INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

# Drug Safety - Pharmacovigilance: A Review

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ARTICLE INFO

Published: 10 Aug 2025
Keywords:
Drug Safety, PV, ADR, AI.
DOI:
10.5281/zenodo.16789208

## ABSTRACT

Pharmacovigilance (PV), also referred to as drug safety, encompasses the science and activities involved in detecting, assessing, understanding, and preventing adverse drug reactions (ADRs) and other drug-related issues1. As the global consumption of pharmaceutical products continues to rise, the importance of robust pharmacovigilance systems in ensuring drug safety has become increasingly critical. This review explores the evolution of pharmacovigilance, its global regulatory framework, and the methodologies employed in monitoring drug safety. It emphasizes the contributions of healthcare professionals, patients, and regulatory authorities in reporting ADRs, alongside the incorporation of advanced technologies such as big data analytics, artificial intelligence, and social media monitoring to enhance pharmacovigilance practices13. The review also addresses key challenges, including underreporting, data quality issues, and the growing complexity of new drug formulations. Looking ahead, the future of pharmacovigilance is expected to involve the adoption of more advanced signal detection techniques, enhanced patient-centered approaches, and greater international collaboration to strengthen drug safety on a global scale. This article aims to provide a comprehensive overview of pharmacovigilance and reporting requirements in several countries.

## INTRODUCTION

Pharmacovigilance (PV), often referred to as drug safety, is the branch of pharmacological science focused on detecting, assessing, understanding, and preventing adverse effects, including both short-term and long-term side effects of medications. As an essential component of clinical research, PV plays a pivotal role in ensuring the safety and efficacy of pharmaceutical products.[1]

A significant global challenge in pharmacovigilance is the underreporting of adverse drug reactions (ADRs), often attributed to

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

constraints like limited time and inadequate access to reporting forms. Recognizing this issue, the World Health Organization (WHO) initiated a program to promote the reporting of all drug-related adverse reactions. Over time, the scope of pharmacovigilance has expanded to encompass herbal medicines, traditional and complementary therapies, blood products, biologicals, medical devices, and vaccines.

The core functions of PV include the identification, quantification, and documentation of drug-related problems to prevent drug-induced harm. In India, national pharmacovigilance programs have been in place since 2005, aiming to raise public awareness about drug safety and enhance reporting practices. This review underscores the critical importance of pharmacovigilance in the daily lives of healthcare professionals, patients, and the pharmaceutical industry, as well as the reporting requirements in several countries.[10,12]

## I. Importance of Pharmacovigilance (PV)

Pharmacovigilance (PV) is a scientific discipline dedicated to studying the efficacy of drugs while monitoring their adverse effects. It involves understanding and explaining the complex nature of adverse drug reactions (ADRs) that may occur in patients receiving medications through oral, parenteral, or intravenous (I.V.) routes for various ailments.[17]

Before being marketed globally, drugs undergo extensive testing, including clinical trials in animals and human subjects, to evaluate their safety and identify potential side effects. However, despite these rigorous assessments, certain ADRs remain undetected until the post-marketing phase. This phase, often referred to as post-marketing surveillance, plays a critical role in identifying rare or long-term side effects that may not have been apparent during clinical trials.

ADRs significantly impact patient health by reducing quality of life, prolonging hospital stays, and increasing mortality rates. A landmark study by Lazarou et al. (1998) revealed that ADRs ranked as the fourth to sixth leading cause of death in the United States. The study further estimated that ADRs accounted for 3–7% of all hospital admissions, highlighting the urgent need for robust pharmacovigilance systems to ensure drug safety and minimize risks.[18]

## II. Need of Pharmacovigilance

Pharmacovigilance is an essential component of public health and safety, primarily focused on monitoring and improving the safety of medicines after they have been approved and released to the market. The need for pharmacovigilance arises from the fact that, despite rigorous testing in clinical trials, adverse effects or unforeseen risks can still emerge once a medicine is widely used by diverse populations over extended periods of time. Here are some key reasons highlighting the need for pharmacovigilance;[19]

### 1. Identification of Adverse Drug Reactions (ADRs) and Safety Signals

- **Unpredictable ADRs:** Clinical trials often involve a controlled, smaller population under specific conditions, which may not capture rare or long-term side effects that could appear when a drug is used in the broader, more diverse population.
- **Safety Signals:** Pharmacovigilance helps in detecting emerging safety signals that were not identified during pre-market trials, allowing for early intervention and minimizing harm.

**2. Real-World Evidence and Post-Marketing Surveillance**

- **Diverse Populations:** After approval, medicines are prescribed to a much broader population with varying age groups, comorbidities, and genetic factors. Pharmacovigilance collects data on how drugs perform in real-world settings, helping to identify adverse events that may not be apparent in clinical trials.
- **Long-Term Monitoring:** Some adverse effects may take years to manifest, such as carcinogenicity or reproductive toxicity. Ongoing surveillance through pharmacovigilance ensures that such risks are monitored over the long term.

**3. Risk Management and Minimization**

- **Risk Mitigation Strategies:** Pharmacovigilance is crucial for developing and implementing risk management plans (RMPs) to minimize known risks, such as dose adjustments, labeling changes, or contraindications. These strategies ensure that patients can still benefit from the drug while minimizing potential harm.
- **Product Recalls and Warnings:** When new safety information emerges, pharmacovigilance enables the timely recall of dangerous products, issuance of warnings, or modifications to drug labels to protect public health.

**4. Public Health Protection**

- **Reducing Public Health Burden:** Pharmacovigilance helps to minimize the number of people affected by ADRs, hospitalization, and fatalities due to unsafe drugs. This reduces the overall burden on healthcare systems, protecting both individual and public health.
- **Preventing Harm:** By identifying problematic drugs or drug interactions, pharmacovigilance contributes to preventing adverse effects that could have significant impacts on the population, especially vulnerable groups like children, the elderly, and pregnant women.

**5. Informing Regulatory Decisions**

- **Regulatory Oversight:** Pharmacovigilance provides essential data to health authorities (like the FDA, EMA, TGA) to inform their regulatory decisions. This can include modifying drug approvals, suspending or withdrawing products, or recommending new safety measures.
- **Labeling Updates and Risk Communication:** Based on the data collected, health authorities can update drug labels, communicate new safety information to healthcare professionals, and take necessary actions to prevent harm.

**6. Optimizing Drug Use**

- **Safe and Effective Prescribing:** Pharmacovigilance helps healthcare professionals to make informed decisions by providing them with accurate, up-to-date information about drug safety. It aids in determining which drugs are most suitable for specific patient populations, ensuring that they benefit from the most effective and safest treatments.
- **Reducing Medication Errors:** By monitoring drug interactions and other safety concerns, pharmacovigilance reduces the risk of medication errors and helps to ensure that drugs are used correctly.

**7. Ensuring Quality of Medicines**

- **Ensuring Drug Efficacy:** Pharmacovigilance also helps in ensuring that medicines continue to provide the intended therapeutic benefits and are free from unacceptable adverse effects once marketed.
- **Pharmaceutical Quality Control:** Pharmacovigilance involves monitoring the production and quality of medicines, detecting quality defects, and ensuring that substandard or counterfeit drugs are identified and removed from the market.

**8. Contributing to Global Safety and Public Confidence**

- **Global Safety Monitoring:** Pharmacovigilance systems enable the sharing of safety data across countries, contributing to the global safety monitoring of medicines. It helps build a global network for tracking the safety of drugs and sharing best practices.
- **Building Trust:** By demonstrating a commitment to drug safety and transparency, pharmacovigilance increases public confidence in healthcare systems and in the regulatory processes that ensure the safety of medicines.

**9. Facilitating Drug Development and Improvement**

- **Feedback for Drug Developers:** Data collected through pharmacovigilance can help pharmaceutical companies improve existing drugs or develop safer and more effective treatments. It can inform drug development processes by identifying gaps in safety data.
- **Post-Marketing Studies:** It can also contribute to designing and conducting post-marketing studies (Phase IV trials) to further explore the long-term effects and new therapeutic uses of existing drugs.

**10. Legal and Ethical Obligations**

- **Regulatory Compliance:** Health authorities across the world require pharmaceutical companies to monitor and report adverse events as part of their legal and ethical obligations. Pharmacovigilance ensures that these obligations are met and helps companies comply with local and international regulations.
- **Patient-Centered Approach:** Pharmacovigilance is ultimately focused on protecting patients, ensuring that the use of medicines does not cause avoidable harm and that patient safety is prioritized in healthcare systems.[4 11]

## III. Aims of Pharmacovigilance

The aims of pharmacovigilance are centered on ensuring the safety and efficacy of medicines and medical products throughout their lifecycle. It involves the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug-related problems. The ultimate goal is to safeguard public health and provide valuable information for healthcare decision-making.[3]

Here are the key aims of pharmacovigilance:

**1. Monitoring Drug Safety**

- **Detection of Adverse Drug Reactions (ADRs):**
  - Identify and monitor ADRs and other adverse effects associated with the use of medicines and vaccines, particularly those that may not have been detected during clinical trials.
- **Early Identification of Safety Signals:**

- Gather data to detect early signs of potential risks and safety issues that may arise once a drug or vaccine is widely used in the population.

**2. Ensuring Public Health Safety**

- **Minimizing Harm to Patients:**
- Ensure that adverse effects or drug interactions do not lead to preventable harm, hospitalization, or fatalities by monitoring and controlling risks.
- **Prompt Action on Safety Concerns:**
- Take timely regulatory actions, such as issuing warnings, updating product information, and recalling products if necessary, to reduce public exposure to unsafe products.

**3. Providing Data for Regulatory Decisions**

- **Informed Decision-Making:**
- Provide healthcare regulators (such as the FDA, EMA, TGA, Health Canada) with data and insights to help make informed decisions on the safety, efficacy, and risk-benefit balance of a medicine.
- **Support Regulatory Changes:**
- Facilitate adjustments in the approved use of drugs, including dosage changes and contraindications based on emerging safety data.

**4. Supporting Risk Management and Risk Minimization**

- **Risk Communication:**
- Effectively communicate identified risks to healthcare professionals and patients, ensuring they understand potential risks and how to mitigate them.
- **Risk Mitigation Strategies:**
- Implement strategies like Risk Minimization Plans (RMPs), Risk Communication Plans, and safety studies to reduce or manage identified risks.

**5. Improving Drug Development**

- **Enhancing Drug Safety Profiles:**
- Contribute to improving the safety profile of drugs by collecting real-world data on ADRs, helping refine product formulations or guide dose adjustments.
- **Post-Marketing Surveillance:**
- Conduct post-marketing surveillance to monitor the safety and efficacy of drugs and vaccines in the general population, identifying rare or long-term side effects not observed during clinical trials.

**6. Educating Healthcare Providers and the Public**

- **Healthcare Provider Awareness:**
- Educate healthcare professionals about new safety information, emerging risks, and how to report ADRs, ensuring they have the latest safety data when prescribing medications.
- **Public Education:**
- Raise public awareness about the importance of reporting ADRs and the role of pharmacovigilance in ensuring medicine safety.

**7. Promoting Safe Use of Medicines**

- **Optimizing Drug Use:**
- Encourage appropriate use of medicines by analyzing data and providing recommendations on safe prescribing practices, especially in vulnerable populations such as children, the elderly, and pregnant women.

**8. Contributing to Global Pharmacovigilance Efforts**

- **Collaboration with Global Bodies:**
  - Work with international organizations such as the World Health Organization (WHO) and regulatory agencies in different countries to standardize pharmacovigilance practices and share safety data globally.
- **Global Surveillance Networks:**
  - Contribute to international drug safety monitoring systems (e.g., WHO's VigiBase) to enhance the global safety profile of medicines.[1, 3 19]

**. Facilitating Drug Development and Improvement**

- **Feedback for Drug Developers:** Data collected through pharmacovigilance can help pharmaceutical companies improve existing drugs or develop safer and more effective treatments. It can inform drug development processes by identifying gaps in safety data.
- **Post-Marketing Studies:** It can also contribute to designing and conducting post-marketing studies (Phase IV trials) to further explore the long-term effects and new therapeutic uses of existing drugs.

**10. Legal and Ethical Obligations**

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## IV. ICSR reporting requirements in few countries;

### A. ICSR reporting requirement in the USA:

Individual Case Safety Report (ICSR) reporting requirements for the **U.S. Food and Drug Administration (FDA)** are outlined in various regulatory guidelines under the **Code of Federal Regulations (CFR)**, primarily 21 CFR Parts 310, 314, 600, and 803. These regulations cover the reporting of adverse events for drugs, biologics, and medical devices. Below are the key points regarding ICSR reporting requirements for the FDA: [2]

**1. Who Must Report?**

- **Manufacturers**: Holders of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs).
- **Importers and distributors**: For medical devices.
- **Healthcare professionals and consumers**: May voluntarily report adverse events through the FDA's MedWatch system.

**2. What Should Be Reported?**

- Any **adverse events** (AEs) or **suspected adverse events** associated with the use of drugs, biologics, or devices.
- Special attention is required for **serious and unexpected adverse events**.

**Definitions:**

- **Serious Adverse Event (SAE):** Includes death, life-threatening events, hospitalization, disability, or congenital anomaly.
- **Unexpected Adverse Event:** An event not consistent with the product's labeling.

**3. Reporting Timelines**

- **Serious and unexpected adverse events**:
  - Must be reported to the FDA **as soon as possible but no later than 15 calendar days** from the date the manufacturer or distributor first becomes aware of the event.
- **Follow-up reports**:
  - Must be submitted **as new information becomes available** and within **15 calendar days** of obtaining this information.
- **Non-serious adverse events**:
  - Typically reported in **Periodic Adverse Drug Experience Reports (PADERs)** or **Periodic Safety Update Reports (PSURs)**.

**4. How to Report?**

- Reports are submitted through the **FDA Adverse Event Reporting System (FAERS)** or **Vaccine Adverse Event Reporting System (VAERS)** for vaccines.
- Electronic submissions via the **Electronic Submissions Gateway (ESG)** are required for:
  - Individual Case Safety Reports (ICSRs).
  - ICSR Attachments (e.g., medical records, laboratory results).

**Tools:**

- **FAERS**: Used for drugs and biologics.
- **eSubmitter**: FDA tool for preparing electronic submissions.

**5. Required Documentation in ICSRs**

- Patient information (age, gender, medical history).
- Description of the adverse event, including dates and outcomes.
- Product information (name, dose, route, lot number).
- Reporter information (healthcare professional, patient, or consumer).

**6. Legal and Regulatory Requirements**

- **21 CFR 314.80**: Post-marketing reporting of adverse drug experiences.
- **21 CFR 600.80**: Reporting for biologics.
- **21 CFR 803**: Medical device reporting (MDR).
- Compliance with these regulations is mandatory, and failure to report can result in enforcement actions, fines, or license revocation.[2],

**B. ICSR reporting requirement in china;**

In China, Individual Case Safety Report (ICSR) reporting is governed by the **National Medical Products Administration (NMPA)** under the framework of the **Good Pharmacovigilance Practice (GVP)** guidelines, which came into effect on December 1, 2021.[20]

**Global Regulatory Partners**

**Key Aspects of ICSR Reporting in China:**

1. **Who Should Report?**

- **Marketing Authorization Holders (MAHs):** Responsible for establishing and maintaining pharmacovigilance systems to monitor the safety of their products
- **Healthcare Professionals and Consumers:** Encouraged to report adverse drug reactions (ADRs) to enhance drug safety monitoring.

2. **What Should Be Reported?**

- All **adverse drug reactions (ADRs)**, with a focus on serious and unexpected events.
- **Serious Adverse Events (SAEs):** Events that result in death, are life-threatening, require hospitalization, or cause significant disability.[20,12]

3. **Reporting Timelines:**

- **Serious and Unexpected ADRs:** Must be reported **immediately**, generally within **15 days** of awareness.
- **Non-Serious ADRs:** Should be documented and reported periodically as per regulatory requirements.

4. **How to Report?**

- Reports are submitted electronically to the NMPA through designated reporting systems.
- MAHs are required to utilize standardized formats, such as the **XML format** for ICSRs, ensuring compatibility with the NMPA's data systems.

National Medical Products Administration

5. **Legal and Regulatory Framework:**

- The **Good Pharmacovigilance Practice (GVP)** guidelines provide a comprehensive framework for pharmacovigilance activities in China.

China PV Hub

- The NMPA conducts inspections to ensure compliance with pharmacovigilance obligations, as outlined in the **Pharmacovigilance Inspection Guidelines**.

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Adherence to these requirements is crucial for ensuring drug safety and maintaining regulatory compliance within China's pharmaceutical,[21,12]

**C. ICSR reporting requirement in the India**

In India, **Individual Case Safety Report (ICSR)** reporting requirements are governed by the **Pharmacovigilance Programme of India (PvPI)** under the supervision of the **Central Drugs Standard Control Organization (CDSCO)**. These regulations align with **Schedule Y** of the **Drugs and Cosmetics Rules, 1945**, and ensure the monitoring of adverse drug reactions (ADRs) and safety signals.[5]

**1. Who Must Report?**

- **Marketing Authorization Holders (MAHs):**
  - Pharmaceutical companies licensed to market drugs in India.
- **Healthcare Professionals:**
  - Doctors, nurses, and pharmacists are encouraged to report ADRs.
- **Consumers and Patients:**
  - Voluntary reports can also be submitted to PvPI.

**2. What Needs to Be Reported?**

- **Serious Adverse Events (SAEs):**
  - Death, life-threatening conditions, hospitalization, disability, or congenital anomalies.
- **Unexpected ADRs:**
  - Reactions not consistent with product labeling or expected outcomes.
- **Other ADRs:**
  - Non-serious adverse events, which can be included in periodic reports.

**3. Reporting Timelines**

- **Serious Adverse Events (SAEs):**
  - Must be reported **within 14 calendar days** of awareness by the MAH or healthcare professional.
- **Clinical Trial ADRs:**
  - SAEs during clinical trials must be reported **immediately**, with a detailed report submitted within **14 calendar days**.
- **Non-serious ADRs:**
  - These are generally reported in **Periodic Safety Update Reports (PSURs)**.

**4. How to Report?**

- **Submission Platforms:**
  - Reports can be submitted to the **Indian Pharmacopoeia Commission (IPC)** or **CDSCO** through:
1. **VigiFlow:** A web-based tool for ICSRs.
2. **ADR Reporting Form:** Available on the PvPI website.
3. **Email or Post:** ADR reporting forms can be sent to regional pharmacovigilance centers or directly to PvPI.

- **Required Information:**
  - Patient details (age, gender, medical history).
  - Drug information (name, dose, route, batch number).
  - Description of the adverse event (onset, outcome, and seriousness).

**5. Periodic Safety Update Reports (PSURs)**

- MAHs must submit PSURs to CDSCO as per the following schedule:
  - **Every 6 months** for the first 2 years after marketing approval.
  - **Annually** for the next 2 years.
  - Beyond 4 years, PSURs may be submitted based on specific CDSCO requirements.

**6. Legal and Regulatory Framework**

- **Schedule Y of the Drugs and Cosmetics Rules, 1945:** Defines pharmacovigilance requirements for clinical trials and marketed products.
- **Pharmacovigilance Programme of India (PvPI):** Established in 2010 to ensure drug safety monitoring.
- **Guidelines for MAHs:** PvPI provides specific guidance on ADR reporting obligations.

**7. Non-Compliance**

Failure to comply with ICSR reporting obligations can result in:

- Suspension or cancellation of marketing licenses.
- Financial penalties or legal actions by CDSCO.[5,12]

**D. ICSR reporting requirement in the United Kingdom**

In the **United Kingdom**, Individual Case Safety Report (ICSR) reporting requirements are governed by the **Medicines and Healthcare products Regulatory Agency (MHRA)**, in accordance with the **UK pharmacovigilance regulations** and the **European Medicines Agency (EMA) guidelines**, which were retained post-Brexit. These requirements apply to both pharmaceutical companies and healthcare professionals for monitoring and reporting **adverse drug reactions (ADRs)** or **adverse events (AEs)**.[22,10]

Key ICSR Reporting Requirements in the UK

**1. Who Must Report?**

- **Marketing Authorization Holders (MAHs):**

- Pharmaceutical companies responsible for the marketing and safety monitoring of drugs in the UK.
- **Healthcare Professionals:**
- Doctors, nurses, pharmacists, and other medical professionals are encouraged to report ADRs.
- **Patients and Consumers:**
- Voluntary reporting is encouraged, with the **Yellow Card Scheme** being the primary mechanism for patient and public reporting.

**2. What Needs to Be Reported?**

- **Serious Adverse Events (SAEs):**
- Events resulting in death, life-threatening situations, hospitalization, disability, or congenital anomalies.
- **Unexpected ADRs:**
- ADRs that are not consistent with the information provided in the product's Summary of Product Characteristics (SmPC).
- **Other ADRs and AEs:**
- All ADRs should be reported, including non-serious events, especially if they could indicate a new risk or safety concern.

**3. Reporting Timelines**

- **Serious and Unexpected ADRs:**
- Must be reported to the MHRA **within 15 calendar days** of first knowledge of the event.
- **Follow-up Reports:**
- If additional information or updates become available, follow-up reports should be submitted **as soon as possible**, and no later than **15 calendar days**.
- **Non-serious ADRs:**
- Non-serious adverse events are typically reported in **Periodic Safety Update Reports (PSURs)**.

**4. How to Report?**

- **UK Yellow Card Scheme:**
- Healthcare professionals and the public can submit ADR reports via the Yellow Card Scheme online or via mobile apps. Patients and healthcare professionals can access the scheme at Yellow Card Scheme.
- **Electronic Reporting:**
- MAHs are required to submit ICSRs electronically to the MHRA through the **EudraVigilance** system or via direct reporting tools.
- **Required Information:**
- Information should include patient demographics (age, gender, etc.), the nature of the adverse event, product details (name, dose, batch number), and the outcome of the adverse event.

**5. Periodic Safety Update Reports (PSURs)**

- **PSUR Submission:**
- MAHs must submit PSURs at specified intervals to provide a comprehensive summary of the safety data and the risk-benefit profile of a product.
- PSURs are typically required **every 6 months** for the first 2 years post-marketing authorization, then **annually** for the next 2 years, and may be required less frequently thereafter.

**6. Regulatory Framework**

- **The Human Medicines Regulations 2012:** The legislation under which pharmacovigilance and ICSR reporting requirements are enforced in the UK.
- **The MHRA:** Responsible for collecting and evaluating ADR reports, conducting signal detection, and taking regulatory actions if necessary.
- **EudraVigilance:** The EU-wide database used for collecting and managing ICSR reports,

which remains relevant for UK post-Brexit in reporting ADRs for centrally authorized products.

**7. Non-Compliance and Penalties**

- Failure to comply with ICSR reporting obligations can result in:
  - Fines, suspension, or revocation of product licenses.
  - Regulatory actions or sanctions by the MHRA, which could include inspection, recall, or market withdrawal.[12,22,23]

**E. ICSR reporting requirement in the Europe**

In **Europe**, Individual Case Safety Report (ICSR) reporting requirements are primarily governed by the **European Medicines Agency (EMA)** and the **European Union (EU) pharmacovigilance legislation**, particularly under **Regulation (EC) No 726/2004** and **Directive 2001/83/EC**. These regulations apply to all EU member states, ensuring the safety and efficacy of medicines and biological products.[3 24]

**Key ICSR Reporting Requirements in Europe**

**1. Who Must Report?**

- **Marketing Authorization Holders (MAHs):**
  - Pharmaceutical companies authorized to market medicines in the EU are responsible for reporting adverse drug reactions (ADRs) or adverse events (AEs) to the relevant regulatory authorities.
- **Healthcare Professionals:**
  - Doctors, nurses, pharmacists, and other healthcare providers are encouraged to report ADRs to the relevant pharmacovigilance centers.
- **Patients and Consumers:**
  - Voluntary reporting by patients and consumers is encouraged through **national reporting systems**.

**2. What Needs to Be Reported?**

- **Serious Adverse Events (SAEs):**
  - Includes death, life-threatening conditions, hospitalization, permanent disability, or congenital anomaly.
- **Unexpected ADRs:**
  - ADRs that are not mentioned in the product's Summary of Product Characteristics (SmPC).
- **Other ADRs and AEs:**
  - All ADRs, including those deemed non-serious, must be reported, especially if they represent a new safety signal.

**3. Reporting Timelines**

- **For Serious and Unexpected ADRs:**
  - Must be reported to the **European Medicines Agency (EMA)** or national authorities **within 15 calendar days** of becoming aware of the event.
- **For Non-serious ADRs:**
  - These are generally included in **Periodic Safety Update Reports (PSURs)** and **Risk Management Plans (RMPs)**.
- **Follow-up Reports:**
  - If additional information becomes available, follow-up reports should be submitted **within 15 calendar days** of receiving the new information.

**4. How to Report?**

- **EudraVigilance System:**
  - EudraVigilance is the European Union's system for the collection and management of ICSRs.

- MAHs are required to submit ICSRs through EudraVigilance using standardized formats (e.g., **E2B** format).
- National reporting systems for healthcare professionals and patients also integrate into EudraVigilance.

- **Required Information for ICSR Reports:**
- Patient demographics (age, gender, medical history).
- A description of the adverse event (onset, severity, outcome).
- Product details (name, dosage, lot number).
- Information on the reporting source (e.g., healthcare professional, patient).

**5. Periodic Safety Update Reports (PSURs)**

- **PSUR Submission:**
- MAHs are required to submit PSURs periodically to the **EMA** or national authorities:
  - **Every 6 months** for the first 2 years post-marketing.
  - **Annually** for the next 2 years.
  - Thereafter, based on risk and regulatory requirements, submissions may be less frequent.
- **Content of PSURs:**
- A detailed analysis of all reported ADRs, including a benefit-risk assessment and any newly identified risks or safety signals.

**6. Legal and Regulatory Framework**

- **Regulation (EC) No 726/2004**: Governs the centralized procedure for the authorization of medicines in the EU and establishes pharmacovigilance requirements.
- **Directive 2001/83/EC**: Lays down the legal framework for human medicines in the EU, including the obligations for pharmacovigilance.
- **EudraVigilance**: The system used for the submission, storage, and analysis of ICSR data in Europe.

**7. Non-Compliance and Penalties**

- Non-compliance with ICSR reporting requirements can lead to:
- Fines, market withdrawal, or suspension of marketing authorization.
- Other regulatory actions by the EMA or national regulatory authorities.

**8. Voluntary Reporting**

- **EudraVigilance** allows healthcare professionals and patients to report adverse events, although most reports are submitted by MAHs or national regulatory bodies. Each EU member state has its own system for collecting voluntary reports, but all reports are forwarded to EudraVigilance [25,11]

**F. ICSR reporting requirement in the Australia**

In **Australia**, Individual Case Safety Report (ICSR) reporting requirements are governed by the **Therapeutic Goods Administration (TGA)**, under the **Therapeutic Goods Administration Act 1989** and the **Australian Pharmacovigilance Guidelines**. These requirements are in line with international pharmacovigilance practices and are designed to ensure the safety of medicines, biologics, and medical devices on the Australian market.[6]

**Key ICSR Reporting Requirements in Australia**

**1. Who Must Report?**

- **Marketing Authorization Holders (MAHs):**

- Pharmaceutical companies responsible for the marketing and safety monitoring of medicines and medical devices in Australia.
- **Healthcare Professionals:**
- Doctors, nurses, pharmacists, and other medical professionals are encouraged to report adverse drug reactions (ADRs) or adverse events (AEs) to the TGA.
- **Patients and Consumers:**
- Voluntary reporting is encouraged through the **TGA's ADR reporting system**.

**2. What Needs to Be Reported?**

- **Serious Adverse Events (SAEs):**
  - Includes events that result in death, life-threatening conditions, hospitalization, disability, congenital anomalies, or significant medical intervention.
- **Unexpected ADRs:**
  - ADRs that are not consistent with the information in the product's **Consumer Medicine Information (CMI)** or **Summary of Product Characteristics (SmPC)**.
- **Other ADRs and AEs:**
  - All ADRs, including non-serious adverse events, are encouraged to be reported, particularly if they could signal new risks or safety concerns.

**3. Reporting Timelines**

- **For Serious and Unexpected ADRs:**
  - Must be reported to the **TGA within 15 calendar days** of first knowledge of the event.
- **For Non-serious ADRs:**
  - These can be reported periodically, often through **Periodic Safety Update Reports (PSURs)**, which may include both serious and non-serious events.
- **Follow-up Reports:**
  - If additional information or updates become available, follow-up reports must be submitted as soon as possible and within **15 calendar days**.

**4. How to Report?**

- **TGA Adverse Event Reporting System (Adverse Event Reporting Portal):**
  - Healthcare professionals, patients, and consumers can report ADRs through the TGA's online portal or via the **AusPAR (Australian Public Assessment Reports)** system.
  - The TGA encourages the use of the **eHealth record system** for reporting, making it easier for healthcare providers to submit safety reports.
- **Required Information for ICSR Reports:**
  - Patient information (age, gender, underlying conditions).
  - Detailed description of the adverse event (including onset, severity, and outcome).
  - Drug information (name, dosage, batch number).
  - Information about the reporting source (e.g., healthcare professional or patient).

**5. Periodic Safety Update Reports (PSURs)**

- **PSUR Submission:**
  - MAHs are required to submit PSURs to the TGA, which provide a summary of all adverse events over a reporting period, usually at the following intervals:
    - **Every 6 months** for the first 2 years after marketing authorization.
    - **Annually** thereafter, depending on the risk profile of the product.
- **Content of PSURs:**
  - PSURs should include a comprehensive analysis of all adverse events, a risk-benefit

assessment, and any new or emerging safety signals.

**6. Regulatory Framework**

- **The Therapeutic Goods Administration (TGA):**
  - Responsible for monitoring the safety of therapeutic goods in Australia, including medicines and medical devices.
  - TGA collaborates with international agencies, including the **World Health Organization (WHO)**, to ensure compliance with global pharmacovigilance standards.
- **Australian Pharmacovigilance Guidelines:**
  - Provide detailed instructions to MAHs and healthcare professionals on how to report adverse drug reactions and the procedures for the safe use of medicines.

7. Non-Compliance and Penalties

- Non-compliance with ICSR reporting requirements can lead to regulatory actions, such as:
  - **Fines**, **suspension**, or **cancellation** of marketing authorizations.
  - Other actions may include product recalls, safety alerts, or market withdrawal.[9 12 6]

## G. ICSR reporting requirement in the Canada

In **Canada**, Individual Case Safety Report (ICSR) reporting requirements are governed by **Health Canada**, specifically under the **Food and Drugs Act** and **Regulations**, as well as the **Canada Vigilance Program**. These regulations ensure that pharmaceutical companies and healthcare professionals monitor and report adverse drug reactions (ADRs) or adverse events (AEs) to ensure drug safety for the public.[7]

**Key ICSR Reporting Requirements in Canada**

**1. Who Must Report?**

- **Marketing Authorization Holders (MAHs):**
- Pharmaceutical companies that hold the marketing authorization for a product in Canada are responsible for reporting adverse drug reactions (ADRs) to Health Canada.
- **Healthcare Professionals:**
- Doctors, nurses, pharmacists, and other medical professionals are encouraged to report ADRs and AEs.
- **Patients and Consumers:**
- Patients and consumers are also encouraged to report ADRs voluntarily through Health Canada's reporting mechanisms.

2. What Needs to Be Reported?

- **Serious Adverse Events (SAEs):**
  - Includes life-threatening events, hospitalization, permanent disability, congenital anomalies, or death.
- **Unexpected ADRs:**
  - ADRs that are not mentioned in the product's **Product Monograph** or **Summary of Product Characteristics (SmPC)**.
- **Other ADRs and AEs:**
  - All ADRs, including non-serious events, must be reported, particularly if they indicate a new risk or safety concern.

**3. Reporting Timelines**

- **For Serious and Unexpected ADRs:**
  - Must be reported to **Health Canada within 15 calendar days** of becoming aware of the event.
- **For Non-serious ADRs:**
  - These can be reported through **Periodic Safety Update Reports (PSURs)** and **Risk Management Plans (RMPs)**.
- **Follow-up Reports:**

- If additional information or updates become available, follow-up reports must be submitted **within 15 calendar days**.

**4. How to Report?**

- **Canada Vigilance Program:**
- The **Canada Vigilance Program** is responsible for collecting and monitoring reports of ADRs for marketed drugs in Canada.
- ADRs can be reported through:
- **Canada Vigilance Online Reporting**: Healthcare professionals and patients can use the online portal to report ADRs.
- **Canada Vigilance Adverse Reaction Report Form**: A downloadable form that can be submitted by mail, fax, or online.
- **Electronic Submissions**: MAHs are required to submit ICSRs electronically through Health Canada's **Canada Vigilance System**.
- **Required Information for ICSR Reports:**
- Patient details (age, gender, relevant medical history).
- Description of the adverse event (onset, severity, outcome).
- Product details (name, dose, lot number, route of administration).
- Information on the reporting source (e.g., healthcare professional, patient).

**5. Periodic Safety Update Reports (PSURs)**

- **PSUR Submission:**
- MAHs are required to submit **PSURs** periodically to Health Canada, which summarize ADR data and the product's safety profile.
- **Every 6 months** for the first 2 years post-marketing approval.
- **Annually** for the next 3 years.
- After 5 years, depending on risk and regulatory requirements, reports may be required less frequently.
- **Content of PSURs:**
- A summary of the safety data, risk-benefit analysis, and any emerging safety signals or new information.

**6. Regulatory Framework**

- **Food and Drugs Act (FDA):** Governs the regulation of therapeutic products in Canada and sets the framework for pharmacovigilance requirements.
- **Health Canada's Canada Vigilance Program:** Oversees the collection and assessment of ADR reports and monitors the safety of drugs and biologics.
- **Drug Submissions and Reports:** Health Canada's guidelines on how to submit safety information for marketed drugs, including the required formats and timelines.

**7. Non-Compliance and Penalties**

- Failure to comply with ICSR reporting requirements can result in regulatory actions, including:
- **Fines**, **warnings**, or **penalties** for non-compliance.
- **Suspension** or **revocation** of marketing authorizations.
- **Product recalls** or market withdrawal if serious safety concerns arise.[9,10,12]

**Conclusion**

The need for pharmacovigilance is driven by the ongoing need to ensure the **safety**, **efficacy**, and **appropriate use** of medicines. By continuously monitoring and assessing drug safety throughout their lifecycle, pharmacovigilance plays a critical role in protecting public health, optimizing drug

use, and informing regulatory decisions. It contributes to the overall effectiveness of healthcare systems, reduces the burden of ADRs, and ensures that patients receive the highest standard of care.[26]

Conclusion on ICSR Reporting Across Different Countries

Individual Case Safety Reports (ICSRs) are a crucial tool in the pharmacovigilance process, aimed at ensuring the safety and efficacy of medicines worldwide. Each country or region has its own regulatory framework, timelines, and requirements for reporting adverse drug reactions (ADRs), but the core objective remains the same: to protect public health by identifying, assessing, and minimizing risks associated with pharmaceutical products.

India:

In India, the **Pharmacovigilance Programme of India (PvPI)**, under the Central Drugs Standard Control Organization (CDSCO), is responsible for ICSR reporting. Reports must be submitted within **14 calendar days** for serious and unexpected ADRs. India has aligned its pharmacovigilance efforts with international standards, collaborating with the WHO's

The **FDA** mandates the submission of ICSRs **Uppsala Monitoring Centre (UMC)**. However, challenges like underreporting and limited access to reporting channels persist

United States FDA

for serious, unexpected ADRs within **15 calendar days** of first knowledge. The **FDA Adverse Event Reporting System (FAERS)** is a robust platform for reporting, which encourages both healthcare professionals and consumers to report ADRs. The regulatory oversight and timeliness of reporting in the U.S. are well-established, and the FDA plays a significant role in ensuring that drugs remain safe throughout their lifecycle.

United Kingdom (MHRA):

The **MHRA** in the UK requires the submission of ICSRs within **15 calendar days** for serious, unexpected ADRs. It is part of the **Yellow Card Scheme**, which encourages voluntary reporting of ADRs from healthcare professionals and patients. The MHRA aligns with international pharmacovigilance standards, ensuring timely and transparent safety reporting.

European Union (EMA):

The **EMA** follows similar guidelines to the UK, requiring ICSRs to be submitted within **15 calendar days**. The **European Medicines Agency (EMA)** coordinates with national pharmacovigilance centers within EU member states to monitor drug safety. The **EudraVigilance database** centralizes ADR reports across Europe, fostering a harmonized approach to pharmacovigilance across the region.

Canada:

In Canada, the **Canada Vigilance Program** under Health Canada mandates the submission of ICSRs for serious and unexpected ADRs within **15 calendar days**. Reports can be submitted via the **Canada Vigilance Online Reporting** system. The Canadian system is well-integrated with global pharmacovigilance practices, providing valuable real-world safety data for regulatory decisions.

Australia (TGA):

The **Therapeutic Goods Administration (TGA)** in Australia requires ICSRs for serious ADRs to be reported within **15 calendar days**. The **Adverse**

**Event Reporting System (AERS)** enables healthcare professionals and patients to report ADRs. The TGA has a strong international collaboration with organizations like WHO, contributing to global pharmacovigilance efforts.

China:

In China, the **National Medical Products Administration (NMPA)** oversees ICSR reporting. The submission timeline is **15 calendar days** for serious and unexpected ADRs. China's pharmacovigilance system is evolving, with increasing emphasis on encouraging healthcare professionals and the public to report ADRs. However, challenges such as underreporting and regulatory complexity still exist

## CONCLUSION:

ICSR reporting is a global, standardized practice essential for the safety and efficacy of pharmaceutical products. While each country or region has its own framework, the **15-calendar day reporting requirement** for serious and unexpected ADRs is a common standard that facilitates timely intervention and risk management. Effective pharmacovigilance not only protects public health by identifying and mitigating risks but also fosters trust in healthcare systems by ensuring medicines are safe and effective over the long term. Global collaboration and continuous improvement in reporting systems will further enhance pharmacovigilance efforts, making drugs safer and improving patient outcomes worldwide.[26,8]

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HOW TO CITE: Anjali Kharad, Minakshi Kaulage Kharad, Baliram Kharad, Drug Safety - Pharmacovigilance: A Review, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 8, 893-911. https://doi.org/10.5281/zenodo.16789208