الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidance on Adverse Drug Events Reporting for Healthcare Professionals

Version 1.0

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Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
1.0	Pharmacovigilance Executive Directorate	21 August 2022	Final

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List of Abbreviations and Acronyms

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
HCPS	Health Care Professionals
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NPC	National pharmacovigilance center
PIDM	Program for International Drug Monitoring
PIL	Patient Information Leaflet
PV	Pharmacovigilance
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

1. INTRODUCTION

Medicines have become one of the essential aspects of global health care systems. Medicines save lives; because of this undeniable truth, the awareness regarding reporting adverse drug reactions (ADRs) is crucial to achieving a rational use of medicines and maximizing medication safety in the community. ADR reporting is an integral element in drug safety surveillance of the Saudi Pharmacovigilance System.

1.1. Purpose

This Saudi Food and Drug Authority (SFDA) document serves as guidance on reporting adverse drug reactions for healthcare professionals (HCPs). It is designed to encourage HCPs to participate in post-market drug surveillance activities by reporting adverse drug reactions of their patients voluntarily.

It covers an introduction to pharmacovigilance that includes sections on how to identify, classify and characterize adverse drug reactions (ADRs) and, most importantly, the requirement of reporting and the method of registration and reporting in the Saudi Pharmacovigilance System. The guideline demonstrates the process for the report's evaluation at the National pharmacovigilance Center (NPC), including the scale used for causality assessments.

All healthcare professionals are advised to engage in pharmacovigilance and report ADRs to ensure all patients have access to safe, effective, and high-quality medicines.

2. PHARMACOVIGILANCE

2.1. Pharmacovigilance (PV) definition:

According to the World Health Organization, pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug/vaccine related problems.

2.2. Objectives of Pharmacovigilance

- To improve patient care, public health and safety in relation to the use of medicines.
- To detect issues related to the prescribed medicines and communicate them with healthcare professionals and public in a timely manner.

- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

2.3.The National Pharmacovigilance Center (NPC)

Accordance to the Law of the Saudi Food and Drug Authority, issued by a Royal Decree, No. (M/6) dated 25/1/1428 H, 13/02/2007, SFDA oversees, regulates, and ensures the safety, efficacy, and quality of medicines marketed in Saudi Arabia. Accordingly, SFDA built the necessary infrastructure to achieve its goals and address these critical priorities. Part of this infrastructure is establishing the national pharmacovigilance center (NPC) for monitoring adverse drug reactions (ADRs) and the quality of medicines. Monitoring and evaluating medicinal products safety issues and communicating with healthcare professionals and the public are vital in safeguarding patient welfare and public health.

The objectives of NPC are to identify as quickly as possible important and serious ADRs to establish a causal relationship between drugs and adverse reactions. NPC has developed data collection and investigation tools to ensure that information on the association between drugs and adverse reactions is complete and reliable. NPC has joined the World Health Organization (WHO) drug safety program in 2009 and is handling ADR reports and other pharmacovigilance data in a manner compatible with the procedures undertaken by the WHO collaborating center for international drug monitoring. This is in order for the pertinent data to be exchanged smoothly between SFDA and the WHO.

2.4.Saudi Vigilance reporting system (تيقظ)

One of the cornerstones of developing an effective national spontaneous drug safety program is establishing an electronic system for ADE reports collection. The current system was established in 2018 as the third iteration of the system, named in Arabic as 'تيقظ'. The system aims to simplify the reporting process and maintain the data, allowing all public, HCPs, and pharmaceutical companies to report adverse drug events, medication errors, or any defect in product quality. Since the system success is best ensured by active and ongoing participation, SFDA strongly encourages all members of the medical field to take part and report via https://ade.sfda.gov.sa/ or the other different channels described in the patient information leaflet (PIL) attached with all marketed medications and the Summary of Product Characteristics (SPC), which can be accessed via Saudi

Drug Information System (SDI) at: https://sdi.sfda.gov.sa/ . (See appendix 1 for how to report via the electronic reporting system "تيقظ").

3. ADVERSE DRUG REACTION and ADVERSE EVENTS

3.1. Definitions

- **Medicinal product:**

A medicinal product is characterized by any substance or combination of substances,

  - Presented as having properties for treating or preventing disease in human beings; or
  - Which may be used in or administered to human beings with a view to either restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action or to make a medical diagnosis.

- **Adverse drug event:**

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 that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function.

  - Adverse drug reactions may arise from the use of the product within or outside the terms of the reaction may be a known side effect of the drug or it may be new and previously unrecognized.
  - Reporting of suspected ADRs where there is a suspicion of a causal relationship between the medicinal product taken and the suspected reaction experienced.

3.2. Classification of Adverse drug reactions

Adverse drug reactions can be classified as:

1. **Type A Reactions**: (augmented) reactions that result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent

- For example, respiratory depression with opioids or bleeding with warfarin.
- Type A reactions also include those that are not directly related to the desired pharmacological action of the drug, for example, dry mouth that is associated with tricyclic antidepressants.

2. **Type B Reactions**: (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug.
    - less common
    - Discovered for the first time after a drug has already been made available for general use
    - Examples include anaphylaxis with penicillin or skin rashes with antibiotics.
3. **Type C**, or 'continuing' reactions, persist for a relatively long time.
    - An example is osteonecrosis of the jaw with bisphosphonates.
4. **Type D Reactions**, or 'delayed' reactions, become apparent sometime after the use of a medicine. The timing of these may make them more difficult to detect.
    - An example is leucopoenia, which can occur up to six weeks after a dose of lomustine.
5. **Type E Reactions**, or 'end-of-use' reactions, are associated with the withdrawal of a medicine.
    - An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines.
6. **Type F reactions,** or unexpected failure of efficacy—these reactions occur when there is a failure of efficacy. Such reactions are common, may be dose-related and are often caused by drug interactions. The reaction is treated by increasing the dose and considering the effects of concomitant therapy.
    - Examples include Resistance to antimicrobials
    - Inadequate dosage or oral contraceptives, particularly when used with specific enzyme inducers.

3.3.Serious adverse event

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe'. The term 'severe' is not synonymous with serious. Hence, the following note of

clarification is provided:

Severe is used to describe the measure of 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) is based on patient/reaction outcome or action criteria serves as a guide for defining regulatory reporting obligations.

Seriousness criteria:

A serious adverse event or serious adverse reaction is any untoward medical occurrence that may cause at any dose one of the following outcomes:

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 if 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.
3. Require or prolongation of hospitalization
   Report if admission to the hospital or prolongation of a hospital stay results because of the suspected adverse reaction.
4. Cause 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).
5. Cause 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).
6. Requires intervention to prevent permanent injury
   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.

3.4.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 the patient information leaflet (PIL) 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 patient information leaflet (PIL) or the summary of product characteristics (SPC).
- The reaction is included in the patient information leaflet (PIL) or the summary of product characteristics (SPC) but showed changes in its known frequency.
- The reaction is included in the patient information leaflet (PIL) 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.

3.5.How to identify adverse drug reactions?

ADRs are difficult and sometimes impossible to differentiate from the disease being treated. Since they may function through the same physiological and pathological pathways. However, when examining suspected drug related ADRs, the following techniques are useful:

1. Ensure that the drug 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 the 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 the actual cause of any new medical problem.

- 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 the 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, and acute extrapyramidal reactions.
    - Laboratory tests are important if the medicine is considered essential in improving patient care or if the laboratory tests results will improve the management of the patient.
    - Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis.
5. Effect of De-challenge and Re-challenge should be determined
    - De-challenge (withdrawal of the suspected medicine): Positive de-challenge is the improvement / resolution of ADR when the suspected medicine is withdrawn in a strong, though not conclusive indication of medicine-induced reaction.
    - Re-challenge (re-introducing the suspected medicine after a de-challenge) re-challenge 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. Re-challenge requires serious ethical considerations.

4. REPORTING OF ADVERSE DRUG EVENTS

4.1. Type of adverse drug events reports

Unsolicited reports (spontaneous reports; definition)

A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to the SFDA that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection systems where adverse events reporting is actively sought.

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.

Why is reporting ADRs in a spontaneous setting important?

- It helps in detecting rare adverse drug events.
- Detection of safety in special populations (e.g., pregnant women).
- Determining long term safety of the products in the market.
- Assessment of drug safety in real-world circumstances (e.g., patients with polypharmacy or patients with co-morbidities).

4.2. What should be reported?

- ADRs resulting from prescription medicines, herbal remedies, and OTC medications can all be reported.
- For established medicines or well-known medicines, report all serious, non-serious, or unusual suspected adverse 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 were 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.

4.3. Characteristics of an ADR report with good quality

The quality of 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 reactions.
2. Suspected and concomitant medicines details (i.e., Name, concentration, dose, dosage form, rout of administration, indication for use, duration of use, including over-the-counter medications, dietary supplements, and recently discontinued medications.
3. Patient characteristics, including initials, age, gender, weight, and baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of the 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 the response to de-challenge and re-challenge; and 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).

4.4. Validity check:

The report must be valid to enable SFDA evaluation. A valid report requires to have the following criteria:

1. Single patient information at least one of the following: patient initials, sex, weight, age at the time of reaction, or date of birth.
2. Suspected medicine
3. Suspected adverse reaction
4. An identifiable reporter (e.g., name, initials, address, contact details, qualification; if a healthcare professional).

All suspected adverse drug events, whether known or unknown, serious or not, should be reported as soon as possible. It is always best practice to submit a report if there is any uncertainty regarding whether or not it is an ADR.

4.5. Will reporting have any negative consequences on the reporter?

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 NPC According to the Personal Data Protection Law, issued by a Royal Decree, No. (M/19) dated 9/2/1443 H, 16/9/2021, the reporter and patient identity are held in strict confidence by SFDA and protected to the fullest extent of the law; information provided by the reporter will be strictly protected and will not be used in any way against him / her.

4.6. Causality Assessment:

Causality assessment essentially means finding a causal association or relationship between a drug and a drug adverse reaction. It is an evaluation of the likelihood that a particular treatment is a cause of an observed adverse drug event (ADE)**.** NPC evaluates adverse drug events with the world health organization (WHO) Uppsala monitoring center (UMC) causality assessment scale.

4.6.1. WHO-UMC system case causality assessment

WHO-UMC scale is the causality assessment used by WHO Program for International Drug Monitoring (PIDM). It is used to study a causal association or relationship between a drug and a drug reaction.

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). • Re-challenge satisfactory, if necessary.
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

	• Re-challenge 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
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
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Un-assessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

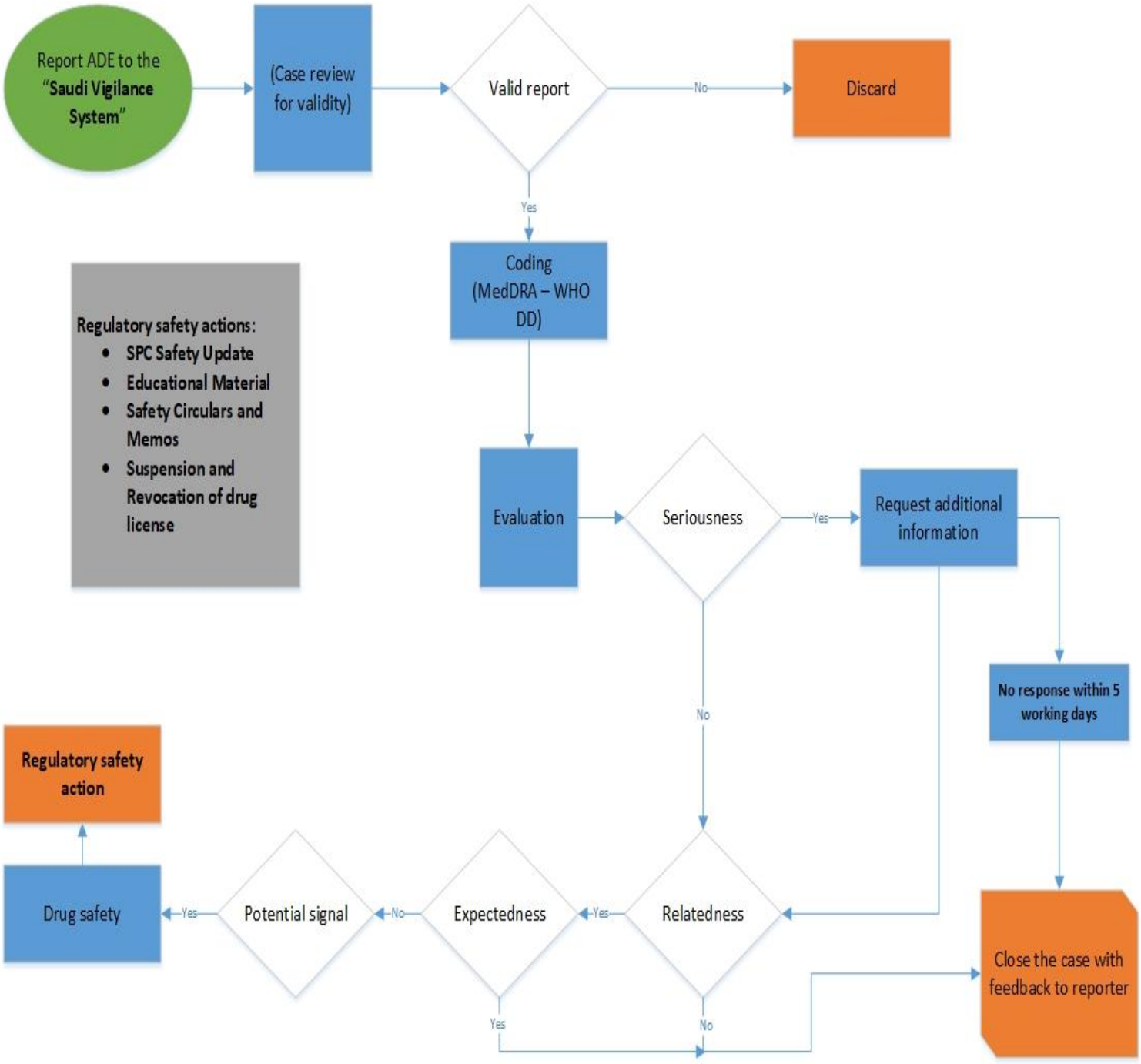
Participate in maintaining drug safety through reporting using the suitable reporting tools:

NPC website	SFDA App (طمني)	Call Center
	Android iOS	19999

We realize that filling out the form requires time to complete, around (5-10 minutes), but reporting adverse drug reactions is indispensable for safe medication use. The SFDA can further judge medicinal products' safety in Saudi Arabia if sufficient information is provided.

Always remember, when in doubt, fill the ADR form out!

5. ADR EVALUATION PROCESS AT SFDA:



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APPENDIX 1

How to register in "Saudi Vigilance System"

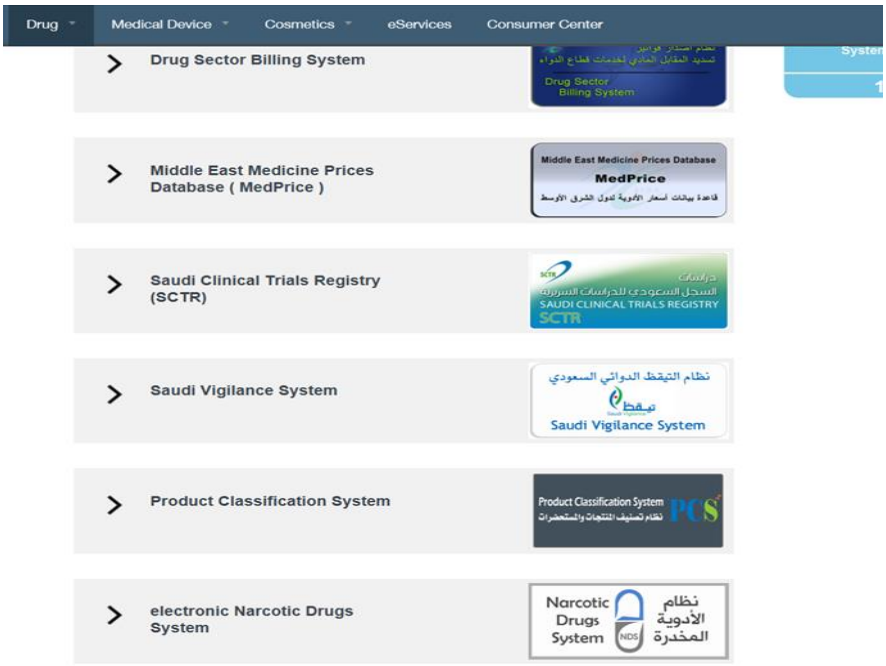
Registration in the "Saudi Vigilance System" would save the reporter time and effort while making data entry more accessible due to enrollment.
As a result, the system would retrieve the registered information, and the reporter will not have to input it again.

Where to find the link for the service?

1. Direct link

   https://ade.sfda.gov.sa/

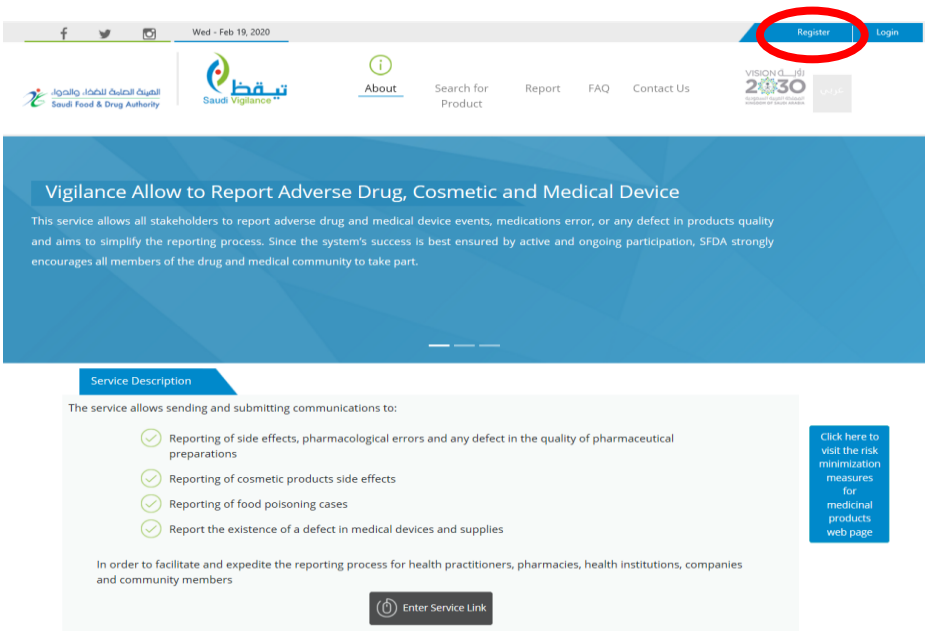
2. OR go to https://www.sfda.gov.sa/en/Pages/default.aspx (SFDA's website)
3. Click on **drug** from the top menu.
4. Click on the **E-services** option.
5. Choose the **"Saudi Vigilance System".**



6. OR google **ADE SFDA**

   - **For organizations**

1- Click the "Register" button on the top of the home page

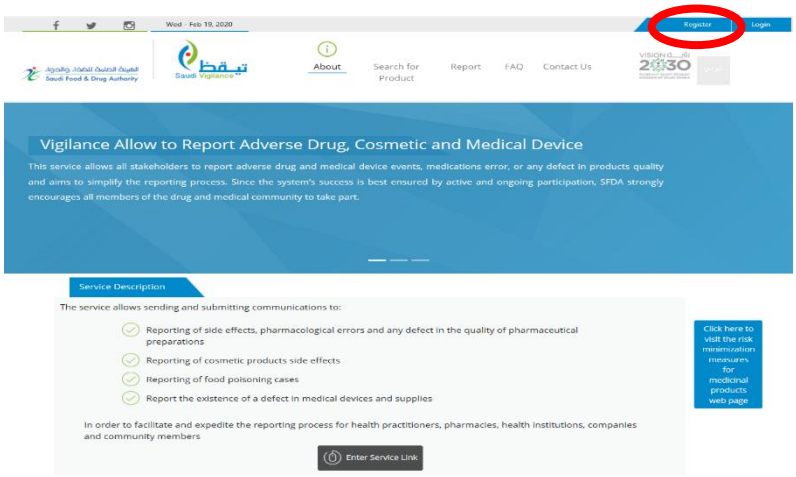


2- Select "Register Organization"

3- Complete the register information, attach the nomination letter, then click "Save"

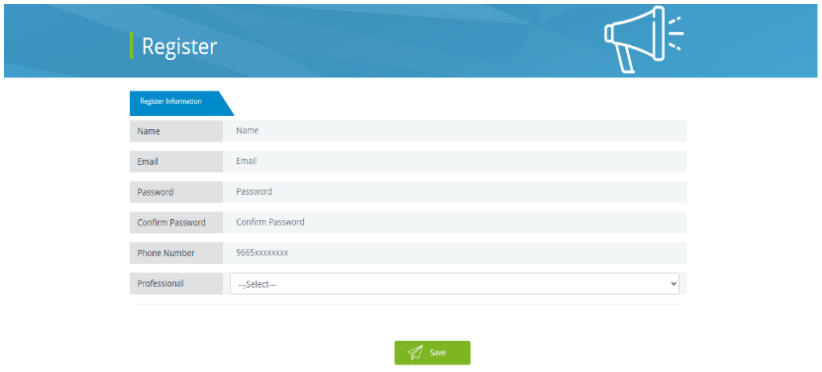
- **For individual user registration**

1- Click the "Register" button on the top of the home page

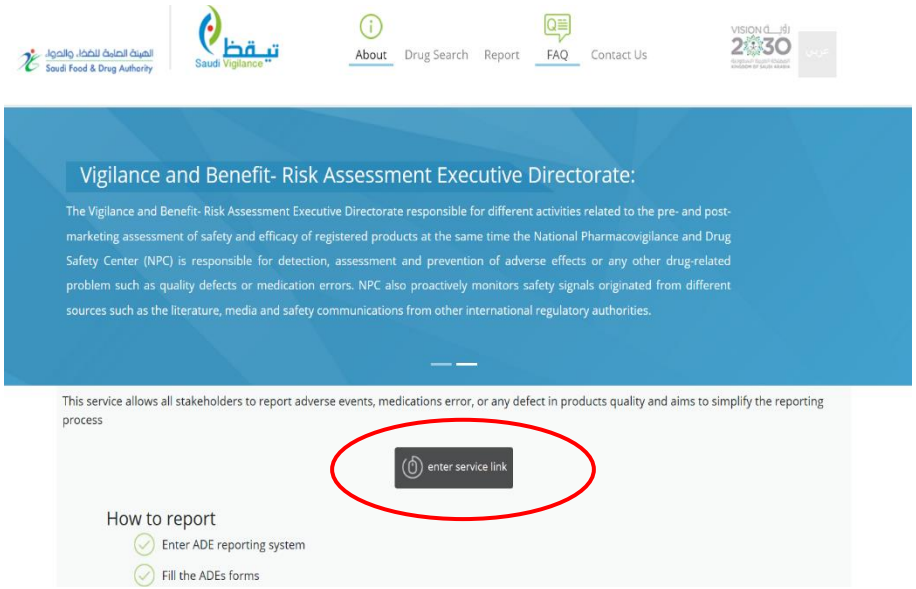


2- Select "individual user"

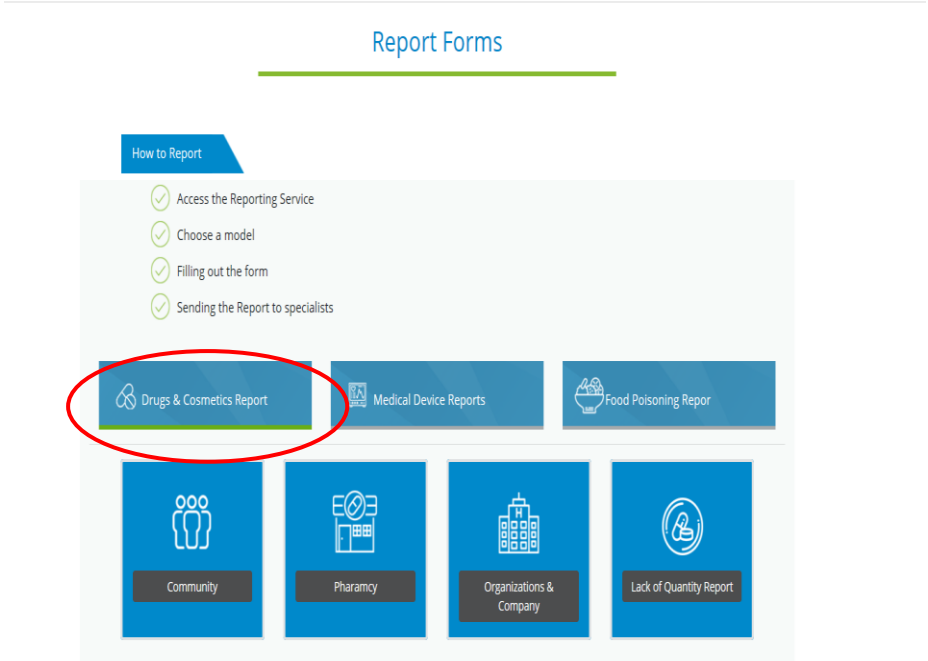
3- Complete the register information then click "Save"



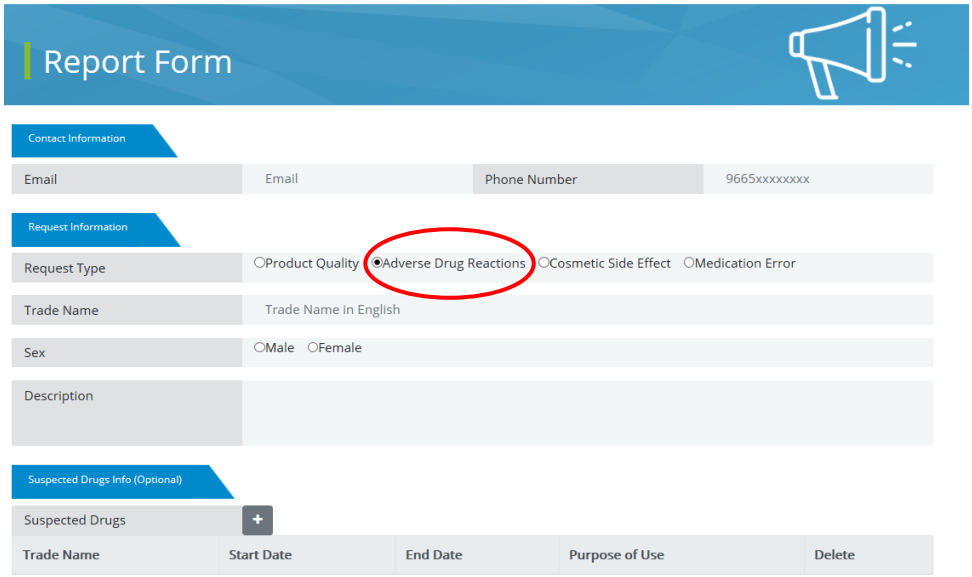
1- Enter the service link



2- Click on "Drugs & Cosmetics Report" icon

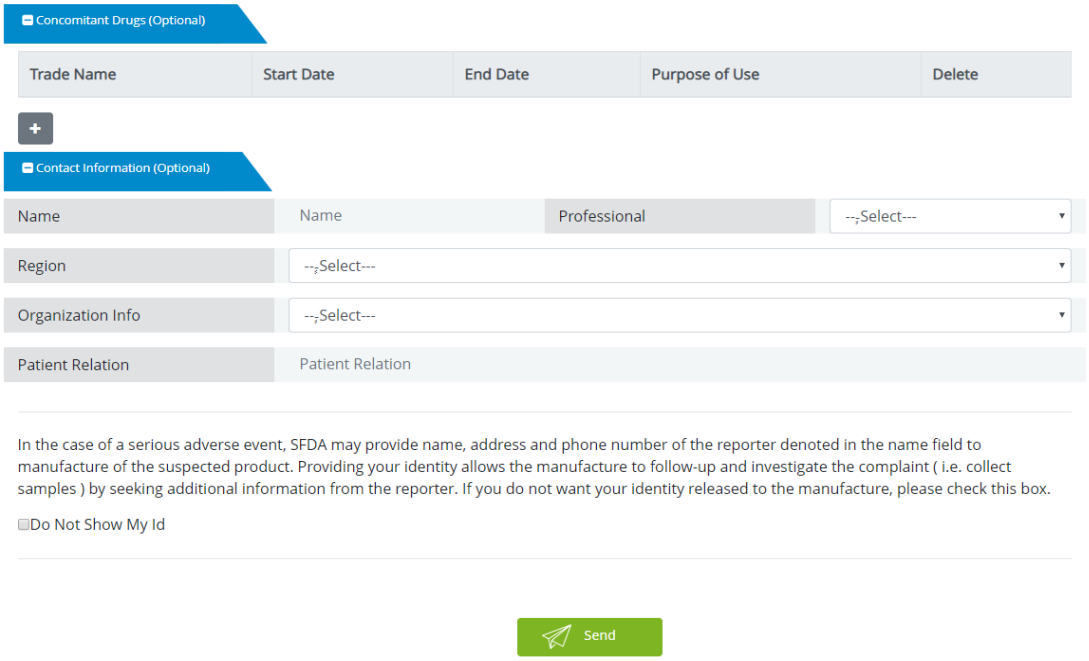


3- Click on "Adverse drug reaction form" in the request type
Alternatively, click other types based on your request



4- Fill out the mandatory fields in the report form

5- Fill out the form and Contact Information then click "Send"


Concomitant Drugs (Optional)
Trade Name
Start Date
End Date
Purpose of Use
Delete
Contact Information (Optional)
Name
Name
Professional
---Select---
Region
---Select---
Organization Info
---Select---
Patient Relation
Patient Relation
In the case of a serious adverse event, SFDA may provide name, address and phone number of the reporter denoted in the name field to manufacture of the suspected product. Providing your identity allows the manufacture to follow-up and investigate the complaint (i.e. collect samples) by seeking additional information from the reporter. If you do not want your identity released to the manufacture, please check this box.
Do Not Show My Id
Send