



Development Safety Update Reports

Andrea Lohée, Pharm-AD
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Development Safety Update Reports

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Development Safety Update Reports General

General

- Should be prepared according to ICH Guideline E2F
- A DSUR should be prepared after the 1st authorisation of a clinical trial world wide = DIBD (Development International Birth Date)
- A DSUR should be submitted to the concerned member state until the last visit of the last patient in that Member State
- The covered reporting period should not exceed 1 year



Development Safety Update Reports General

- For IMPs without a marketing authorisation, (unlicensed), the Development International Birth Date (DIBD) is the date of the first authorisation by the sponsor of a clinical trial in any country (worldwide) for the investigational product.
- For IMPs with a marketing authorisation (licensed), the DIBD is the (International Birth Date (IBD) which is the date when the product was first given a marketing authorisation in any country worldwide
- The DIBD must be indicated within the DSUR or in the covering letter



Development Safety Update Reports Objective

Objective

The objective of a DSUR is to present a comprehensive annual review and evaluation of safety information collected within the reporting relevant to the IMP.

Information should be reported based on the previous knowledge of a product's safety. Any new issues that may impact the overall program or specific clinical trials are required to be described in detail.



Development Safety Update Reports Content and format

Content and format

A single DSUR is required to include safety data from all clinical trials conducted with the investigational drug using all indications, all dosage forms, and all intended populations. This includes multiple clinical trials, multiple sponsors if there is a formal agreement, and combination products (fixed combination drug, multidrug regimen trials).



Development Safety Update Reports

Content and format

Content and format

The DSUR should provide safety information from all ongoing clinical trials and other studies the manufacturer is conducting or has completed during the review period including

- Safety information obtained by the sponsor during the reporting period
 - Analyses of any new information based on the previous knowledge of the IMP
 - Changes to the safety profile of the IMP and any change in the benefit-risk ratio



Development Safety Update Reports Content and format

Content and format

The DSUR should provide safety information from all ongoing clinical trials and other studies the manufacturer is conducting or has completed during the review period including:

- Safety information obtained by the sponsor i.e.
 - clinical trials using the investigational drug (both ongoing and completed)
 - clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase 4))
 - therapeutic use of an investigational drug
 - clinical trials conducted to support changes in the manufacturing process of medicinal products



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- Analyses of any new information based on the previous knowledge of the IMP
- Changes to the safety profile of the IMP and any change in the benefit-risk ratio

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

- Observational or epidemiological studies
- Non-clinical studies
- Related DSURs, if applicable to investigational drug
- Manufacturing or microbiological changes



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- studies recently published in medical journals
- clinical trials with results indicating a lack of efficacy that could have a direct impact on subject safety
- any other source of relevant safety findings for products in the same therapeutic class
- clinical trials conducted by co-development partner, if permitted by contractual agreement



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Content and format

The date should be presented in the format provided in ICH guideline E2F which includes data presented in line listings and summary tabulation

- Interval line listings of SARs for the reporting period
- Cumulative summary tabulations of SAEs since the DIBD
- Subject exposure to the IMP (number of subjects treated in the reporting period)



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Other aspects

Other aspects

The reference safety information is the Investigator Brochure (IB). Local product labels should also be used as reference safety information when an IB is not required.

Emphasis on:

- Actions taken in the reporting period for safety reasons, which includes a description of significant actions related to safety during the reporting period by the sponsors, regulators or data monitoring board



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Other aspects

- Summary of important risks, which should provide a concise, cumulative, issue-by-issue list of important identified and potential risks
- Such risks might include toxicities known to be associated with a particular molecular structure or drug class or concerns based on accumulating non-clinical or clinical data. Each risk should be re-evaluated annually and summarized as appropriate, based on the current state of knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent upon the stage of drug development.



Development Safety Update Reports DSUR and IND Annual Report

DSUR and IND Annual Report

Submission of a DSUR currently is mandated only in the EU and accepted in the US in lieu of a US Investigational New Drug application (IND) annual report.¹³ When a US IND annual report is compared with a DSUR, several differences are found, which are summarized here:



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- Individual Study information, which requires a brief summary of the status of each ongoing and completed study in the previous year for IND annual report, whereas DSUR assembles all individual studies, but does not identify which one is under IND, which one is IRB waiver and which one is listed under www.clinicaltrials.gov. Moreover, a DSUR does not include non-interventional and long-term extension (LTE) studies, which are included under an IND



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Summary of Information in IND AR consists of:

- narrative or tabular summary of most frequent and most serious adverse experiences by body system
- summary of IND safety reports
- list of subjects who died with cause of death
- list of dropouts due to adverse events
- mechanism of action
- list of non-clinical studies
- summary of significant manufacturing or microbiological changes



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In contrast, a DSUR needs full data under an IND for LTE studies. Registries and observational studies may or may not be under an IND. Moreover, it does not include non-clinical and manufacturing update with stability studies



Development Safety Update Reports DSUR and IND Annual Report

The advantages of submitting a DSUR are:

- It harmonize clinical safety data management with pharmacovigilance and provides a current safety profile.
- It decreases the number of reports
- It provides a comprehensive, thoughtful annual review and increased assurance of protection for the trial subjects.
- The two new sections in the DSUR should provide a concise, cumulative, issue-by issue list of important identified and potential risks
- Regulators and sponsors review the same information at the same time



Development Safety Update Reports DSUR and IND Annual Report

The disadvantage of using a DSUR is:

- In order to complete the section “Action taken in the reporting period for safety reasons,” large pharmaceutical companies that run many clinical trials in various countries have to collect the data related to safety from their affiliates within a very short period of time