Journal of Advanced Nursing Practice

Journal homepage: www.mcmed.us/journal/janp

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) AND RECENT GUIDANCE

AlokBandyopadhyay

Department of Psychopharmacology, Medicine Faculty of Federal University of São Paulo (UNIFESP), São Paulo, Brazil.

Article Information

Received 14/02/2014; Revised 18/02/2014;
Accepted 30/03/2014

Corresponding Author

Dr.AlokBandyopadhyay
E mail: akbandy@gmail.com

ABSTRACT

Adverse Event (AE) reporting procedure in an Investigational Drug (IND) safety report for clinical studies is based on single subject. Beyond the clinical trials, an effort has been directed towards post marketing safety since a large number of patients are exposed to marketed drugs. Adverse drug reaction (ADR) reporting is fundamental in the post marketing surveillance of a medicinal drug. It is, therefore, important to capture information regarding ADR*'s* in a structured manner and to the highest possible quality standards to support accurate detection and analysis of drug safety updates.

Key words: Adverse Event, Adverse drug reaction.

INTRODUCTION

This process requires timely submission for initiating mutual exchange of safety data between regulators and the sponsors. With the advancement of technology, a large number of Individual Case Safety Reports (ICSRs) are submitted electronically. In addition sponsors are required to collate, evaluate, and report the analyses of AEs in the IND Annual Reports in US and Annual Safety Reports (ASRs) in Europe. For the management of AEs of individual drugs within a defined period in post approval clinical studies, quarterly periodic safety reports are introduced to provide an aggregate review and analysis of all AE reports received over a defined time period[1-5]. Examples of these aggregate reports are the Periodic Safety Update Report (PSUR), the Periodic Adverse Drug Experience Report (PADER), and the Periodic Adverse Experience Report (PAER). Since there is some confusion over the term "adverse drug experience", FDA has eliminated the term and replaced it with "adverse event" and "adverse reaction". An "*adverse event* is simply, any adverse event observed during clinical study", whereas "an *adverse reaction* is an adverse event for which there is a reasonable possibility that the drug caused the adverse event" [1-5].

The electronic exchange of information for ADR reports between regulators and sponsors allows the data to be available for qualitative signal detection and evaluation. This is key for the evaluation of risks and benefits of the drugs. Both regulators and sponsors realize a balanced evaluation of risks will include the actual benefits. In the meantime, the International *Conference on Harmonization* (ICH) has proposed a new idea to ensure the convergence of local regulations with a decreased burden on regulators and sponsors. Since regulators can share and discuss assessments of products in the post marketing phase, the ICH revised guideline E2C on the basis of modular approach to promote safety in the new guideline E2C(R2 or PBRER)[6]. Subsequently, the FDA initiates a process of accepting PBRERs in lieu of a PADER upon granting a PADER Waiver [7]. The purpose of this article is to discuss the intentions of employing PBRER to promote a consistent approach to periodic post marketing safety reporting and to enhance efficiency by reducing the

number of reports generated for submission to regulatory authorities.

PBRER and its content:

Each PBRER is a stand-alone document. It should provide information on all approved indications, dosage forms, and the regimen for the active substances over a defined set of dates. The end date of this period is defined as Data Lock Point (DLP). In certain circumstances, it is appropriate to present data either by indication, dosage form, dosing regimen, or subjects' population (e.g. children vs. adults) within the relevant sections of the PBRER.

In case of clinical studies with combination drugs, where both drugs are marketed separately- information on the fixed combination may be reported either in a separate PBRER or included as separate presentation in the report for one of the individual substances, depending on the circumstances [6].

Each report should include cumulative data as well as interval data for the period covered. If multiple PBRERs have the same DLP but different durations, the cumulative sections of those PBRERs are the same, whereas the interval sections may differ. Taking into consideration, the cumulative data sections from the most recent PBRER can be submitted along with updated interval data. The content of PBRER is shown below:

- Executive Summary
- Worldwide Marketing Approval Status
- Actions Taken in the Reporting Interval for Safety Reasons
- Changes to Reference Safety Information
- Estimated Exposure and Use Patterns
- Summaries of Significant Findings from Clinical Trials during the Reporting Period
- Findings from Non-interventional Studies
- Information from Other Clinical Trials and Sources
- Non-Clinical Data
- Literature
- Other Periodic Reports
- Lack of Efficacy in Controlled Clinical Trials
- Late Breaking Information
- Overview of Signals New, Ongoing or Closed Clinical Studies
- Signal and Risk Evaluation along with Benefit Evaluation
- Integrated Benefit-Risk Analysis for Approved Indications

For license renewals in EU, the PBRER data are incorporated into an Addendum to the Clinical Overview, which is a part of a renewal dossier [8,9].

Timelines for PBRER:

Time interval between DLP and the submission of PBRER should be as follows:

- PBRER covering intervals of 6 or 12 months: Within 70 calendar days
- PBRER covering intervals in excess of 12 months: Within 90 calendar days

Evaluation of benefit-risk for PBRER:

During pre- and post-market phases of drug development, the AE and ADR are collected and stored in databases for safety experts to examine regularly potential and true signals as well as other events of interest. A safety signal for a drug indicates that a specific drug event is reported more frequently relative to the drug than other events or other drugs and the specific event of interest. However, whether the safety signal (e.g. ADR) is due to a specific drug or drug-drug interaction can only be understood based on detailed medical review of relevant and appropriate ICSRs, case series analysis, and other available information including clinical and preclinical toxicology data. Sponsors have placed such systematic efforts attempting to identify new risk or any changes in the known safety profile of the product

For the preparation of PBRER or other safety reports, sponsor collects data of patient exposure from different countries and collates the data from different groups and different ethnicities at a defined interval. Furthermore, these data are evaluated for benefit & risk through signal evaluation and then stratify with special populations. PBRER provides an update as well as evaluation of the data collected from worldwide safety experiences in regards to a medicine for the same intervals along with benefit-risk of an approved medicine in the light of new or changing post-approval information. Such benefit-risk evaluation may also require stratification by special populations in order to align with the Developmental Safety update report (DSUR) [10].

When a drug is approved for marketing, the conclusion has been made that the product's benefits outweigh the risks. However, as new information about the drug product emerges during the marketing experience, benefit-risk evaluation should be carried out to determine whether the benefits continue to outweigh risks. Also consideration should be placed to determine whether steps are necessary for improving benefit-risk relationship through risk minimization activities e.g. labeling changes, communications with prescribers, or others.

When a product is manufactured and/or marketed by more than one company, the data received from partner companies should be utilized in the benefit-risk or safety analyses. Any new information should be incorporated into the product information and be included in PBRER.

PSUR verses PBRER:

The PSUR is based on the ICSR and reports the evaluations of each Med Watch within a reporting period. In contrast, the PBRER does not report the evaluations of each Med Watch, but includes signal analysis and the benefit-risk of the drug. A comparison between PSUR and PBRER is presented in Table 1.

Advantages of PBRER:

There are several advantages of PBRER:

PBRER utilizes the resources efficiently and facilitates management of different frequencies of submission. This may enhance the consistency and quality of the PBRER. When the clinical development of a drug product continues following marketing approval, the submission of both PBRER and DSUR are required. The former is based on International Birth Date (IBD) and the latter based on Development International Birth Date (DIBD). If these time period are synchronized in the IBD based cycles, then a PBRER can be prepared at the same time with DSUR [10].

A PBRER can be developed in such a way that the content of several sections may be used for sections of other documents as a basis for a modular approach like other ICH guidances e.g. E2E, E2F. Several sections of the PBRER overlap with DSUR e.g. (a) Summary of significant safety findings from clinical trials duringthe reporting period (b) Findings of Non-interventional Studies (c) Information of other Clinical Trials and sources (d) Non-clinical data (e) Other Periodic Reports (e) Lack of Efficacy in controlled Clinical Trials (f) Late Breaking Information.

- PBRER also reduces the number of reports and decreases the burden on sponsors and regulators.
- It provides a listing of any non-interventional study(s) with the primary aim of identifying, characterizing quantifying a safety hazard, confirming the safety profile of the drug product, and measuring the effectiveness of risk management of the completed or ongoing clinical studies during the reporting interval (i.e. post authorization safety studies (PASS)) are to be included in the Appendix. Progress or final study reports generated during the reporting period for PASS should also be included as a regional Appendix to the report.

PBRER of post-approval drug products for a defined time point provides not only an update of global safety experience but also provides a comprehensive and critical analysis of the benefit-risk balance of the medical product and cumulative information, as well as new or emerging information (safety, efficacy and effectiveness). The process of benefit-risk evaluation will provide no duplication effort and the risk management is more productive with respect to public health.

Table 1. Comparison between PSUR and PBRER

PSUR	PBRER
1. Large number of case listings (collecting, analyzing, and reporting AE information and listing of all Med Watch) and Summary Tabulations,	1. No case listings and limited to Summary Tabulations: Cumulative Summary Tabulations of serious adverse events (SAEs) from interventional clinical study conducted with the therapeutic investigational product Cumulative and interval summary Tabulations of Serious and Non-serious Adverse Reactions from Post-Marketing Data Sources
2. Estimations of basic cumulative clinical exposure estimations even in post-marketing and no requirement to discuss the signal detection	2. Clinical exposure and demographics for all interventional clinical trials since DIBD to align with DSUR Significant emphasis on signals from the reporting interval including Tabular summary of safety signals in the Appendix Overview of signals in new, ongoing, closed or completed clinical studies Stratification by special population in post-marketing.
3. Only a summary of updates to risk minimization process is required	3. Risk evaluations, significant risk content Effectiveness of risk minimization measures Summary of ongoing safety concerns and reporting results from post-marketing safety studies It is required to provide proposal for additional data on pharmacovigilence, risk minimization activities and product information

4. Emphasis on trials conducted for safety	4. All interventional trials need reporting in the PBRER when Clinical study report (CSR) is finalized a. Other trial-related safety and efficacy data to be included where relevant (e.g. non-interventional) b. Specific Appendix of trials: Listing of all Interventional trials with the Primary Aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the medicinal product. Listing of all non-interventional studies conducted with the Primary aim of identifying , characterizing or quantifying safety hazard, confirming the safety profile of the medicinal product, or of measuring effectiveness of risk management measures.
5. Individual case safety report (ICSR) orientated	5. Evaluation orientated- data evaluation used for benefit-risk analysis No narratives beyond those for important cases (e.g. index cases received in the late breaking period)
6. Limited reference to benefit of efficacy	6. Benefit evaluation required
7. Actions taken for Safety limited mainly to post-marketing use	7. Alignment with the DSUR means actions taken for safety with the investigational product
8. No specific requirement for non-clinical data	8. A section exists for non-clinical data
9.. Data from Late-breaking period is not clearly defined	9. A list of information is to be confirmed in 20 days post-DLP including references, new signals, CCDS updates)

CONCLUSION

Due to the progression in technology and widespread use of electronic reporting of ICSR, ICH E2C has been revised to ICHE2C (R2) or PBRER which provides not only a new thinking but also ensures convergence of local regulations which decreases burdens on regulators and industry. PBRER utilizes the resources efficiently and facilitates the management of submission frequency. A PBRER can be developed in such a way that the content of several sections may be used for sections of other documents as a basis for a modular approach like other ICH guidances e.g. E2E, E2F. If the IBD of the PBRER is aligned with the DIBD of the DSUR of the same product, then both reports can be prepared at the same time. Realizing the advantages of PBRER, the FDA adopted a process of accepting the PBRER in lieu of the PADER upon granting a PADER Waiver.

PBRER is evaluation orientated. It evaluates the patient drug exposure data from different countries along with the stratification of special population. Data from new, ongoing, closed or completed clinical studies are examined for the true signals as well as events of interest. Systematic efforts are placed to identify new risk or any changes in the known safety profile of the product. Evaluation of the signal analyses update the safety section of various reports including Company Core Safety Information (CCSI), Development of Risk Management Plan (DRMP), Company Core Data Sheet (CCDS), which allows for routine assessment and reassessment of the safety data. Benefit-risk analysis is incorporated into the PBRER.Earlier aggregated reports, e.g. PSUR, PADER are ICSR orientated, whereas the PBRER is based on benefit-risk analyses of interventional and non-interventional clinical studies.

Overall, PBRER utilizes the resources efficiently and the submission of this report reduces the number of reports to be submitted and decreases the burden on the sponsors and regulators. More discussions between sponsors and regulators may be required to optimize further evaluation of the benefit-risk balance and risk minimization activities.

REFERENCES

1. 21 CFR 312.32- IND safety reports.
2. Guidance for Industry : E6 Good Clinical Practice: Consolidated Guidance
3. www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf
4. Guidance for Industry :Addendum to E2C Clinical: Safety Data Management:
5. Periodic Safety Update Reports for Marketed Drugs www.ich.org/ichnews/.../ich-e2cr2-reached-step-2-of-the-ich-process
6. Guideline on good pharmacovigilance practices (GVP) Module VII. www.ema.europa.eu/ema/pages/includes /.../open _ document.jsp.

7. ICH Harmonized Tripartite Guideline Pharmacovigilance Planning E2E Current Step www.ich.org/fileadmin/Public.../ ICH.../E2E/.../ E2E _Guideline.pdf
8. ICH guideline E2C (R2) :Periodic benefit-risk evaluation report (PBRER)
9. Step 5
10. Gaffney A. FDA provides new guidance on submitting safety update reporting, RAPS Latest News, Posted 5 April 2013
11. http://www.raps.org/focus-online/news/news-article-view/article/3136/fda-provides-new-guidance-on-submitting-safety-update-reporting.aspx
12. Guideline on the Processing of Renewals in the centralized Procedure (EMA/CHMP/2990/00 ec.europa.eu/health/files/eudralex/vol-2/2012-06_gpr.pdf
13. CMDh Best Practice Guide on the processing of Renewals in the Mutual Recognition and decentralized procedure (CMDh/004/2005)
14. ICH guideline E2F :Note for guidance on development safety update reports:
15. Step 4 www.ema.europa.eu/ema/pages/includes/.../open_document.jsp.