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Review Article

PERIODIC SAFETY UPDATE REPORT: A DRUG SAFETY MONITORING TOOL IN PHARMACOVIGILANCE

Ms. Nikita P. Shinde[1], Ms. Archana Gawade[2]

1. Assistant Professor, HSBPVT's GOI, College of Pharmacy, Kashti, Ahmednagar.and Advance Diploma in Pharmacovigilance and clinical research Scholar from Elite institute of Pharma Skills Pune.
2. Managing Director, Elite Institute Of Pharma Skills, Pune

Address for correspondence:

Ms. Nikita P. Shinde, Assistant Professor, HSBPVT's GOI, College of Pharmacy, Kashti, Ahmednagar.and Advance Diploma in Pharmacovigilance and clinical research Scholar from Elite institute of Pharma Skills Pune.

E-mail- nikitaps98@gmail.com

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ABSTRACT

Pharmacovigilance plays an important role in examining the safety of pharmaceutical product. Pharmacovigilance (PV) data are pivotal to make sure a safety and efficacy of medicines once the drugs get marketing approval. The periodic safety update report is a documental concept which is used as an important tool in pharmacovigilance to deliver a safety update of medicinal product to a society. The concept of PSUR was established in the year of 1992 and in November 1996, the ICH inscribe the ICH E2C i.e., the guideline for the periodic safety update report for the safety of marketed drugs. The periodic safety update report (PSUR) come up with a required process to control the drug marketing agencies to ensure that pharmaceutical products which are marketed does not harm the public health by their side effects. Considering the importance PSUR in in drug safety, this article reviews the Significance, principal preparation of PSUR, objectives, timeline to submit the periodic safety update report as per the ICH E2C guidelines.

Keywords: Pharmacovigilance, Periodic safety update report, ICH E2C, Adverse drug effects

INTRODUCTION:

PV is in charge of monitoring the safety of medications in everyday clinical practise and during clinical trials. Its main goal is to reduce drug-related risks while maximising their benefits. [1-2] The research and practises connected to the detection, assessment, understanding, and prevention of side effects and all other problems related to pharmaceuticals are referred to as pharmacovigilance (PV). Globally, national pharmacovigilance systems rely on spontaneous reporting, in which health professionals, manufacturers, or patients report suspected adverse drug reactions (ADRs) to a national coordinating centre.[3]

Pharmacovigilance (PV) data are essential for ensuring the continuous safety and effectiveness of medications, as well as for providing information about regulatory actions such as drug safety alerts, labelling modifications, drug recalls, and drug withdrawal from the market. [4] Good PV will uncover hazards linked with medicines in a short amount of time, and when well presented, this knowledge will enable for rational, evidence-based pharmaceutical use, potentially preventing many unpleasant reactions. The World Health Organization and its regional offices play a critical role in assisting countries in establishing and establishing long-term monitoring systems. It acts as a repository for PV data and disseminates it in an appropriate manner.[5] The existing spontaneous report handling and regulatory reporting procedure, as well as the IT tools that enable it, are actually sub-processes. A rigorous post-marketing surveillance (PMS) approach is required for true risk management to assess the safety of a company's products in the global marketplace. The parent process is the PMS process. A rigorous 'good post-marketing surveillance process' (GPMSP) includes an integrated philosophy of drug safety, sources of high-quality data, good scientific practises and skills, specified output products, clear decision points, and action plans, as well as good data and document management processes and a set of clear and enforced standard operating procedures (SOPs). [6] The purpose of this GPMSP is to learn about the safety profile of all of a company's products in a clinical setting. The integrated drug safety strategy is to continue building on the knowledge database that was started in the premarket sections of the new drug application (NDA) or market application. According to this idea, a company's PMS software should be capable of compiling a continuous integrated safety summary (i.e., a continual-ISS) in the form of an ICH-E2C compliant periodic safety update report (PSUR) that includes an actively assessed safety profile. To construct and assemble such a PSUR, multiple sources of high-quality data from clinical practise environments will be required. [7] The PSUR (periodic safety update report for marketed medications) is a stand-alone document that allows for a periodic but complete examination of a marketed drug's or biological products worldwide safety data. The PSUR can be a valuable resource for identifying new safety signals, determining changes in the benefit-risk profile, communicating risk effectively to regulatory authorities, and determining the need for risk management initiatives, as well as a tracking mechanism for monitoring their effectiveness. As a result, the PSUR has the potential to be an important pharmacovigilance tool. [8]

Periodic Safety Update Report (PSUR):

PSURs are designed to proactively present, assess, and evaluate new or changing safety data from any source in relation to estimates of product exposure, albeit in practise, entire coverage of data sources may have constraints. Marketing authorization holders (MAHs) create PSURs, which are then submitted to regulatory agencies for review at predetermined intervals. [9] PSURs must also be provided with applications to extend the first marketing authorisation, which is valid for five years in the European Union (EU). PSURs are created and assessed with significant resources by both regulatory bodies and MAHs. The results of these efforts, however, have not been clearly characterised. [10] PSUR evaluations were found to contribute to 38% of post authorisation regulatory actions in a sample of biopharmaceuticals in a previous study on the drivers of safety-related regulatory actions for biopharmaceuticals. [11]

Objectives of the periodic update safety report:

A PSUR's major goal is to give a complete, concise, and critical analysis of the medical product's risk-benefit balance, taking into consideration new or emerging evidence in the context of cumulative risk and benefit information. The PSUR is thus a mechanism for post-authorization evaluation at specific times in a product's lifecycle. It is vital to continue examining the risks and benefits of a medicine in everyday medical practise and long-term usage in the post-authorization phase for the objectives of lifecycle benefit-risk management. This could include assessing demographics and endpoints that were not able to be studied in the pre-authorization clinical studies. As more information regarding safety is revealed by pharmacovigilance, a new risk-benefit balance may emerge. As a result, the holder of a marketing authorization should re-evaluate the risk-benefit balance of its own pharmaceutical products among populations that are exposed. This structured assessment should be carried out in conjunction with continuing pharmacovigilance and risk management (see Module V) in order to optimise the risk-benefit balance through effective risk minimization. The appropriate mechanism should be used to report urgent safety information. In the initial instance, a PSUR is not designed to offer notification of substantial new safety or efficacy findings or to serve as a means of detecting new safety risks. It is understood that a study of the data in the PSUR could uncover additional safety concerns. [12]

Principles for the preparation of PSURs:

Unless competent authorities specify otherwise, the holder of a marketing authorization must prepare a single PSUR for all of its medicinal products containing the same active substance, with information covering all of the authorised indications, routes of administration, dosage forms, and dosing regiments, regardless of whether they were approved under different names and through different procedures. Data relating to a specific indication, dosage form, route of administration, or dosing regimen must be included in a distinct section of the PSUR when applicable, and any safety concerns must be addressed accordingly [IR Art 34(6)]. There may be uncommon circumstances where preparing distinct PSURs is warranted, such as when there are different formulations for completely different indications. In this instance, consent from the necessary responsible authorities should be sought as soon as possible after approval. When case narratives are critical to the

scientific examination of a signal or safety concern, they must be included in the relevant risk evaluation section of the PSUR [IR Art 34(4)]. Case narratives refers to clinical analyses of particular cases rather than CIOMS narratives in this context. The actual CIOMS narrative text included in the individual case safety report (ICSR) should not be required, but rather a clinical review of noteworthy or illustrative cases in the context of the evaluation of the safety concern/signal. When data obtained from a partner that could contribute meaningfully to the safety, benefit, and/or benefit-risk analyses and influence the reporting marketing authorisation holder's product information is included and discussed in the PSUR, it should be included and addressed. All PSURs must follow the format and table of contents outlined in IR Art 35, and each report must include both interval and cumulative data. Summary bridging reports and addendum reports, as proposed in the ICH-E2C(R1) standard, will not be recognised because the PSUR should be a single stand–alone document for the reporting interval, based on cumulative data. When developing a PSUR, the GVP Modules on Product- or Population-Specific Considerations3 should be used as needed. [13]

According to the ICH E2C (R1) rules, the PSUR's key goals are as follows: [14]

- To establish the relationship between patient exposure data and safety data
- To summarise the marketing authorization status globally and any changes in approvals due to safety reasons
- To establish the overall safety evaluation periodically
- To specify whether changes to product information should be made in order to optimise the use of the product

Advantages of PSUR: [15]

- The most efficient and trustworthy way for analyses is to use a huge database, and the implementation of such a database in different nations could improve the quality of information on adverse drug reactions (ADRs).
- The ability to comprehend and prioritise the most important data, as well as to evaluate it using data mining, is quite beneficial.
- This system is simple to use and provides a quick reporting method for both reporters and health authorities.

Regulations of PSUR In India: [16]

PSURs for novel medications must be filed to the DCG's office in accordance with Schedule "Y" of the Drugs and Cosmetic Rules (I).

- For the first two years, PSUR must be submitted every six months; for the next two years, PSUR must be presented annually.
- PSURs for a reporting period must be submitted within 30 calendar days of the reporting period's conclusion.

The PSURs should be structured according to clause (v) of Schedule "Y" and the report should be particular to India.

- A title page with the following information: PSUR for the product, applicant's name, report period, date of approval of new medicine, approved indication, date of marketing of new drug, and reporting date.
- Introduction
- Current global market authorization status
- Updates on safety actions taken
- Changes to reference safety information
- Estimated patient exposure
- Presentation of individual case histories
- Studies
- Other information
- Overall safety evaluation
- Conclusion
- Appendix with material on indications, dosing, pharmacology, and other related topics.[17]

Submission timeline for PSUR: [18]

PSURs must be submitted to the European Medicines Agency (via a PSUR repository) within the following time frames:

- within 70 calendar days of the data lock point (DLP), which is considered Day 0, for PSURs covering intervals up to 12 months;
- within 90 calendar days of the DLP for PSURs covering intervals greater than 12 months.

For all medicinal products containing the same active substance, a single PSUR must be prepared, with information covering all authorised indications, routes of administration, dosage forms, and dosing regiments, regardless of whether they are authorised under different names and through different procedures. Data pertaining to a specific indication, dosage form, route of administration, or dosing regimen will be included in a distinct section of the PSUR when applicable, and any safety concerns will be addressed accordingly.

The PSUR must include an explicit assessment of the benefit-risk balance's current state. Any medicinal product's potential benefit must be weighed against its possible risk, and MAH should give an integrated benefit-risk balance based on scientific assessment of new safety data in order to keep the benefit-risk balance up to date based on interval data. The PSUR's PBRER format is intended to make the presentation of safety, effectiveness, and benefit data collected throughout the reporting period as simple as possible, as well as to give an explicit risk-benefit analysis in the context of what was known at the beginning of the interval. [19] A PBRER is a thorough, concise, and critical examination of new or emerging information on the medicinal

product's risks and benefits in approved indications in order to assess the product's overall benefit risk profile. The evaluation includes:

- Presentation of data received throughout the reporting period is part of the evaluation. A brief description of data relevant to the medicinal product's benefit and dangers from all sources, including case reports, clinical and nonclinical safety studies, published reports, and an overview of signals, categorised as new, ongoing, or closed, is included.
- a critical evaluation of new safety, effectiveness, and benefit-related information This assessment considers the impact of new knowledge on the pharmaceutical product's risk-benefit balance. This assessment also takes into account information on unintended drug use, such as medication errors, misuse, abuse, overdose, off-label use, and use in particular groups like children and pregnant women. As the risk assessment should be based on populations exposed, patient exposure should be reported based on the location, patient information, and formulations, among other things.
- a summary of any risk-mitigation actions taken or planned in accordance with the risk management plan (RMP).
- a plan for evaluating a signal or risk, including dates and/or a suggestion for more Pharmacovigilance activities.

The PSUR conclusion should provide a preliminary recommendation for improving or evaluating the risk-balance. Further evaluation or optimization conclusions should be integrated into the RMP's Pharmacovigilance and Risk Minimization Plans. The relevant risk evaluation part of the PSUR must include a case narrative, which is critical to the scientific study of a signal or safety concern. [20]

Conclusion:

Pharmacovigilance is an important part of patient treatment and monitoring. Its goal is to get the greatest possible result from medicine and medicinal products treatment. This review article backs up the vital relevance of putting in place drug safety networks and safety update reporting mechanisms on a regular basis. The concept of a PSUR-focused, drug-specific AE monitoring programme arises from viewing the PSUR as a systematic compilation of a manufacturer's AE surveillance and interpretive operations throughout time, rather than as a solely statutory requirement.

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