DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

An Overview and its contents

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Why learn Aggregate reports?

- These skills are in great demand:
  - ❑ CROs, BPOs and Consulting firms
  - ❑ Pharmaceutical Companies are looking to hire candidates with only hands-on experience.

- Learning these basic Periodic/Aggregate reports – DSUR, PSUR/PBRER, Signal detection and Risk Management Plan (RMP) is very important for better career opportunities and is considered one of the highest paying jobs as it involves a lot of analytical, logical and medical judgment skills.

Introduction

The development safety update report (DSUR) proposed in this guidance is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. U.S. and European Union (EU) regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the U.S. investigational new drug application (IND) annual report and the EU annual safety report, respectively, and can therefore take the place of these existing reports. This guidance defines the recommended content and format of a DSUR and provides an outline of points to be considered in its preparation and submission.

Overview

- **What is a Development Safety Update Report (DSUR)?**

Development Safety Update Reports are new, internationally-harmonized, safety documents covering the safety summary of medicinal products during. **their development or clinical trial phase.**

They are based heavily on the PSUR format already used for updating the safety record of drugs in their marketing phase.

Reference document :

- ✓ **ICH E2F guideline on development safety update report**

Objective

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

(1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;

(2) describing new safety issues that could have an impact on the protection of clinical trial subjects;

(3) summarising the current understanding and management of identified and potential risks; and

(4) providing an update on the status of the clinical investigation/development programme and study results.

Objective

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug.

All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

Scope of DSUR

The main focus of the DSUR is data and findings from interventional clinical trials (hereafter referred to as “clinical trials”) of drugs and biologicals that are under investigation, whether or not they have a marketing approval.

Because, clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies should also be included in the DSUR. The DSUR should concentrate primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects.

Scope of DSUR

The DSUR should provide safety information from all on-going clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

- Clinical trials using an investigational drug (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase IV);
- Therapeutic use of an investigational drug (e.g., expanded access programmes, compassionate use programmes, particular patient use, single patient INDs, and treatment INDs); and
- Clinical trials conducted to support changes in the manufacturing process of medicinal products.

Scope of DSUR

The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:

- Observational or epidemiological studies;
- Non-clinical studies (toxicological and in vitro studies);
- Related DSURs, if applicable to the investigational drug;
- Manufacturing or microbiological changes;
- Studies recently published in the literature;
- Any other source of relevant safety findings for products in the same therapeutic class;
- Clinical trials conducted by a co-development partner, if permitted by the contractual agreement.

Format and contents

- Title page
- Executive Summary

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Periodicity and DSUR Data Lock Point

The Development International Birth Date* (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.

When the sponsor's first clinical trial is conducted in a country without a formal authorization process, the sponsor should designate an appropriate date linked to the commencement of the first clinical trial. Where clinical trials are ongoing in one country and are later initiated in another country, the original DIBD should be maintained and used for all countries in preparing the DSUR.

Periodicity and DSUR Data Lock Point

The data lock point of the DSUR should be the last day of the one-year reporting period. For administrative convenience, if desired by the sponsor, the data lock point of the DSUR can be designated as the last day of the month prior to the month of the DIBD.

When clinical development of a drug continues following a marketing approval in any country worldwide, both a PSUR and a DSUR should be submitted as specified by national or regional laws or regulations. If desired by the sponsor, a DSUR can be prepared based on the PSUR International Birth Date (IBD) so that the DSUR and the PSUR can be synchronized. In synchronizing the data lock points for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.

Duration of DSUR Submissions

The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR data lock point.

DSURs should continue to be submitted for as long as indicated by national or regional laws or regulations. When submission of an annual report is no longer required in an individual country or region, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug in that country or region. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

PERIODIC SAFETY UPDATE REPORT (PSUR)

An Overview and its contents

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Overview

- **What is a Periodic Safety Update Report (PSUR)?**

Periodic safety update reports (PSURs) are Pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.

Guidance documents:

- GVP module – VII- Periodic safety update report
- FDA-Guidance document –E2C (R1)

Objective

To present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefit to enable an appraisal of overall benefit risk.

To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:

- ✓ Examine whether new information is in accord with previous knowledge of the benefit risk profile and summarises
- ✓ Relevant new safety information that may impact the benefit risk profile
- ✓ Any important new efficacy and effectiveness information
- ✓ Conduct an integrated Benefit/Risk evaluation (where new important safety information has emerged).

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19. Conclusions and actions
20. Appendices to the PSUR

Standard submission schedule of PSURs

Marketing authorization holders for products authorised, shall submit PSURs according to the following submission schedule:

- at 6 months intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.

Submission of PSURs

Submission of PSURs on demand of a competent authority in a Member State Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a Member State.

However in special circumstances competent authorities in Member States can directly request the submission of a PSUR. When the timeline for submission has not been specified in the request, marketing authorisation holders should submit the PSUR within 90 calendar days of the data lock point.

Where are PSURs Submitted?

As of 13 June 2016, MAHs are required to submit all PSURs in the EU to the central PSUR repository using the eSubmission Gateway/ Web Client.

Use of the PSUR repository is mandatory for both centrally and nationally authorised medicines, whether they follow the EU single assessment or a purely national assessment procedure.

For the US FDA: regulatory submissions in electronic format to FDA's Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

Precedence for Granting PSUR Waivers

Applicants can request a waiver to submit PSURs to the FDA based on the month and day of the international birth date of the product instead of the month and day of the anniversary date of U.S. approval of the product.

The waiver request should specify that these PSURs would be submitted to the FDA within 60 calendar days of the data lock point (i.e., month and day of the international birth date of the product or any other day agreed on by the applicant and the FDA).

Procedures applicants should follow to submit a PBRER

Applicants With a PSUR Waiver:

If applicants already have a PSUR waiver for an approved application, FDA will consider the existing PSUR waiver to permit applicants to submit a PBRER instead of a PSUR under the conditions described below, because the PBRER replaces the PSUR for postmarketing periodic safety reporting. If applicants wish to substitute the PBRER for the PSUR with no changes in

the DLP or frequency of reporting, applicants can do so without submitting a new waiver request.

Procedures applicants should follow to submit a PBRER

However, if applicants wish to change any conditions of their PSUR waiver other than the format, applicants should submit either a notification or new waiver request, depending on the circumstances described below.

1. Change in the Date of the DLP for the PBRER – Submit Notification
2. 2. Longer PBRER Reporting Intervals But No Change in Frequency – Submit

Periodic Benefit Risk Evaluation Report (PBRER)

An Overview and its contents

Guidance document:

- ✓ ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)

Introduction

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.

Regulators from EU, Japan, and the US believe that the PBRER may be used to meet prevailing national and regional requirements for periodic safety and/or benefit-risk reports for approved medicinal products.

This guideline defines the recommended content and format of a PBRER and provides an outline of points to be considered in its preparation and submission.

Introduction

This guidance describes the conditions under which applicants can use an alternative reporting format, the International Council for Harmonisation (ICH) E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), in place of the U.S. periodic adverse drug experience report (PADER), U.S. periodic adverse experience report (PAER), or ICH E2C Periodic Safety Update Report (PSUR), to satisfy the periodic postmarketing safety reporting requirements.

This guidance also describes the procedures applicants should follow if they wish to submit a PBRER in place of a PADER, PAER, or PSUR. The steps will differ, depending on whether or not the applicant has an approved waiver in place to substitute the PSUR for the PADER/PAER.

Background

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials.

Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

Background

In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (e.g.,severe liver injury).

These factors underlie the need for continuing analysis of relevant safety, efficacy, and effectiveness information throughout the lifecycle of a medicinal product promptly, as important findings occur and periodically, to allow an overall assessment of the accumulating data

Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

Background

The ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, achieved Step 4 in 1996, and was intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide safety experience of a medicinal product at defined times post-approval.

At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the product information in order to optimise the use of the product. The guideline was revised in 2003, to provide needed clarification, as well as to provide additional guidance and flexibility.

Background

- The pharmacovigilance environment has evolved, however, prompting reassessment of the role of the PSUR in the spectrum of safety documents submitted to regulatory authorities. This reassessment highlighted several factors that led to consensus for revision and refocus of the guideline, to enhance its usefulness in light of advances in the field:

- significant progress in the technology and science of pharmacovigilance, including electronic submission of individual case safety reports (ICSRs) to regulatory authorities, automated data mining techniques, and more attention to benefit-risk evaluation;

Background

- Greater emphasis on proactive and documented risk management planning;
- increasing recognition that meaningful evaluation of important new risk information should be undertaken in the context of a medicinal product's benefits; and
- Overlap in the content of ICH guidelines related to pharmacovigilance documentation, particularly between ICH guideline E2C, the safety specification component of ICH guideline E2E, and ICH guideline E2F, the Development Safety Update Report (DSUR).

Important

A formal evaluation of benefit is a new feature of the PBRER; however, it is recognised that a concise discussion of benefit will usually be sufficient, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals,* and benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.

The frequency of submission of reports to regulatory authorities is subject to national or regional regulatory requirements, and may differ, depending on a number of factors. The guideline includes specific advice on managing different frequencies of PBRER submission in different regions.

Important

The PBRER has been developed in such a way that the content of particular sections of the report could be identical to that of corresponding sections of other regulatory documents, specifically the safety specification described in the ICH guideline E2E and the DSUR described in ICH guideline E2F.

Thus, the content of these sections of the PBRER is envisioned to be suitable for use in the other reports. This “modular approach*” would allow sections or modules to be submitted at different times to multiple authorities, across separate documents (i.e., the PBRER, DSUR, and safety specification).

Only modules that include new information would need to be updated when submitting the PBRER and is expected to improve efficiency for MAHs and regulatory authorities in their preparation and review of these documents, respectively.

Objectives

The main objective of a PBRER is to present a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

The PBRER should be submitted to regulatory authorities, and will contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval in the context of cumulative information by:

- examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile;

Objectives

- summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- summarising any important new efficacy/effectiveness information that has become available during the reporting interval; and
- where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When desired by the MAH, a list of the sources of information used to prepare the PBRER can be provided as an appendix to the report.

Objectives

A PBRER should be concise and provide sufficient information to assure regulatory authorities that the MAH is adequately monitoring and evaluating the evolving risk profile of a medicinal product.

All pertinent new safety information discovered during the reporting interval should be discussed in the appropriate sections of the PBRER.

Urgent safety information should be reported through the appropriate mechanism; the report is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns are detected.

Scope of the PBRER

The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information that may have become available since the International Birth Date (IBD):

- the date of the first marketing approval in any country in the world, or
- the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country

The PBRER should include cumulative knowledge of the product while retaining focus on new information, i.e., the overall safety evaluation and integrated benefit-risk evaluation will take into account cumulative information.

Scope of the PBRER

Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER.

Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate.

The PBRER should provide summaries of significant safety, efficacy/effectiveness information from data sources available to the MAH, when relevant to the benefit-risk evaluation.

Relation of the PBRER to other ICH documents

At present, some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements within the post-approval period:

- the PSUR (ICH guideline E2C(R1)) for periodic reporting of the safety of approved medicinal products

- the DSUR (ICH guideline E2F) for periodic reporting on the safety of medicinal products that remain in clinical development, and the safety specification component of ICH guideline E2E (Pharmacovigilance plan) that might be submitted at the time of marketing application and/or PSUR submission to aid in the planning of pharmacovigilance activities.

Relation of the PBRER to other ICH documents

As these documents have different regulatory purposes, different periodicities, and can be reviewed by different divisions within a single regulatory authority, each document needs to be complete in its own right – a comprehensive document that can stand alone.

Nevertheless, overlap and repetition between the content of the DSUR, PSUR, and safety specification can lead to inefficiencies – both in the production of the documents by the MAH, and in the review of the documents by regulatory authorities.

This guideline aims to address this duplication and facilitate flexibility by encouraging the use of individual modules, where they pertain to more than one report – to be used at different times, for different authorities, and for different purposes.

Reference information

An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison.

Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient, and consistent approach to the safety evaluation and make the PBRER a unique report accepted in all countries and regions.

Reference information

It is a common practice for MAHs to prepare their own "Company Core Data Sheet,*" CCDS, which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the "Company Core Safety Information,*" CCSI.

The latest CCDS in effect at the end of the reporting interval should be used as the reference for both the benefit and risk sections of the PBRER. The national or regional approved product information, which can differ from the CCDS, continues to be the reference document upon which labeledness or expectedness is based for the purpose of national or regional expedited post-marketing safety reporting.

Reference information

It is important to highlight any differences between the CCSI and the national or regional product information/labelling in the cover letter or a regional appendix accompanying submission of the PBRER.

The MAH should continuously evaluate whether any revision of CCDS/CCSI is needed whenever new safety information is obtained throughout the reporting interval. All changes to the CCDS/CCSI made during the interval should be described in Section 4 (“Changes to Reference Safety Information*”) and/or Section 16 (“Signal and Risk Evaluation”) of the PBRER. The MAH should provide a copy of the current version of the CCDS(s) referred to in the PBRER as an appendix to the report.

Level of detail within PBRER

The level of detail provided in certain sections of the PBRER should depend on the medicinal product's known or emerging important benefits and risks.

This approach is applicable to those sections of the PBRER in which there is evaluation of safety data, efficacy/effectiveness data, safety signals, and benefit-risk. Therefore, the extent of information provided in such PBRER sections will vary among individual PBRERs.

Level of detail within PBRER

For example, when there is important new safety information, a detailed presentation of that information should be included, plus any other relevant contextual information (e.g., updated full benefit information) needed to facilitate a robust benefit-risk analysis.

Conversely, when little new important safety information has become available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit-risk evaluation would consist primarily of an evaluation of updated interval safety data, with the recognition that the benefit-risk profile has not changed during the reporting interval.

Benefit-risk evaluation

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks.

As new information about the drug emerges during marketing experience, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the benefit-risk relationship through risk minimisation activities,* e.g., labelling changes, communications with prescribers, or other steps.

This assessment may include evaluation of populations and/or endpoints that were not investigated in the registrational clinical trials.

Periodicity and PBRER data lock point

International birth date and data lock point

The date of the first marketing approval for the medicinal product in any country in the world is the IBD. For medicinal products that are on the market in many countries, it is possible that there are several national or regional birthdates. Such different birthdates should be harmonized with the IBD with agreement of regulatory authorities.

Through PBRERs prepared with harmonised IBDs, the same updated safety and benefit-risk information can be reviewed globally by all regulatory authorities. The data lock point is the date designated as the cut-off for data to be included in a PBRER, based on the IBD.

Periodicity and PBRER data lock point

For administrative convenience, if desired by the MAH, the data lock point of the PBRER can be designated as the last day of the month of the end of the reporting interval, with a corresponding change to the start date of the next reporting interval.

When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), which might be approved at different times, the original IBD should be maintained to determine the data lock point for purposes of the unified PBRER.

When clinical development of a medicinal product continues following marketing approval, the starting point of the DSUR reporting interval can be synchronized with the IBD-based cycle, so that both the DSUR and PBRER can be prepared at the same time.

Format and presentation of PBRER

The full ICH guideline E2C(R2) format should be used for all PBRERs. When no relevant information is available or a PBRER section is not applicable, this should be stated. In some countries and regions, the PBRER requirement may be linked to other regulatory documents for pre-approval periodic reporting (i.e.,DSUR), post-marketing pharmacovigilance planning and/or risk management.

The regulatory authorities and MAHs can take advantage of the modular approach of the PBRER (i.e., sections that can be separated and submitted independently or combined with other documents) to facilitate such regulatory needs, maximize the utility of the content, and reduce duplicate work.

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15. Overview of signals: new, on-going, or closed
16. Signal and risk evaluation
17. Benefit evaluation
18. Integrated benefit-risk analysis for approved indications
19. Conclusions and actions
20. Appendices to the PBRER

Time interval between data lock point and the submission

As a result of the expanded scope of the PBRER, the time interval between the data lock point 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
- Ad hoc PBRERs: 90 calendar days, unless otherwise specified in the ad hoc request

Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.

Issues and challenges

There are quite number issues/challenges faced during and after drafting of report for e.g. literature data and data tabulations which can significantly impact:

- **Quality of the report**
- **Misinformation and misinterpretation**
- **Delivery within timelines**

➢ How to handle them?

Certain proven strategies, tips and tricks needs to be implemented to complete the report in short time at the same time deliver high quality.

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