International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 7; Issue 2(I); February 2018; Page No. 10230-10234
DOI: http://dx.doi.org/10.24327/ijcar.2018.10234.1722

Research Article

PERIODIC SAFETY UPDATE REPORT (PSUR) WORLDWIDE UPDATE: A REVIEW

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A R T I C L E I N F O

Article History:
Received 7th November, 2017
Received in revised form 13th December, 2017
Accepted 3rd January, 2018
Published online 28th February, 2018

Key words:
PSUR, PBRER, Pharmacovigilance.

A B S T R A C T

In the rapidly developing era, Pharmacovigilance plays an important role in the healthcare system to put necessary brakes and obtains valuable additional information, building up the scientific data contained in the original report and making it more informative.As we all know that the regulatory agencies like EMA, USFDA, CDSCO etc. are very stringent in approving the drugs, They have framed several rules and imposed strict timelines for reporting the necessary documents pertaining to drugs. Alongwith the agencies the PvPI Programme, UPPSALA monitoring center(UMC) collaborated with WHO play important role in adverse event reporting. This review brief several aspects of PSUR in different countries, necessary processes and format in which it needs to be submitted, pitfalls and ways to overcome such situations have been discussed in brief. Therefore, it is the collective responsibility of both Regulatory agencies and the drug companies to ensure a good quality PSUR is produced with its benefits outweighing the risk of the drug for the suffering human population.

INTRODUCTION

The periodic safety update report (PSUR) is a document that allows a periodic, comprehensive assessment of the worldwide safety data of a marketed drug or a biological product. In 1992, The concept was introduced to the ICH. In November 1996, the ICH endorsed the ICH E2C Periodic Safety Update Report Guideline (E2C guideline), which established the PSUR as a harmonized format for post-market periodic safety reporting for approved drugs and biologic products, and described the format, content, and timing of PSUR submissions. FDA adopted that guideline and, in May 1997, published it as FDA guidance for industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C guidance).

On April 11, 2012, FDA announced the availability of a draft guidance for industry entitled E2C (R2) Periodic Benefit-Risk Evaluation Report (PBRER), which describes the format, content, and timing of the PBRER as presented in the ICH step 2 guideline. This new ICH guideline updates and combined with the E2C guideline and an addendum to the E2C guideline in particular, it replaces the PSUR with the PBRER for post-market periodic safety reporting, and describes the recommended format, content, and timing of PBRER submissions. Like its predecessor, the PSUR, the harmonized PBRER is intended to promote a consistent approach to periodic post-market safety reporting among the ICH regions and to enhance efficiency by reducing the number of reports generated for submission to the regulatory authorities.[1]

Advantages of PSUR

1. Use of large database for analyses is the most efficient and reliable method and the implementation of such data base in different countries could increase the quality of the quality of the information on adverse drug reactions (ADRs).
2. Ability to understand and prioritize the most important data and to use data mining to evaluate it is very advantageous.
3. This system is ease of use and fast reporting mechanism both from reporters, but also between health authorities

It is administratively simpler and less labour intensive than cohort event monitoring, it is less costly, easy to implement, is applicable to all medicines, rare reactions can be identified and it is the method most commonly used in pharmacovigilance.

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PvPI role in PSUR

Pharmacovigilance Programme of India (PvPI)

The evaluation of PSURs is a part of overall pharmacovigilance activity and also one of the important sources for signal detection. Thus the major work of PvPI is recommendation of the signal detection to the agencies where they are evaluated by higher authorties.Thus it is only natural and appropriate to consider the review and analysis of such reports as a part of PvPI. The PvPI at IPC has established a Signal Review Panel for signal identification/review from the committed ICSRs to WHO-UMC. The results of the cases discussed in the Signal Review Panel of the PvPI will be shared with CDSCO. These results will be used as additional evidence during causality assessment by the CA sub-committee and finalised by the committee. As a part of the condition of the marketing authorization, the MAH is also required to submit PMS/PSUR after licensure of the product. This strategic decision was taken during a high level meeting organized in Delhi between the CDSCO and IPC officials on 30th March 2015. During the meeting, DCG (I) stressed that the PSURs submitted by the pharmaceutical industries should be made accessible to the PvPI for further enhancing the drug safety monitoring process. Currently, the PSURs are not linked to the PvPI and are submitted to the CDSCO only[7]

Pv division shall be responsible for

1. the coordination with NCC-PvPI (IPC) for the various AE/ADRs reported from MAHs
2. to attend various meeting with the stake holders for coordination purpose or whenever situation arises
3. the AE/ADRs reported by the PvPI shall be reviewed by the expert committee constituted for this purpose for taking further regulatory action

WHO role in PSUR

World Health Organization

WHO's work in the drug regulatory area is based on a number of principles, in particular

- The primary goal of regulatory work is to protect public health by ensuring the regular availability of good quality, safe and efficacious pharmaceuticals and by contributing to their rational use.(Schedule Y)
- Global norms and guidelines are a frame of reference; for their effective implementation, they need to be adapted to meet the specific needs, priorities and conditions of individual countries.(ICH guidelines)
- International harmonization of regulatory requirements is a gradual process that can contribute to meeting public health goals when it is undertaken in relatively homogeneous groups of countries and when it takes into account existing gaps among national regulatory capacity and aims at bridging them.(Uppsala centres)

Uppsala monitoring Centre (UMC) role in PSUR

WHO is the leading organization in the area of pharmacovigilance through its Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

Uppsala Monitoring Centre

Its major roles are

- to coordinate the WHO Programme for International Drug Monitoring and its more than 60 participating countries,
- to collect, assess and communicate information to participating countries about the harms and risks of drugs and other substances used in medicine, in order to improve patient therapy and public health worldwide,
- to collaborate with Member States in the development and practice of the science of pharmacovigilance.

PBRER (periodic benefit risk evaluation report)

PSUR term got changed to PBRER according to ICH E2C (R2) step 4 guideline and focus is more on critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

As the scope of the PBRER has been extended to include benefit as well as safety, the reference information for the report also should take this new factor into account.

- Encompasses all parameters that contribute towards the benefit-risk evaluation (i.e., benefit, efficacy/effectiveness, indication(s) and safety information).
- Is common to all ICH regions.
- Addresses all circumstances (e.g., generics, products licensed in one country only).[4]

These proposals incorporate the original ICH E2C (Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs) concept of reference safety information eg

Company core data sheet (CCDS)

A document prepared by Marketing Authorization Holder (MAH) containing material relating to indication, dosing, pharmacology and additional information concerning the product as well as to safety information.

Company core safety information (CCSI)

All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be

listed in all countries where the company markets the drug, except as soon as the local regulatory authority specifically needs a modification. This is the reference information with which listed and unlisted are determined for the goal of periodic reporting for marketed products, but not by way of expected and unexpected are determined for expedited confirming.

International birth date (IBD)

Date of the first marketing authorization for necessary granted in any country of the world.

Data lock point (DLP)

Cut-off date to be included in the PSUR, it may be set according to the international birth date (IBD) from the medicinal product. After obtaining marketing authorization for a medicinal product, the MAH is requested to inform the Agency of their choice of birth date and of the chosen first data lock point (1st DLP).

Regulations in PSUR
In India

As per the requirements of Schedule "Y" of the Drugs and Cosmetic Rules, PSUR of new drugs are required to be submitted to the office of DCG (I).

- Every 6 months for the 1st 2 years
- For the next 2 years PSUR shall be submitted annually.
- PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

The PSURs should be structured as per clause (v) of Schedule "Y" which is under and the report should be India specific

- A title page stating: PSUR for the product, applicant's name, period covered by the report, date of approval of new drug, approved indication, date of marketing of new drug and date of reporting.
- Introduction
- Current worldwide market authorization status
- Update of actions taken for safety reasons
- Changes to reference safety information
- Estimated patient exposure
- Presentation of individual case histories
- Studies
- Other information
- Overall safety evaluation
- Conclusion
- Appendix providing material relating to indications, dosing, pharmacology and other related
- information[3]

In Usa

US FDA requires 3 months once the actual first 3 years, then annual reports needs pertaining to being submitted. They follows the ICH E2C(R2) guidelines.

In European Union

EMA (European Medicines Agency) requires reports initially every several weeks for the first 2 years, then annually for the subsequent 3 years which is usually 5 years at the time of renewal of registration.PSUR is structured as per module (VII) of good pharmacovigilance practices(GVP).

In Japan

Secretary of state for health requires reporting every 6 months for the first 3 years and annually thereafter.

General principles in pbrer
Single pbrer for a productive substance

The PBRER should showcase all approved indications, dosage forms, and regimens for that active substance, with merely one DLP. In most circumstances, it will appropriate to give data by indication, dosage form, dosing regimen, or population (e.g., children or. adults) within the relevant areas of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an engaged substance implemented in two formulations for systemic and topical administration in entirely different indications. During these cases, the regulatory authorities should be notified in addition agreement obtained, preferably is now the top approval.

Pbrers for Fixed Dose Combination Product

For mixtures of substances also marketed individually, information for your fixed combination may be reported in a choice of a separate PBRER or included separate presentations your market report for starters of the litigant substances, with regards to the circumstances. Listing related PBRERs is considered important.

Pbrer Process

The main objective of a PBRER is to present a comprehensive, concise and critical research into the risk benefit balance of this medicinal product considering new or emerging information in the context of cumulative information on risks and benefits. The PBRER is therefore a tool for post-authorization evaluation at defined time points in the lifecycle of a service or product.

The evaluation should involve

1. Critically examining the information offers emerged during the reporting interval to discover whether it has produced new signals, contributed to the identification of recent potential or identified risks or led to knowledge of previously identified risks.
2. Critically summarizing relevant new safety, efficacy and effectiveness information that will have an impact relating to the risk-benefit balance for the medicinal product.
3. Summarizing any risk minimization actions that may are taken or implemented during the reporting interval, as well as risk minimization actions that are planned to be implemented.
4. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional Pharmacovigilance activities.

Time Interval between Data Lock Point and the Submission

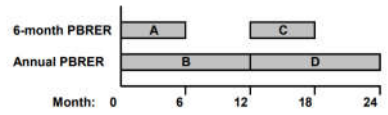
As a result of the expanded scope of the PBRER, the time interval between the DLP and submission of PBRERs should be as follows

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days;
- PBRERs covering intervals in excess of 12 months: within 90 calendar days;

- PBRERs: 90 calendar days, unless otherwise specified in the cause request.

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission. Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.[5]

Figure 1: Submission of 6-Month and Annual PBRERs



Region 1 requests 6-month PBRER, and receives PBRER A, B, C, and D (assuming agreement has been reached with pertinent regulatory authority or authorities).

Region 2 requests annual PBRER, and receives PBRER B and D.

Format of PBRER

Electronic Periodic Benefit Risk Evaluation Report format is as follows

1. Part I: Title page including signature
2. Part II: Executive Summary
3. Part III: Table of Contents

1. Introduction
2. Worldwide marketing authorization status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
• Cumulative subject exposure in clinical trials
• Cumulative and interval patient exposure from marketing experience
6. Data in summary tabulations
• Reference information
• Cumulative summary tabulations of serious adverse events from clinical trials
• Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
• Completed clinical trials
• On-going clinical trials
• Long-term follow-up
• Other therapeutic use of medicinal product
• New safety data related to fixed combination therapies
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, on-going or closed
16. Signal and risk evaluation
• Summaries of safety concerns
• Signal evaluation
• Evaluation of risks and new information
• Characterization of risks
• Effectiveness of risk minimization (if applicable)
17. Benefit evaluation
• Important baseline efficacy and effectiveness information
• Newly identified information on efficacy and effectiveness
• Characterization of benefits
18. Integrated benefit-risk analysis for authorized indications
• Benefit-risk context- Medical need and important alternatives
• Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the PBRER
• Company Core Data sheet
• Marketing authorization status
• Line listing of case report
• Summary tabulation of events.

Problems faced during PBRER process at various stages

1. Intake of ADR information
2. Case processing
3. Data retrieval
4. Data analysis
5. Medical review and risk assessment

Intake of ADR information

Adverse reaction data from the following sources are potentially available to the MAH and so would be likely to be included a PBRER if they exist. The reaction terms used in PBRER will be generally derived from MedDRA (Medical Dictionary for Regulatory Activities).

The source for PBRER can be obtained as follows

1. Direct reports to the MAH: Internal revenue service reports regarding example spontaneously notified by Clinical professionals, from MAH-sponsored studies, from named patient or compassionate use schemes and from patients or potential clients.
2. Adverse reaction reports from literature.
3. Adverse reaction reports received from regulatory authorities' database. This may include nonmedically confirmed patient or consumer answers.
4. Reports using sources with regard to those using their company companies, from registries, from poison control centers or epidemiological data banks.[4]

Case Processing

The actual information is obtained from the reporter, the situation is entered onto a safety database, a story of the case is prepared and MedDRA term is assigned for the ADRs described each morning case. Inconsistencies in connection with case classification, serious/non-serious, labelled/unlabelled, arise the actual case processing. Case classification inconsistencies increase with the quantity of individuals responsible for processing cases; manual coding of MedDRA can also leads to several inconsistencies. Thus the totality out of all these inconsistencies during the situation handling process for giant volume PBRERs will likely have a considerable cause problem for the accuracy belonging to the PBRER and weaken the ability to recognize new signals or do a proper evaluation.

Data Retrieval

Specialists the most rate-limiting and time-consuming steps for high volume PBRERs, usually taking far over originally planned. To generate better accuracy and consistency, data retrieval can be performed by data managers or programmers rather compared to medical writers or reviewers. Also commercially ready databases can be employed for this project.

ADR Analysis

Troubles faced in the ADR analysis are underreporting of ADRs, difficulty in calculating the exposure, and reporting the tendencies. In order to overcome these difficulties data mining methods pertaining to example Multi-Item Gamma Poison Shrinker (MGPS) method, Bayesian Confidence Propagation Neural Network (BCPNN), and Proportional Reporting Ratios (PRR), will automatically generate safety signals, from large ADR databases, without relying on incidences, and a most promising tool in signal sensors.

Medical Review and Risk Assessment

Market strength of PBRER is the capability to review aggregate data which needs an all-inclusive look at many places such as summary tabulations and article on individual cases curiosity and also different sure whether the pattern of ADRs collected during the reporting interval has evolved. It is also essential to ensure whether any medically important events previously unlisted, but now emerged with a stronger causal relationship to the thing. Thus Medical review process needs a time to strengthen the PBRER which indirectly implies that if any of these processes, for instance if a process like data retrieval analysis is delayed it will seriously hamper the time for medical review and risk assessment and resulting within a poor quality PBRER.

Recommendations and Future Challenges

1. Electronic PBRER format recently been proposed however the compliance of industry adhere to it in order to be affirmed
2. Resource planning needs become clearly planned regarding the time, cost, training (in product, clinical, MedDRA training) and effective operations of PBRER.
3. Growing involving newer immunomodulatory therapies also pose a strong challenge in identifying lengthy term risks.
4. Risk management plan strategies needs turn out to be more precise and end up being served with regard to efficient tool in PBRER.
5. Deadlines for submissions of PBRER its impact on your quality on the report end up being the greater responsibility among the MAH.
6. Human factor management consists of SOPs, identifying the source of the human being errors and proper leadership and distance learning.

Cost Assessment of PSUR

For a pharmaceutical company MAH to be able to spend around €6000 to acquire small PBRER (<100 ADR cases), €14000 for a medium PBRER (101-500 cases) and €28000 for an immense PSUR (>500 cases). However spending this much money isn't a waste because PBRER is successful at signaling possibility and can prevent further adverse scores.

Month wise distribution of ICSRs received at NCC-PvPI (2015-16)

Apr -15	**4707**	**Oct -15**	**5129**
May -15	4391	Nov -15	5213
Jun -15	4601	Dec -15	5704
July -15	4844	Jan -16	5428
Aug-15	5208	Feb-16	5242
Sep -15	8326	Mar -16	5177

CONCLUSION

The field of Pharmacovigilance has crafted a tremendous journey since work out plans recognized the actual early 1960s after the thalidomide accident. Inevitably several new drugs like immunomodulators, anticancer medicine is on the raise which further adds a huge responsibility towards the regulatory agencies regarding the chance and advantages of such biological products Undoubtedly PBRERs plays an natural part and is relied on as an important tool involving field of pharmacovigilance but however the oversight is clearly to be able to ensure that this product's benefit continue to outweigh its risks, and PBRER facilitate the weighing and monitoring of such events at predetermined time points.

Acknowledgment

I would like to express my deep gratitude to Dr. J Swaminathan for his valuable and constructive suggestions,enthusiastic encouragement and useful critiques for this article work.His willingness to give his time so generously has been very much appreciated.Finally, I wish to thank my parents for their support and encouragement throughout my study.

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How to cite this article:

Pooja and Saminathan J (2018) 'Periodic Safety Update Report (PSUR) Worldwide Update: A Review', *International Journal of Current Advanced Research,* 07(2), pp. 10230-10234. DOI: http://dx.doi.org/10.24327/ijcar.2018.10234.1722

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