CONCEPT NOTE
CIOMS WORKING GROUP XVI ON
THE DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

28 October 2024

BACKGROUND

In countries that adhere to the 2010 principles of the International Conference (now Council) 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 discussed in 'Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials' (CIOMS Working Group VII, 2006) and further described in the ICH E2F Guideline.

As per current ICH DSUR guidance, sponsors should use the DSUR to present an 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). However, a periodic report, such as the DSUR, is not intended to be the first notification of relevant safety information to clinical trial safety boards or regulatory authorities, or the way signal detection activities are performed.

The ICH E2F Guideline achieved Step 4 in August 2010. Since then, safety activities for clinical trials have been expanded to include technological improvements (e.g. electronic reporting systems, use of artificial intelligence tools), emphasis on proactive risk mitigation measures, and benefit-risk assessment.

Post-marketing update reports have evolved from focusing only on the safety of an approved medicinal product[1] [Periodic Safety Update Report (PSUR)] to providing an assessment of both the risks and benefits of the drug [Periodic Benefit-Risk Evaluation Report (PBRER), see ICH E2C(R2) Guideline]. Similarly, DSURs should evolve from reports that focus only on safety to provide a more comprehensive and transparent picture of available information of both the risks and benefits of a medicinal product under development. During the clinical development phase, signal detection can occur in a variety of ways and should lead to prompt communication of new safety issues through updates to the investigator's brochure and, where appropriate, through urgent risk mitigation measures. The assessment of cumulative safety data in the DSUR should be used to inform risk assessment and management.

Currently, DSURs include listings of serious adverse reactions observed during the reporting period, cumulative summary tabulations of serious adverse events, evaluations of the risks, summary of important risks, and benefit-risks considerations. However, they lack a structured and clear description of how sponsors identified the risks, what signals were assessed during the reporting period, and how efficacy data contributed to the conclusion drawn regarding the benefit-risk evaluation.

Some National Competent Authorities already require sponsors to provide additional information about how they performed their due diligence during the reporting period. The National Competent Authorities of the Member States of European Union (EU) (1), the UK Medicines and Healthcare products Regulatory Agency

[1] In this concept note "drug" and "medicinal product" are used interchangeably.

(MHRA) and Health Canada require that the region-specific information section of the DSUR be used to describe how sponsors have assessed safety signals for the drug under development (2).

OBJECTIVES

1. CIOMS should establish a working group to recommend improvements to the content and format of the DSUR in accordance with expanding safety activities and evolving regulatory requirements.
2. The working group should discuss how the DSUR can be updated to better communicate information about the safety and benefit-risk balance of the investigational drug to the regulatory authorities.

IMPACT

The DSUR is crucial in maintaining adequate oversight of the safety profile of medicinal products under development. Improving the quality of the DSURs will ensure protection of trial participants and facilitate creating more optimal development safety updates useful both for sponsors and regulators.

COMPOSITION OF THE WORKING GROUP

a) Regulators
b) Industry
c) Academia

DELIVERABLES

The working group will write a report providing recommendations regarding the content and format of the DSUR. In particular, the working group will provide advice regarding the following points:

i. whether the DSURs should be expanded to include a summary of the process used by the sponsor to review the global safety data relating to the investigational drug (e.g. regular analyses of accumulating data, internal safety review meetings, presence of a Safety Review Committee overseeing all trials of the investigational product, implementation of Data Monitoring Committees/Data Safety Monitoring Boards overseeing individual trials);

ii. whether the DSUR should provide an overview of the safety signals that have been evaluated during the reporting period (including a description of the reasons why they were closed or left open at the end of the reporting period);

iii. whether the DSUR should include a more detailed benefit-risk analysis. The benefit-risk assessment should be appropriate to the stage of development and should contribute to the conclusions and actions (e.g. changes to the reference safety information, additional risk minimization activities).

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: https://cioms.ch/publications/product/development-safety-update-report-dsur-harmonizing-format-content-periodic-safety-report-clinical-trials-report-cioms-working-group-vii/

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. Source: ICH E2F 2010: https://database.ich.org/sites/default/files/E2F_Guideline.pdf

3) *Signal*: A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. Source: CIOMS Working Group VI 2005; https://cioms.ch/publications/product/management-of-safety-information-from-clinical-trials-report-of-cioms-working-group-vi/ ; ICH E2C (R2) 2012: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

4) *Sponsor*: An individual, company, institution, or organisation that takes responsibility for the initiation, management and arrangement of the financing of a clinical trial. A clinical trial may have one or several sponsors where permitted under regulatory requirements. All sponsors have the responsibilities of a sponsor set out in this guideline. In accordance with regulatory requirements, sponsors may decide in a documented agreement setting out their respective responsibilities. Where the agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors. Source: ICH E6 (R3), Draft version 2024: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

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. Source: ICH E2C (R2) 2012: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

REFERENCES

1. The rules governing medicinal products in the European Union. VOLUME 10 - Guidance documents applying to clinical trials. CLINICAL TRIALS REGULATION (EU) NO 536/2014. QUESTIONS & ANSWERS. VERSION 6.9, 7.43. https://health.ec.europa.eu/system/files/2023-12/regulation5362014_qa_en_0.pdf
2. 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, 2021 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993808/DSUR-Guideline-08June2021.pdf