report quickly to the Egyptian Pharmacovigilance center.

- **Strong suspicion and follow-up**
  - Continue your strong suspicion of the medicine-induced illness in the same patient and in other patients
  - Keep a vigil for signs and symptoms that may now enhance or exclude the possibility of a medicine induced reaction
  - All follow - up / supplementary information should be documented and submitted to the Egyptian Pharmacovigilance center "FOLLOW - UP REPORT" clearly indicated on the top right corner of the form.
  - Make sure that the patient names and patient code are the same in the 1st report & the Follow up report. As it is very important that follow-up reports are accurately identified and linked to the original report.

- **Accuracy and completeness**
  - Ensure that each reported Suspected ADR Reporting Form is filled in accurately and with all the necessary information, as much as is available to you. This is very important for assessing the causality of the medicine to have caused that reaction.
  - Remember the 4 basic components that make a report reliable are:

    i. An identifiable patient
    ii. An identifiable health-care professional
    iii. An identifiable Adverse reaction or product problem
    iv. An identifiable medicine (suspected)

    If the above information is missing, the report may not be useful.
  - Remember to fill in all information accurately and in clear legible writing

Processing of Adverse drug reactions reports

What happens to the reported ADRs?

1. The information obtained from the report will be used to promote safe use of medicines in the local, national and international levels.
2. The submitted report will be entered into the national database of adverse drug reactions and be analyzed on a regular basis.

   A well - completed and duly submitted ADR reported may result in:

   - Additional investigations into the use of the medicine in Egypt
   - Appropriate changes in the package insert
   - Change the schedule of the medicine
   - Enhancing educational initiatives to improve the safe use of that medicine
   - Other regulatory and health promotion interventions as the situation may warrant including withdrawal / recall. **.**

Thus, the ultimate purpose of ADR reporting and monitoring is to reduce risks associated with drug prescribing and administration and improve patient care, safety and treatment outcome

Causality assessment

Causality assessment is the method by which the extent of relationship between a medicine and a suspected reaction is established i.e. to attribute clinical events to medicines in individual patients or in case reports

The WHO scale of assessment and the Naranjo's scale are the most commonly used scales.

WHO probability scale

Term	Description
Certain	▪ A clinical reaction, including laboratory test abnormality, occurring in a plausible time relationship to medicine administration, and which ▪ Cannot be explained by concurrent disease or other medicines or chemicals. ▪ The response to withdrawal of the medicine (dechallenge) should be clinically plausible. ▪ The reaction must be definitive pharmacologically or phenomenologically, (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) ▪ Using a satisfactory rechallenge procedure if necessary.
Probable / Likely	▪ A clinical reaction, including laboratory test abnormality, with ▪ A reasonable time sequence to administration of the medicine, ▪ Unlikely to be attributed to concurrent disease or other medicines or chemicals, and which ▪ Follows a clinically reasonable response on withdrawal (dechallenge). ▪ Rechallenge information is not required to fulfill this definition.
Possible	▪ A clinical reaction, including laboratory test abnormality, with ▪ A reasonable time sequence to administration of the medicine, but which could also be explained by concurrent disease or other medicines or chemicals. ▪ Information on medicine withdrawal may be lacking or unclear.
Unlikely	▪ A clinical reaction, including laboratory test abnormality, with ▪ a temporal relationship to medicine administration which makes a causal relationship improbable, and ▪ Other medicines, chemicals or underlying disease provide plausible explanations.
Conditional/ Unclassified	▪ A clinical reaction, including laboratory test abnormality,
Unassessable/ Unclassified	▪ More data is essential for a proper assessment or the additional data are under examination.

Various causality terms are in use but the above are used most widely. Some people, however, do not use all the terms. For instance, many do not believe that a "certain" classification is possible for a single report and others make no distinction between "probable" and "possible".

Where only "possible" or "unlikely" are used to describe reactions it must be understood that "possible" include those reactions which are called by others "probable" and "certain", as well as "possible".

Whilst "conditional/unclassified" and "unassessible/unclassifiable" are not causality terms, they describe the status of adverse reaction reports and therefore allow for practical communication about ADR issues.

NARANJO's Algorithm

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse reaction appear after the suspect medicine was administered?	+2	-1	0
Did the AR improve when the medicine was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when 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
Did the reaction reappear when a placebo was given?	-1	+1	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 reaction confirmed by objective evidence?	+1	0	0

Scoring for NARANJO's Algorithm

- > 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR

Glossary of important terms used in Pharmacovigilance

Adverse Event/ Adverse Experience
Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction
A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.
An adverse drug reaction, contrary to an adverse reaction, is characterized by the suspicion of a causal relationship between the medicine and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

Case Control Study
Study that identifies a group of persons with the unintended medicine effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a medicine to the medicine reaction is examined by comparing the groups exhibiting and not exhibiting the medicine reaction with regard to how frequently the medicine is present.

Clinical Trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.
Clinical trials are generally classified into Phases: I to IV. Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance.

Cohort Study
A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.

Causality assessment
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

Drug/ Medicine
Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug/medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

Drug Alerts
The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.

Dechallenge
The withdrawal of a medicine from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.

Individual Case Safety Report (ICSR)
A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time.

Lack of Efficacy
Unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.

National Pharmacovigilance Centre
A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze and give advise on all information related to medicine safety.

Pharmacoepidemiology
The study of the use and effects of medicines in large numbers of people.

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Prescription Event Monitoring
A system created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified medicine.

Rechallenge
The point at which a medicine is again given to a patient after its previous withdrawal. *(see Dechallenge)*

Record Linkage
Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Serious Adverse Event or Reaction
A serious adverse event 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
- Persistent or significant disability/incapacity
- Congenital Anomaly
- Medically important event or reaction

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided:
The term 'severe' is not synonymous with serious. In the English language, 'severe' is used to describe the intensity (severity) of a specific reaction (as in mild, moderate or severe); the reaction itself, however, may be of relatively minor medical significance (such as severe headache).
Seriousness (not severity) which is based on patient/reaction outcome or action criteria serves as guide for defining regulatory reporting obligations.

Side Effect
Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the medicine.

Signal
Reported information on a possible causal relationship between an adverse reaction and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the reaction and the quality of the reaction and the quality of the information.

Spontaneous Reporting
A system whereby case reports of adverse drug reactions are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

Unexpected Adverse Reaction
An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the medicine.

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Annexes I: Yellow Card English

Ministry of Health
Central Administration of Pharmaceutical Affairs (CAPA)
Egyptian Pharmacovigilance Center (EPVC)

Adverse Drug Reactions Reporting Form

** If you suspect that an adverse reaction may be related to a certain drug, or a combination of drugs, you should complete this form and send it to the address shown at the end of the card.*
** Please report all serious and minor adverse reactions.*

A – Patient Details

Name/ initials:———— Sex: □ Male □ Female Weight: ——kg Age:———
(Optional)

B – Suspected Drug(s)

Drug Name *(Generic & trade)*	Concentration	Used for	Dose	Route	Date started	Date stopped
•						
•						
•						

C – Suspected Reaction(s)

•Please describe the reaction(s): ————————————————

•Date reaction(s) started: ———— Date reactions(s) stopped: ————

•Does the Reaction Stopped after stopping the drug? □ Yes □ No □Don't Know

•Does the Reaction Reappear after retaking the drug? □ Yes □ No □Don't Know

•Seriousness of ADR: □ Patient Died □ Life threatening □ Hospitalization
□ Prolonged Hospitalization □ Congenital Anomaly □ Permanent Disability
□ Required intervention to prevent Damage □ Other, specify _____

D – List of other drugs taken (Please list any other drugs taken during the last month prior to the reaction- *other than the suspected drug/s*)

Drug Name *(Generic & trade)*	Concentration	Used for	Dose	Route	Date started	Date stopped
•						
•						
•						

E – Reporter Details

The One who fill in this form: □ Patient □ Physician □ Pharmacist □ Nurse □ Other, specify_____

Name: ---------- Specialty *(if physician)*: ----------
Address: ----------
e-mail: ---------- Telephone/ mobile :----------
Signature: ---------- Date of reporting: ----------

•The information in this report is confidential and totally protected including both the Patient and Reporter identity.
•You can send voluntarily the Adverse Drug Reactions (ADRs) Reports to the Egyptian Pharmacovigilance Center.
•Reporting for ADRs is Vital for Safely usage of drugs . Enough information will help the Center to evaluate the Safety of the Drugs marketed in our Country.

Central Administration of Pharmaceutical Affairs (CAPA)
Egyptian Pharmacovigilance Center (EPVC)
21 Abd Elaziz Al Souad st. – Manial – Cairo
Tel no: 02 25354133 – 02 25354130 Fax no: 02 23684194 e-mail: pv.center@eda.mohp.gov.eg

Annexes II: Yellow Card Arabic

نموذج الإبلاغ عن الآثار العكسية للأدوية

- *في حالة حدوث أى آثار عكسية عند تناولك دواء معين أو مجموعه من الأدوية، فعليك بملىء هذا التقرير و إرساله إلى العنوان المبين فى أسفل النموذج.*
- *من فضلك سجل جميع الآثار العكسية سواء كانت عادية أو خطيرة.*

أ - بيانات المريض

الإسم/ الحروف الأولى: _____ النوع: □ ذكر □ أنثى الوزن: ____كجم العمر:____
(إختيارى)

ب - الأدوية المشتبه بها

إسم المستحضر (التجاري والعلمي)	التركيز	يستخدام لعلاج	الجرعة	طريقة التعاطي	تاريخ بدء العلاج	تاريخ وقف العلاج

ج - الآثار العكسية المشتبة بها

- من فضلك صف الأثر العكسي الذي ظهر :_____
- تاريخ بدء الأثـر: _____ تاريخ إنتهاء الأثـر: _____
- هل توقف الأثر بعد وقف العلاج؟ : □ نعم □ لا □ لا أعرف
- هل ظهر الأثر بعد إعادة العلاج؟ : □ نعم □ لا □ لا أعرف
- **مدى خطورته:** □ تسبب في الوفاة □ مهدد للحياة □ تسبب في دخول المريض المستشفى
  □ تسبب في إطالة مدة البقاء في المستشفى □ تسبب في عيوب خلقية للأجنة □ تسبب في إعاقة دائمة
  □ تطلب تدخل طبي أو جراحي لمنع حدوث إعاقة أو تلف دائم □ أخرى (حدد):_____

د - بيانات عن الأدوية الأخرى المتناولة (أذكر الأدوية الأخرى المتناولة حالياً وكذلك المتناولة قبل ظهور الآثار العكسية بشهر)

إسم المستحضر (التجاري والعلمي)	التركيز	يستخدام لعلاج	الجرعة	طريقة التعاطي	تاريخ بدء العلاج	تاريخ وقف العلاج

هـ - بيانات عن مقدم التقرير

االذى قام بملىء التقرير: □ المريض □ الطبيب □ الصيدلى □ التمريض □ أخرى (حدد):_____

الإسم: _____ التخصص *(للطبيب)*:_____

العنوان: _____

التليفون/محمول:_____ البريد الإلكتروني: _____

التوقيع: _____ التاريخ:_____

- *يتم التعامل مع المعلومات الواردة في التقرير بسرية تامة وهي محمية بشكل كامل بما في ذلك هوية المريض و معد التقرير.*
- *تستطيع إرسال تقارير الآثار العكسية لمركز اليقظة الدوائية المصرى بشكل تطوعى.*
- *إن الإبلاغ عن الآثار العكسية أمر حيوي وهام لتحقيق الاستخدام الآمن للدواء. كما أن المعلومات الكافية المقدمة من قبل المرضى تمكن المركز من تقدير مدى مأمونية المستحضرات المتداولة في بلادنا.*

الإدارة المركزية للشئون الصيدلية - مركز اليقظة الدوائية المصري
21 ش عبد العزيز آل سعود – المنيل – القاهرة
تليفون: 0225354130 –0225354133 فاكس: 0223684194
بريد إلكتروني: pv.center@eda.mohp.gov.eg

AnnexIII: Examples of serious ADRs

Blood
Bone marrow dyscrasias
Coagulopathies
Haemolytic anaemias

Cardiovascular
Arrhythmias
Cardiac arrest
Cardiac failure
Cardiomyopathy
Circulatory failure
Hypertension
Hypotension
Myocardial
Ischaemia/infarction
Sudden death

Central nervous system
Anorexia nervosa
Catatonia
Cerebrovascular accident
Coma
Confusional state
Dependence
Depression
Epilepsy (inc exacerbations)
Extrapyramidal reactions
Hallucinations
Hyperpyrexia
Intracranial pressure
Myasthenia
Neuroleptic malignant

Gastrointestinal
Colitis
Haemorrhage
Hepatic cirrhosis
Hepatic dysfunction
Hepatic fibrosis
Ileus
Pancreatitis
Perforation
Peritonitis (inc fibrosing)
Pseudo-obstruction

Immunological
Anaphylaxis
Arteritis
Drug fever
Lupus syndrome
Graft rejection
Polyarteritis nodosa
Vasculitis

Malignancy
Any

Metabolic
Acidosis
Adrenal dysfunction
Diabetes
Hypercalcaemia
Hyperkalaemia
Hyponatraemia
Hypokalaemia

Musculoskeletal
Arthropathy
Aseptic bone necrosis
Osteomalacia
Pathological fracture

Renal
Renal dysfunction
Urinary retention

Reproduction
Spontaneous abortion
Antepartum haemorrhage
Congenital abnormalities
Eclampsia, pre-eclampsia
Infertility
Uterine haemorrhage, perforation

Respiratory
Alveolitis (allergic, fibrosing)
Bronchospasm (inc exacerbation)
Pneumonitis
Respiratory failure
Thromboembolism

Skin
Angioedema
Bullous eruptions
Epidermal necrolysis
Exfoliation (generalised)

Special senses
Cataract