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ICH Guides*

*This document is a summary of the ICH guidelines developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
The background content is not authored by FIFARMA.

Pharmacovigilance

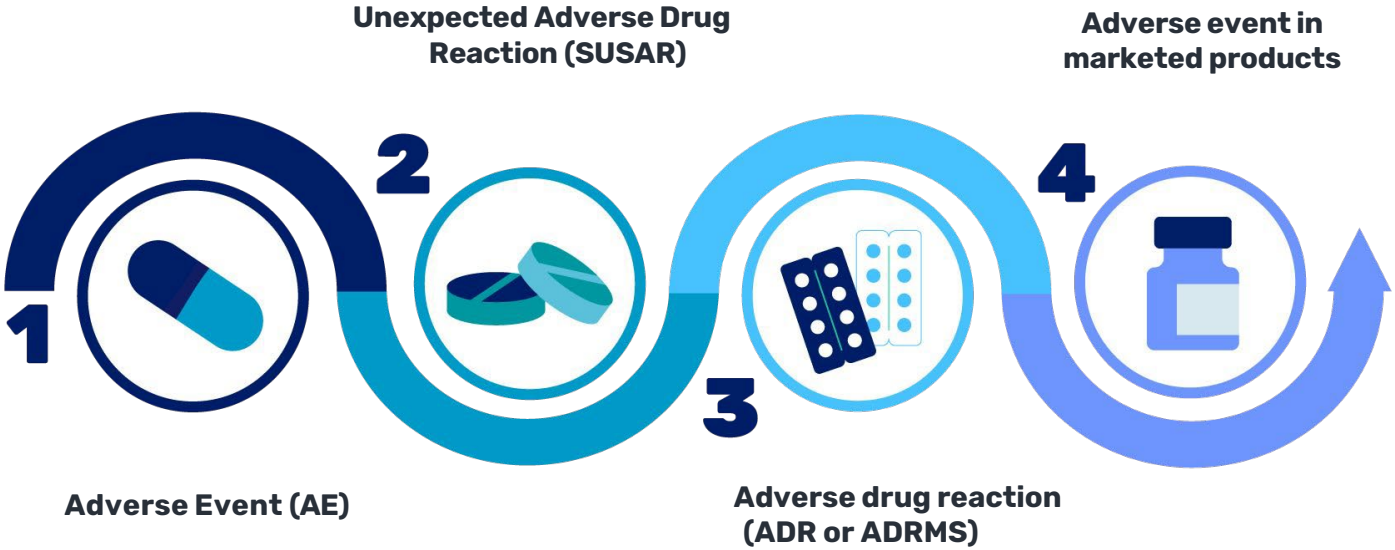
Objective

"To make recommendations to obtain greater harmonization in the interpretation and application of guidelines and technical requirements for **product registration**, with the finds of reducing or avoiding the need for duplication of analyses performed during the research and development of new drugs.“

E2A
E2B
E2C
ICH
E2D
E2E
E2F

E2A

Pharmacovigilance data management:
Definitions and standards for E2A accelerated notification.



E2A

Serious events or adverse drug reactions:

Follow-up in severe, life-threatening cases.

Intensity of a specific effect, which could have minor medical significance.

Based on the results of a life-threatening event.

Severity criterion: any adverse event at any dose that results in death, life-threatening, requires hospitalization, results in disability, incapacity and congenital anomaly.

E2A

Predictability of an adverse drug reaction:

Accelerated notifications to regulators, researchers and consumers.

Expected Effects:

- Medicines that have not been approved for marketing in the country.
- Reports of significant specific or severity information.

Standards for expedited notification:

- Spontaneous Sources .
- Clinical or epidemiological research.
- Cases not reported to the sponsor or manufacturer.

Deadline for submission of reports:

- **Unexpected fatal or life-threatening AMR:** 7 calendar days after the report, followed by a report within 8 calendar days.
- **Unexpected serious adverse reactions (ADRs):** All must be notified, before 15 calendar days.

E2A

Minimum criteria for notification:

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1. Identifiable Patient
2. Suspicious Medicine
3. Identifiable Reporter
4. Event identified as serious and unexpected

CIOMS

CIOMS: Expedited notification of adverse reactions.

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Case management of "Blind Therapy":

Double-blind study → It breaks down.

Miscellaneous Issues:

- **• Reactions associated with active purchaser or placebo treatment:** Sponsor is responsible for notification of adverse reactions and placebo does not meet criteria.

- **Products with more than one presentation or use:** Different dosage forms, formulation and delivery systems of the active ingredients can be studied and marketed for different presentations if there are clinical safety profiles.

- **• Post-study events:** Causality assessment and a decision is made as to whether or not expedited reporting is required.

E2B

Electronic transmission of individual case safety reports.

ICSR

- **Important pre-marketing and post-marketing use of ICSRs.**
- Information focuses on adverse events, patient reactions and all important medical information.
- AE notification methods.

Exchange of information by electronic means (E2B)

E2B → **ICSR**

E2B

Collaborating institutions of the International Drug Monitoring Centers.

01 Regulatory Authorities

02 Ethics Committees

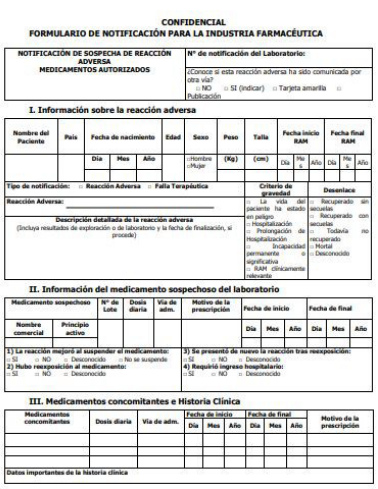
03 Pharmaceutical Companies

04 WHO (World Health Organization)

05 Clinical Researchers

E2B

Notification of adverse effects:



CONFIDENCIAL
FORMULARIO DE NOTIFICACIÓN PARA LA INDUSTRIA FARMACÉUTICA

NOTIFICACIÓN DE SOSPECHA DE REACCIÓN ADVERSA
MEDICAMENTOS AUTORIZADOS

Nº de notificación del Laboratorio:

¿Conoce si esta reacción adversa ha sido comunicada por otra vía?
NO SI (indicar) Tarjeta amarilla
Publicación

I. Información sobre la reacción adversa

Nombre del Paciente	País	Fecha de nacimiento			Edad	Sexo	Peso	Talla	Fecha inicio RAM			Fecha final RAM		
		Día	Mes	Año		Hombre Mujer	(Kg)	(cm)	Día	Mes	Año	Día	Mes	Año

Tipo de notificación: Reacción Adversa Falta Terapéutica

Criterio de gravedad

Desenlace

Reacción Adversa:

Descripción detallada de la reacción adversa
(Incluya resultados de exploración o de laboratorio y la fecha de finalización, si procede)

II. Información del medicamento sospechoso del laboratorio

Medicamento sospechoso		Nº de Lote	Dosis diaria	Vía de adm.	Motivo de la prescripción	Fecha de inicio			Fecha de final		
Nombre comercial	Principio activo					Día	Mes	Año	Día	Mes	Año

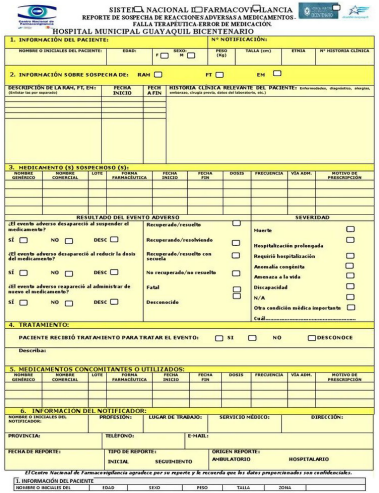
1) La reacción mejoró al suspender el medicamento: SI NO Desconocido No se suspendió
2) Hubo reexposición al medicamento: SI NO Desconocido
3) Se presentó de nuevo la reacción tras reexposición: SI NO Desconocido
4) Requirió ingreso hospitalario: SI NO Desconocido

III. Medicamentos concomitantes e Historia Clínica

Medicamentos concomitantes	Dosis diaria	Vía de adm.	Fecha de inicio			Fecha de final			Motivo de la prescripción
			Día	Mes	Año	Día	Mes	Año	

Datos importantes de la historia clínica

CIOMS Reports



SISTEMA NACIONAL DE FARMACOVIGILANCIA
REPORTE DE SOSPECHA DE REACCIONES ADVERSAS A MEDICAMENTOS.
FALLA TERAPEUTICA ERROR DE MEDICACION
HOSPITAL MUNICIPAL GUAYAQUIL BICENTENARIO

1. INFORMACIÓN DEL PACIENTE:
Nº NOTIFICACIÓN:
NOMBRE O INICIALES DEL PACIENTE: EDAD: SEXO F M PESO (KG) TALLA (cm) ETNIA Nº HISTORIA CLÍNICA

2. INFORMACIÓN SOBRE SOSPECHA DE: RAM FT EM

DESCRIPCIÓN DE LA RAM, FT, EM: FECHA INICIO FECHA ALTA HISTORIA CLÍNICA RELEVANTE DEL PACIENTE:

3. MEDICAMENTO (S) SOSPECHOSO (S):
NOMBRE GENÉRICO NOMBRE COMERCIAL LOTE FORMA FARMACÉUTICA FECHA INICIO FECHA FIN DOSIS FRECUENCIA VÍA ADM. MOTIVO DE PRESCRIPCIÓN

RESULTADO DEL EVENTO ADVERSO
¿El evento adverso desapareció al suspender el medicamento? SÍ NO DESC
¿El evento adverso desapareció al reducir la dosis del medicamento? SÍ NO DESC
¿El evento adverso reapareció al administrar de nuevo el medicamento? SÍ NO DESC
Recuperado/resuelto
Recuperado/resolviendo
Recuperado/resuelto con secuela
No recuperado/no resuelto
Fatal
Desconocido

SEVERIDAD
Muerte
Hospitalización prolongada
Requirió hospitalización
Anomalía congénita
Amenaza a la vida
Discapacidad
N/A
Otra condición médica importante
Cuál

4. TRATAMIENTO:
PACIENTE RECIBIÓ TRATAMIENTO PARA TRATAR EL EVENTO: SI NO DESCONOCE
Describa:

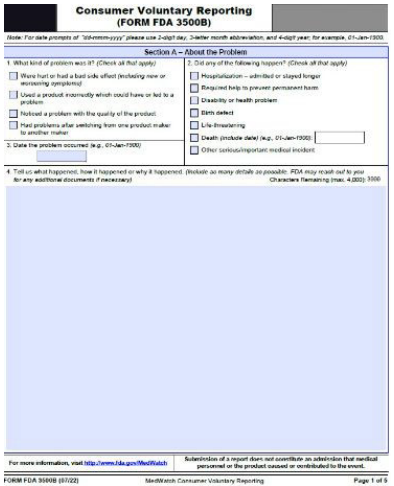
5. MEDICAMENTOS CONCOMITANTES O UTILIZADOS:
NOMBRE GENÉRICO NOMBRE COMERCIAL LOTE FORMA FARMACÉUTICA FECHA INICIO FECHA FIN DOSIS FRECUENCIA VÍA ADM. MOTIVO DE PRESCRIPCIÓN

6. INFORMACIÓN DEL NOTIFICADOR:
NOMBRE O INICIALES DEL NOTIFICADOR: PROFESIÓN: LUGAR DE TRABAJO: SERVICIO MÉDICO: DIRECCIÓN:
PROVINCIA: TELÉFONO: E-MAIL:
FECHA DE REPORTE: TIPO DE REPORTE: INICIAL SEGUIMIENTO ORIGEN REPORTE: AMBULATORIO HOSPITALARIO

El Centro Nacional de Farmacovigilancia agradece por su reporte y le recuerda que los datos proporcionados son confidenciales.

1. INFORMACIÓN DEL PACIENTE
NOMBRE O INICIALES DEL EDAD SEXO PESO TALLA ZONA

Yellow Card



Consumer Voluntary Reporting
(FORM FDA 3500B)

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jan-1900.

Section A – About the Problem

1. What kind of problem was it? (Check all that apply)
Were hurt or had a bad side effect (including new or worsening symptoms)
Used a product incorrectly which could have or led to a problem
Noticed a problem with the quality of the product
Had problems after switching from one product maker to another maker

2. Did any of the following happen? (Check all that apply)
Hospitalization – admitted or stayed longer
Required help to prevent permanent harm
Disability or health problem
Birth defect
Life-threatening
Death (include date) (e.g., 01-Jan-1900)
Other serious/important medical incident

3. Date the problem occurred (e.g., 01-Jan-1900)

4. Tell us what happened, how it happened or why it happened. (Include as many details as possible. FDA may reach out to you for any additional documents if necessary)
Characters Remaining (max. 4,000): 3000

For more information, visit http://www.fda.gov/MedWatch
Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

FORM FDA 3500B (07/22) MedWatch Consumer Voluntary Reporting Page 1 of 5

Medwatch Forms

E2B

Advantages of ICSRs

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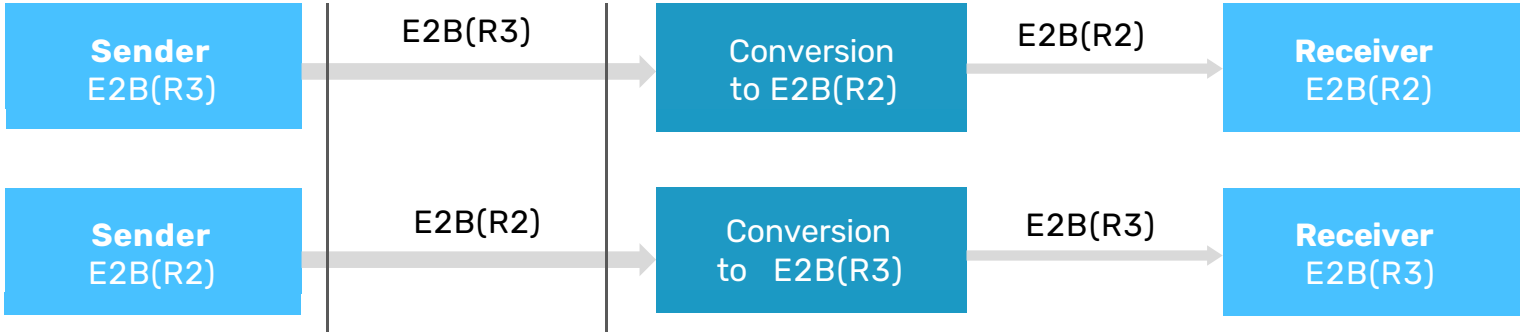
- Processing of information from **different documents** (adverse reaction cases).
- **Increased collection and analysis** of pharmacovigilance reports.
- **Rapid evidence** of adverse reaction reports.
- Identification and evaluation of **serious problems**.
- Dissemination of security information.
- **Cost reduction.**
- Improved **Global Pharmacovigilance.**

E2B

XML is a text-based, portable, non-proprietary, non-proprietary format used in different pharmacovigilance platforms around the world.

Conversion from E2B(R2) a E2B(R3)



Recommendations for E2B case changes

Date format (with two separate fields), code mappings, deletion, addition, field length, masking and structure.

E2C

Periodic performance and risk assessment report (PBRER).

- Safety and eficiency.
- Benefit-risk assessment of marketed products is performed.

General Principles

PBRER in different presentations:

- Active Substance.
- Combined Products.
- Products manufactured and/or marketed for a company.

Scope of application of the PBRER

Eficacia/effectiveness from dates such as:

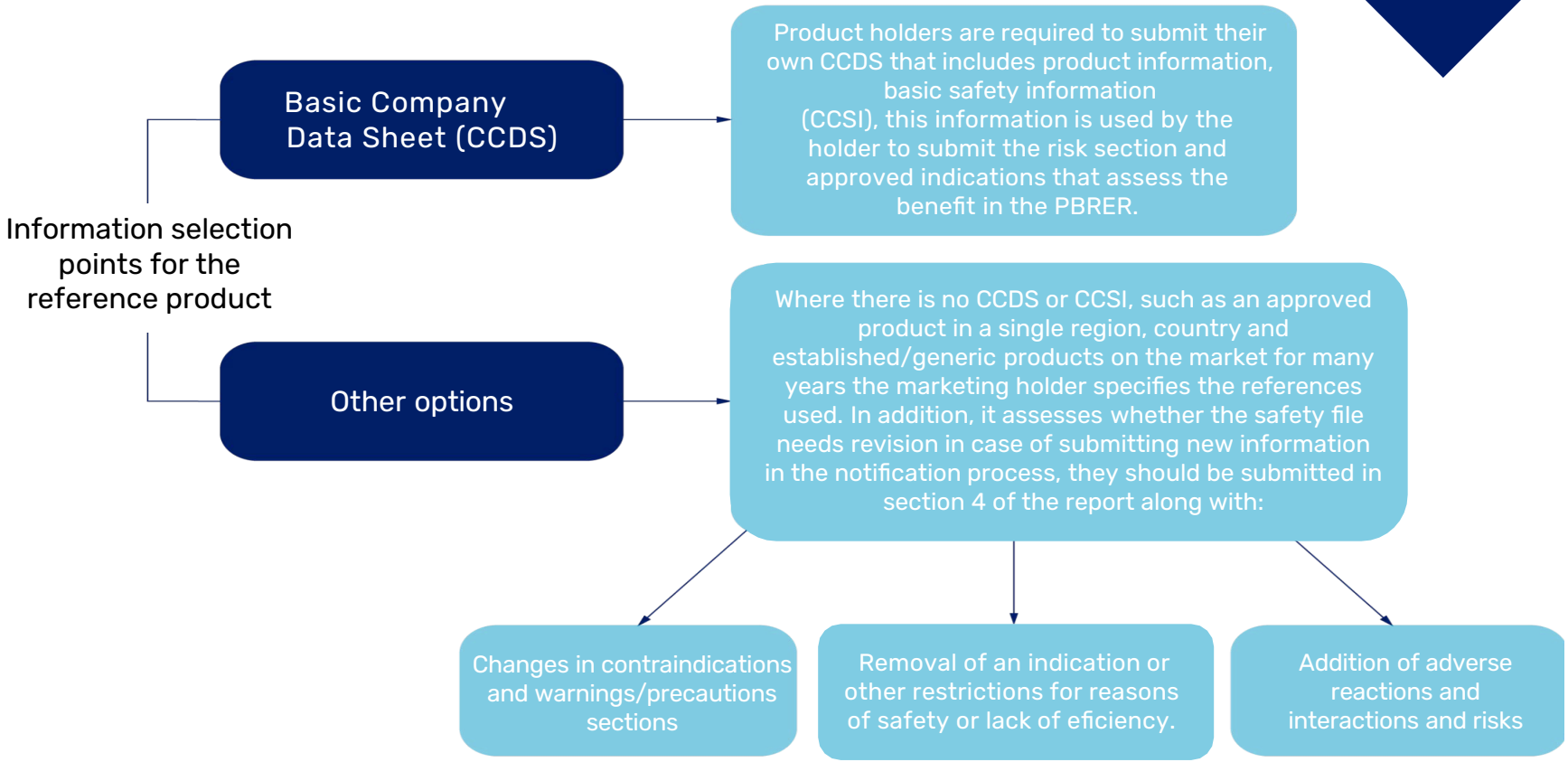
- International Birth Certificate (IBD).
- International Development Bank (DIBD).

Relationship of the PBRER with other ICH documents

PSUR ---
DSUR

E2C

Points to be taken into account by health care waste managers for the selection of reference product information in the PBRER report



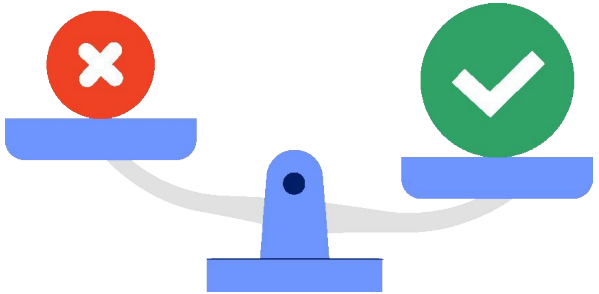
E2C

Efficiency and effectiveness

- **Efficiency:** Evidence of benefits in controlled clinical trials.
- **Effectiveness:** Daily medical practice.

Benefit-risk assessment

The benefit is expected to outweigh the risk.



Period and data blocking points

- **Date from date of birth international and point of lock from data:**
  - International date of birth and data blocking point:
- **• PBRER submission frequencies: Periodic reports of 6 months or more.**

E2C

Ad hoc reports (for cause)

Reports that fall outside of routine reporting.

Time interval between data lock point and presentation:

Interval	Calendar days
6-12 months	70d
12 months	90d
Ad hoc	90d *
DLP (Day 0)	70-90d

***Unless otherwise specified *.**

E2C

PBRER format and presentation

Cover

Index Summary

- Introduction
- Worldwide marketing authorization.
- Notification interval measurements for safety.
- Changes in reference safety information.
- Estimated exposure and usage patterns
- Data from summary tables.
- Summaries of safety findings from clinical trials during the notification interval.
- Results of non-interventional studies.
- Information from other clinical trials and source.
- Non-clinical data
- Literature
- Other periodic reports
- Lack of efficiency in controlled clinical trials.
- Last minute information
- Summary of signals: new, in progress or closed.

E2C

PBRER format and presentation

- Signal and risk assessment
- Evaluation of presentations
- Integrated benefits and risks analysis for approved indications.
- Conclusions and actions
- Summary of security issues

E2D

Post-approval safety data management definitions and standards for accelerated reporting.

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Sources of safety reports in individual cases:

Unsolicited sources:

- Spontaneous reports
- Literature
- Internet
- Other sources

Sources requested

- Contractual Agreements
- Regulatory Authority Sources

E2D

Accelerated reporting standards

Aspects to be reported

- **Serious ADR**: Their notification is rapid and varies between countries. All cases that are reported by healthcare professionals fall into this category.
- **Remarks**: Any report that changes the benefit-risk relationship must be communicated to the Regulatory Authorities.
- **Lack of efficiency**: Any report that changes the benefit-risk relationship must be communicated to the Regulatory Authorities.
- **Overdose**: If it has no associated AE they should not be notified as accelerated and conversely. The owner is responsible for the collection of information.

E2D

Minimum reporting criteria

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- **Deadlines for reporting:** Serious and unexpected RAMs should be notified as soon as possible, within 15 calendar days.
- **RAM no Graves:** They should be included in the periodic safety report.
- **Good case management practices:** The information must be presented accurately, completely and authentically in order for the holder and the regulatory authorities to evaluate the ADR reports.
- **Patient and reporter identification assessment:** Identifiable when they present; age, sex, initials, date of birth, name, ID.
- **Narrative:** Summarizes all the important information of the case, including the patient's experiences.
- **Clinical Case Evaluation:** It is expected that adverse reaction case information will be reported by a health care professional, the recipient should carefully review the report for quality and completeness.

Tracking information

When ADR cases are received, the information is usually incomplete, so more information should be sought, and reports should be prioritized according to their importance:

- Serious and expected.
- Serious and unexpected.
- Not serious and unexpected

Exposure during pregnancy: The embryo or fetus exposed to drugs.

How should it be reported? There is no standard way, the most commonly used is the CIOMS form.

E2E

Pharmacovigilance Plan
Focus on the planning of a post-marketing Pharmacovigilance plan for medicines.

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It consists of three sections:

1. **Safety specifications:** It summarizes important risks, potential risks, missing drug information, populations at risk.

2. **Specification Elements:** Nonclinical and Clinical (Database limitations, population studied in pre-approval phase, AEs and RAMs, identified and potential interactions, epidemiology and pharmacological class effects.

3. **Pharmacovigilance Plan.**

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Pharmacovigilance plan → **Summarizes the different risks (identified, potential and missing information)**

Routine Pharmacovigilance Practices

- Security action plan
- Summary of actions to be taken, including milestones.
- Pharmacovigilance Methods

They are divided in two:

Passive surveillance:

- Spontaneous reports
- Case Series
- Stimulated reports

Active Surveillance:

- Sentinel Sites
- Drug event monitoring
- Registrations

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Design and conduct of observational studies

- Comparative Observational Studies:
  - Transversal
  - Cases and controls
  - Cohort
- *Descriptive Studies*
- Directed Clinical Investigations:
  - Nature of the disease
  - Drug utilization (DSU)

E2F

Development Security Update Report (DSUR)

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The primary purpose of DSURs is to present a comprehensive and reflexive annual review and evaluation of safety information collected during the notification period, marketed or not.

Scope of application of the DSUR

It focuses on the presentation of data and results of interventional clinical trials of drugs and biological products in the research phase, whether or not they have been approved for marketing, as well as all relevant information from post-marketing studies.

Relationship of the DSUR to the Periodic Security Update Report (PSUR). → DSURs can overlap with PSURs

E2F

DSUR Benefits - Annual Report

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General Principles

- **Single DSUR for an active substance:** A single report for all indications and patient populations under study with the investigational drug.
- **Periodicity and blocking point of DSUR data:** The start of the annual period for the DSUR is the month and date of the DIBD, the DSUR data lock point is the last day of the one-year notification period, it is prefered to be the last day of the month prior to the month of the DIBD.
- **Duration of DSUR presentation:** As required by the authorities.
- **DSUR for combination therapies:** Sponsor has to take the criteria according to drug characteristics justified in the report, a single DSUR report must be prepared.
- **Reference safety information:** The Investigator's Brochure (IB) is used.

E2F

DSUR Content

- Cover
- Executive Summary
- Index
- Introduction
- Marketing Authorization
- Actions taken in the reporting period
- Changes in reference safety information.
- Interval of clinical trials in use and finalized during the reporting period.
- Estimated cumulative exposure
- Data in line listing and recapitulated tabulations.
- Significant results of clinical trials during the reporting period.
- Safety results from non-interventional studies.
- Other safety information from clinical trials/studies.
- Safety conclusions
- Non-clinical data
- Literature
- Other DSUR
- Lack of efficiency
- Region-specific information
- Last minute information
- Global security assessment
- Summary of significant risks
- Conclusions

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