

Guideline on how to increase transparency when presenting safety information in the Development Safety Update Report (DSUR): region-specific requirements for Canada and the United Kingdom

Background

In countries that adhere to the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) the Development Safety Update Report (DSUR) is considered the standard report for informing regulators of the evolving safety profile of drugs under development.

The content and format of a DSUR are described in the ICH guidance E2F¹ (current Step 4 version dated 17 Aug 2010) and further discussed in Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials (CIOMS Working Group VII, 2006).

Periodic analysis of safety information is essential to identify and mitigate the risks associated with the administration of an investigational drug.

By preparing DSURs on an annual basis sponsors can reassure the regulators that they have adequate oversight of the safety profile of the investigational drug.

Scope

This document will provide guidance on how sponsors can disclose in the DSUR the way they have recorded safety information during the reporting period and reviewed it in the context of the cumulative safety profile of the investigational drug. The guidance describes the requirements for DSURs submitted to the regulatory authorities of Canada, and the United Kingdom. This guidance applies to both marketed and non-marketed drugs that are used in clinical trials and applies to DSURs prepared by the manufacturer and/or marketing authorisation holder of the investigational drug.

MedSafe, the regulatory authority of New Zealand, is also in agreement with the guidance and will take it into consideration when reviewing their national legislation.

Legal basis and relevant guidelines

This document has to be read in conjunction with:

- ICH guidance E2F (current Step 4 version dated 17 Aug 2020)
- Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials (CIOMS Working Group VII, 2006)
- Applicable clinical trial legislation:

Canada Division 5 of the *Food and Drug Regulations*: Drugs for Clinical Trials Involving Human Subjects

¹ https://database.ich.org/sites/default/files/E2F_Guideline.pdf

Transparency in presenting safety information in the DSUR

Sponsors should use the DSUR to present a comprehensive annual review of pertinent safety information collected during the reporting period and to evaluate whether it is consistent with the previous knowledge of the safety profile of the investigational drug (ICH E2F, 1.2).

Taking into consideration the safety data from the new reporting period and the cumulative data recorded from the Development International Birth Date the sponsor should provide an interpretation of the information and its implications in terms of risk mitigation strategies (ICH E2F, 3.18).

While it is understood that signal detection can occur through various means and that the DSUR should not be used to communicate new safety issues (which should be done via updates of the investigator's brochure and, if applicable, via urgent safety measures) it should describe the actions taken to address safety concerns identified during the reporting period.

The DSURs currently submitted for regulatory review provide listings of serious adverse events and reactions. However, even though sponsors will have conducted specific assessments regarding previous or newly identified safety concerns during the reporting period, these detailed safety assessments are not part of the document.

There is a need for sponsors to be more transparent about how they have reviewed, evaluated and interpreted the data included in a DSUR. The increased quality of the information included in the DSUR will facilitate the regulatory review process, will reduce additional requests of information from the regulatory authorities and ultimately demonstrate that the investigational drug is used in a safe manner.

Region-specific information section

Sponsors are reminded that the ICH E2F guidance recommends that the overall safety of an investigational drug is assessed taking into consideration the reporting period data in the context of the cumulative experience with the drug itself (ICH E2F, 3.18). In the interest of transparency it is not required that new procedures are implemented or additional actions taken, but it is expected that sponsors explain how they performed their due diligence during the reporting period.

The region-specific information section of the DSUR should be used to include a summary description of the process used by the sponsor to review the worldwide safety data of the investigational drug (for example: regular analyses of accumulating data, in-house safety review meetings, proposal of specific pharmacovigilance activities, substantial modifications of protocol, etc.).

In addition, the region-specific information section needs to describe how each signal, that is an event with an unknown causal relationship to the investigational drug considered worthy of further exploration, identified during the reporting period was evaluated as well as how a decision was made regarding the signal itself. The possible decisions regarding a signal are:

- the signal is closed because the signal evaluation has been completed during the reporting period. The outcome of evaluation can be that the signal is refuted because the sponsor concluded that there is no causal relationship with the investigational

drug. In this case the sponsor is expected to explain why the signal was refuted. Alternatively, the signal is closed because it is considered to be either a potential or an identified risk. In this case the sponsor should describe how the risk will be mitigated. Reference to either section 3.18 and/or 3.19 of the DSUR is acceptable.

- the signal is kept open because additional surveillance is needed to determine whether it can be closed or whether an association with the investigational drug can be suspected (potential risk) or is confirmed (identified risk).

This signal evaluation description can be provided in the form of a table similar to that in section 16.2 of the Periodic Benefit Risk Evaluation Report² (PBRER) template. However, the use of the PBRER-style table is not mandatory and any other table or text description can be used.

An example of PBRER-like table is provided below:

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Anaemia	04 March 2015	Ongoing	NA	Single serious case	The signal consisted of a single report of....	Individual case analysis; Review of relevant scientific literature. Reassessment of preclinical and clinical development safety data.	Review at the next Safety Review Team meeting

Definitions

- 1) Investigational drug: to indicate only the experimental product under study or development. Note: This term is more specific than “investigational medicinal product” which includes comparators and placebos. Source: (CIOMS Working Group VII, 2006)
- 2) Reporting period: the year ending on the anniversary of the Development International Birth Date (DIBD). The DIBD is the date at which the sponsor received its first authorisation to conduct a clinical trial in any country.
- 3) Signal: A report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance. (CIOMS VI)

² https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

- 4) Sponsor: An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial. [ICH E6 (R1)]
- 5) Periodic Benefit-Risk Evaluation Report (PBRER): common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions. [ICH E2C (R2)]