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WHAT IS A DSUR?

A Development Safety Update Report (DSUR) is a periodic regulatory safety report used for drugs under development and for marketed products that are under further study among the ICH regions. The purpose of the DSUR is to provide a comprehensive annual analysis of the product's safety information, including ongoing assessment of the benefit-risk evaluation and safety profile, based on safety information collected during the reporting period.

The DSUR follows a common standard based upon ICH guideline E2F

GENERATING A DSUR

What is a DSUR?

A Development Safety Update Report (DSUR) is a periodic regulatory safety report used for drugs under development and for marketed products that are under further study in the ICH (International Council for Harmonisation) regions. The DSUR provides a comprehensive annual analysis of the product's safety information, including ongoing assessment of the benefit-risk evaluation and safety profile, based on safety information collected during the reporting period. It is submitted annually to regulators (and may be submitted to the US authorities in lieu of the IND Annual Report). One DSUR should be generated for each product, and must include data for the reporting period from all ongoing and completed studies.

The DSUR follows a common standard based on ICH guideline E2F, which aims to harmonize the format, content, and frequency of reporting safety-related information and to ensure consistency in reporting. The DSUR should provide information on the status of the clinical investigation/development program and study results; safety of the product and any issues which may affect the safety of subjects; a summary of the current understanding and management of the identified and potential risks; and a statement indicating whether the data from the current reporting period aligns with the study drug's known safety profile.

Generation, Frequency, & Content

DSURs must be generated and submitted annually on the Development International Birth Date (DIBD), which is the date of the first approval (or authorization) to conduct an interventional clinical trial in any country.

The reporting period start date is based on the DIBD; the end date is based on the Data Lock Point (DLP), the last day of the annual reporting period (ie, one day prior to the DIBD). For administrative convenience, a sponsor may designate the last day of the month prior to the month of the DIBD as the DLP.

The DSUR is submitted to all concerned regulatory authorities, ethics committees, and investigators as required by country regulations and timelines. For many countries, the submission timeline is required within 60 calendar days of the DLP. However, some countries may utilize different reporting timelines.

DSUR generation and submission must continue annually until such time that the product is granted marketing approval and the final DSUR is submitted, or until the final clinical study report (CSR) is submitted.

As stipulated in ICH guideline E2F, DSUR contents include (but may not be limited to) the following:

- Executive Summary
- Cumulative subject exposure data
- Safety data from all clinical trials on the product ongoing or completed during the reporting period
- Significant non-clinical data
- Reference Safety Information (RSI), eg, Investigator's Brochure (IB)

- The IB in effect at the start of the reporting period is the Reference Safety Information used to determine if the safety information received within the reporting period is the same as what is previously known for the safety profile for the investigational product. If the RSI has been revised during the reporting period and not submitted to the regulatory authorities prior to the current DSUR submission, the sponsor should provide the copy of the IB as an attachment to the DSUR. Revision of case assessment should be performed when the RSI has been updated during the DSUR reporting period, as cases reported after the RSI revision would have been assessed using the updated RSI during real-time case processing.

- Findings from literature review

- Overall safety assessment including findings from signal detection and benefit-risk evaluation

- Region-specific information
  - Regional appendices based on country requirements. Examples include:
    - Cumulative summary tabulation of serious adverse reactions (SAEs)
    - List of subjects who died during the reporting period
    - List of subjects who dropped out of clinical trials in association with an AE event during the reporting period
  - US regional appendices include the following:
    - Significant Phase I protocol modifications with respect to a US IND
    - Significant manufacturing changes
    - Description of the general investigation plan for the coming year with respect to a US IND
    - Log of outstanding business with respect to a US IND

If the DSUR contains unblinded data—and to prevent inadvertent unblinding by reviewers—include a notation on the cover page stating that the report contains unblinded data.

Submission

DSUR submissions should be performed in accordance with country requirements and timelines. These requirements may include submission of only the DSUR Executive Summary with a line listing of SAEs or the full DSUR. The submission format may vary by country, and may require special paper or electronic formats, ie, eCTD, email, or submission via portal.

For early stage studies less than a year in duration, submission of the DSUR is not required if the study is completed and the CSR is finalized and submitted prior to the DSUR DLP. However, when more than one early stage study of less than a year in duration was completed in the reporting period, a DSUR is recommended, as the individual study reports do not include a comprehensive analysis of safety information across trials.

Correlation with the Periodic Safety Update Report (PSUR)

When clinical trials continue for a product after it has received marketing authorization in any country, separate submissions of a DSUR and a PSUR are required. This is necessary as information from marketing experience—which is included in the PSUR—may also be relevant to clinical development; as such, it should also be included in the DSUR. Clinical trial data and safety findings for marketed products that are included in the DSUR may also be pertinent to post-marketing surveillance and therefore, should also be included in the PSUR. The reports should be comprehensive, standalone documents, as they focus on different subject matter.

It is important to note that the DSUR and PSUR have different reporting frequencies and recipients; however, if decided by the sponsor, the DSUR can be generated and submitted based on the PSUR International Birth Date (IBD); this allows the DSUR and PSUR DLPs to be synchronized, as long as the period covered in the DSUR does not exceed one year.

REFERENCES

1. EMA ICH guideline E2F on development safety update report, Step 5, September 2011, EMA/CHMP/ICH/309348/2008 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf

2. Guidance for Industry E2F Development Safety Update Report, August 2011 http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073109.pdf

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Minimizing patient risk is crucial as we endeavor to bring new medicinal products to the marketplace.

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Joash Krishna, Associate Director in Safety and Risk Management at PRA is a pharmacist with 26 years of clinical experience and 15 years as a pharmacovigilance professional. He has seven years of experience in drug safety as a manager and lead for a Drug Safety and Pharmacovigilance department and 3 years' experience in clinical data management/medical coding. He has strong therapeutic expertise in pharmacy, ophthalmology, dermatology, immunology, and oncology. Mr Krishna joined PRA Safety & Risk Management in 2012. During his time at PRA, he has developed expertise in aggregate safety reporting (DSUR) signal detection set-up and management activities and literature search/review. He is also a trainer in the implementation of Argus Safety Database and Rave Safety Gateway and as mentor to safety scientists and drug safety associates.

Amy Mazzei, Safety Scientist

Ms Mazzei has 12 years of clinical research experience supporting Safety & Risk Management with global Phase I-IV clinical trials and post-marketing studies in various therapeutic areas, including 3 years as a safety scientist and 7 years as a lead drug safety associate (DSA) responsible for safety management and oversight of deliverables. Her experience as a safety scientist includes DSUR and literature review oversight, coordination, generation and review; assisting in signal detection and review of signal detection reports; and serving as an SRM trainer. DSA experience includes plan generation, report processing, data entry and MedDRA/WHODrug coding, narrative writing, safety letter creation and distribution, and SAE-AE reconciliation. Ms Mazzei also has been active interviewing and mentoring staff and developing/improving processes. Her therapeutic experience includes oncology, neurology, psychiatry, hematology, respiratory, immunology, genitourinary, and cardio-metabolic and infectious diseases.