Pharmacovigilance

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Editorial

The Pharmacovigilance section of this issue is related to the first Meet & Share online event held in December 2021 by the EMWA Pharmacovigilance Special Interest Group (PV SIG) – with more than 70 attendees!

Subject matter experts shared their experience and thoughts on the impact of recent guidance, e.g. the Clinical Trials Regulation in the European Union (EU-CTR), the British Medicines and Healthcare products Regulatory Agency (MHRA) guidance, Japanese and Chinese requirements on development safety update reports (DSURs), and on Japan's Sakigake approach (first-in-class first-in-world accelerated approval). Stefanie Rechtsteiner was one of the presenters in the online event, and here shares with our readers some of the topics and thoughts that were discussed there.

If you have experience with the topics, or questions or comments related to the article, please contact the PV SIG at info@emwa.org. We hope to have further discussions and learn more together in our next meeting!

Happy reading,
Tiziana

Guidance impact on Development Safety Update Reports

By Stefanie Rechtsteiner
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The Development Safety Update Report (DSUR) guidance, issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[1] was introduced in 2011. ICH E2F has not been updated since implementation, unlike other safety guidances, such as Good Pharmacovigilance Practices (GVP) Modules V or VII. Nevertheless, the DSUR has been keeping safety writers on their toes. This is not only because this concise and well-structured document covers a broad spectrum of topics and both the pre- and post-marketing life-phase of a drug, but also because of its alliance to other documents, such as the Risk Management Plan (RMP), the Periodic Benefit Risk Evaluation Report (PBRER), or the Investigator's Brochure (IB).

The DSUR summarises important safety information from clinical trials. It is submitted to health authorities across the ICH region and therefore addresses requirements and needs of recipients across the world and brings all of them to the same level of knowledge about a drug under development. It seems natural that new or updated regulations, directives, or guidance documents associated with clinical trials will potentially impact the DSUR.

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Recent guidances are the Clinical Trial Facilitation Group (CTFG) Question & Answer (Q&A) document,[2] the latest Clinical Trials Regulation in the European Union (EU-CTR) No 536/2014 Q&A,[3] and guidance text released by the British Medicines and Healthcare products Regulatory Agency (MHRA)[4] and by the MHRA together with Health Canada (HC).[5] CTFG and EU-CTR are EU initiatives to harmonise the preparation, submission, and review of clinical trial applications, and the conduct of clinical trials. Among many other topics, they describe which Reference Safety Information (RSI) should be used for determining the expected terms in the cumulative summary tabulation of serious adverse reactions (SAR) that is provided as an appendix of the DSUR. The RSI, i.e. usually a specific subsection of the IB,[2] is used for determining the expectedness of SARs. If a serious event is considered related to the investigational drug and the serious reaction is not included in the RSI, it is categorised as a suspected unexpected serious adverse reaction (SUSAR) and must be reported to health authorities (and possibly ethics committees) as per statutory timelines. The ICH E2F guideline[1] does not go into this level of detail and simply states that the RSI (here the IB in general) that is effective at the beginning of the reporting interval should be used for the assessment of new safety information.

Unfortunately, the definition of the RSI version to be used for the DSUR in the new EU guidance seems to be in conflict with the guidance provided in ICH E2F in 2011. This conflict has resulted in confusion and discussion within companies responsible for writing DSURs, and between these companies and health authorities outside the EU.

CTFG Q&A document on RSI

The CTFG updated their Q&A on the RSI in November 2017 and advised sponsors that the primary purpose of the RSI is to serve as the basis for expectedness assessment for expedited reporting of SUSARs and for annual safety reporting. This had an impact on the version of the RSI that was used for the identification of expected SARs in the DSUR cumulative summary tabulation of SARs. The instructions for update, submission, and applicable version of the RSI for the DSUR are summarised in Table 1.

CTFG determines that the most recently approved RSI is the relevant one for the DSUR.

Table 1. Reference Safety Information and Data Safety Update Report

	CTFG Q&A	EU-CTR Q&A	MHRA Inspectorate blog
When to update RSI?	The RSI should only be updated once a year.	Recommendation to update the RSI once a year, in alignment with the DSUR.	–
When to submit updated RSI?	The RSI should be submitted together with the DSUR, "on the same day or shortly thereafter".	The updated RSI should be submitted in parallel to the DSUR, or at the latest within one month of submission.	The MHRA refers to the instructions provided in the CTFG Q&A document, according to which the RSI should be submitted in parallel with the DSUR (on the same day or shortly thereafter).[2]
Which RSI version is relevant for the DSUR?	For the identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions", the version of the RSI most recently approved in all member states should be used. This most recently approved version should at the same time be considered as the "RSI in effect at the start of the annual reporting period".	For the identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions", the RSI in effect at the start of the annual reporting period should be used. The RSI in effect at the start of the annual reporting period should be the version of the RSI in the IB most recently approved in at least one member state in which clinical trials are ongoing with the investigational drug.	For DSURs for trials in the United Kingdom and also other EU countries, MHRA requires sponsors to use the RSI that was approved at the beginning of the reporting period by both the MHRA and European member states.

Source: CTFG Q&A, EU-CTR Q&A, MHRA Inspectorate blog[2–4]

Abbreviations: CTFG, Clinical Trial Facilitation Group; DSUR, Development Safety Update Report; EU-CTR, Clinical Trials Regulation in the European Union; IB, Investigator Brochure; MHRA, Medicine and Healthcare products Regulatory Agency; RSI, Reference Safety Information; SUSAR, Suspected unexpected serious adverse reaction

If the RSI is updated and submitted with a DSUR, and approved some time afterwards, then this newly approved RSI would be the most recently approved for the next DSUR. Since after RSI submission the previous RSI remains in effect until the new one is approved, the RSI in effect at the start of the annual DSUR reporting period would not be the same as the one most recently approved. Figure 1 is from the CTFG Q&A document and illustrates which RSI version is relevant for the DSUR.

Figure 1 shows that for the purpose of identifying unexpected terms in the cumulative SAR tabulation of the current DSUR, the version of the RSI created at the time of the last DSUR (DSUR no. 9, IB no. 6) and submitted in parallel (or shortly thereafter) should be used. Consequently, it would be the RSI version in effect at the end of the DSUR reporting period (IB no. 6) and not the one in effect at the beginning of the DSUR reporting period (IB no. 5) that is relevant for determining the expectedness of terms. This seems to be contradictory to ICH E2F.[1] The CTFG resolved this contradiction by determining that the RSI

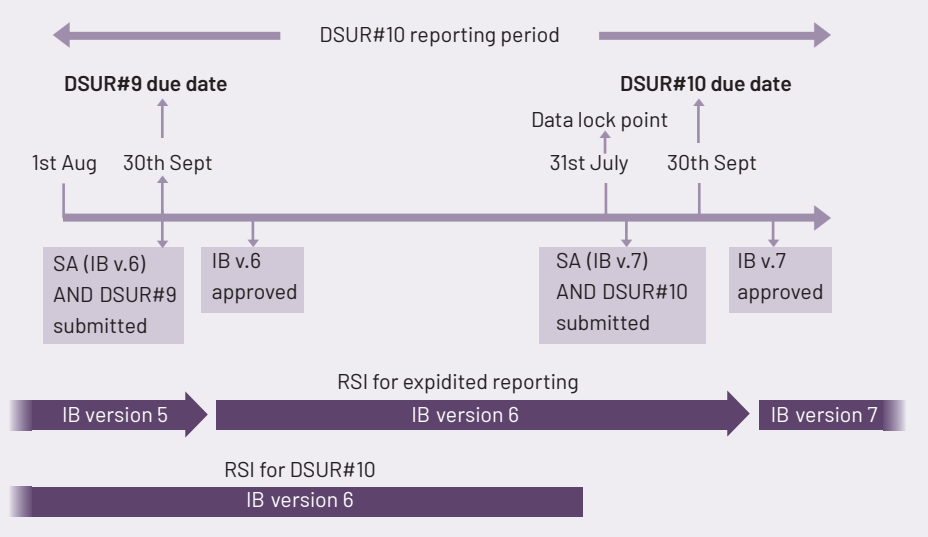

Figure 1. CTFG Q&A – DSUR and RSI version

Source: https://www.hma.eu/fileadmin/dateien/ Human_Medicines/01-About_HMA/ Working_Groups/CTFG/2017_11_ CTFG_Question_and_Answer_on_ Reference_Safety_Information_ 2017.pdf

most recently approved in all member states "should be considered to be the 'RSI in effect at the start of the annual reporting period'".[1,2]

Regulation (EU) No 536/2014 Q&A on RSI

The new EU-CTR 536/2014 (Regulation [EU] No 536/2014 of the European Parliament and of the Council of April 16, 2014 on Clinical Trials on Medicinal Products for Human Use, and repealing Directive 2001/20/EC) was issued in May 2014. Since December 2014, the related Q&A document has been discussed progressively, and the final version (version 5) was released in January 2022.[3] The regulation also came into effect on January 31, 2022.

The EU-CTR Q&A guidance requests the RSI in effect at the start of the annual reporting period to be used for SUSAR identification in the DSUR.[3] This would be in line with ICH E2F. However, in the sentence that follows it is defined that the " 'RSI in effect at the start of the annual reporting period' should be the version of the RSI in the IB most recently approved […]".[3] So the CTFG and EU-CTR Q&A documents use almost the same wording, just in changed order. Both documents refer to ICH E2F. Both require sponsors to use the latest approved RSI version, and at the same time consider this latest approved version to be the one that was also in effect at the start of the DSUR reporting period. The EU-CTR Q&A even shows the same figure as the CTFG Q&A to illustrate which version of the RSI is relevant for which DSUR. Both guidance documents have resolved what could be seen as a contradiction with ICH E2F, by stating that the most recently approved RSI should be considered as the one in effect at the start of the annual reporting period.

MHRA "Inspectorate" blog on RSI

In February 2021, the MHRA released an article in its "MHRA Inspectorate" blog[4] in which the authors describe common findings in inspections and how to avoid these, and which also addressed the RSI.

In the section on the DSUR, one of the findings that the blog article describes is that "the RSI used for the DSUR listings is not the same RSI in place at the start of the reporting period".[4] The authors point this out, even with an exclamation mark at the end of their sentence: "Please remember that for the purpose of writing the DSUR for trials conducted in the UK, as well as other EU countries, you need to use the RSI that was approved at the beginning of the reporting period by both the MHRA and European member states!"[4] If cases are presented in the DSUR listings with their expectedness based on a version of the RSI different from that approved at the beginning of the DSUR reporting period, the MHRA will consider this as incorrect – following ICH E2F with this decision.[1,4] Consequently, SARs in the DSUR should be presented as unexpected if they are not included in the RSI valid at the beginning of the DSUR reporting period. This rule should be adhered to even if the next version of the RSI (the one submitted with the previous DSUR, which comes into effect during the current DSUR's reporting period and is therefore the latest one approved) does include this SAR. The MHRA considers the RSI "to be fixed at the start of the reporting period in order to set a baseline for review of all safety data received in comparison with this".[4]

> … for the purpose of identifying unexpected terms in the cumulative SAR tabulation of the current DSUR, the version of the RSI created at the time of the last DSUR [...] and submitted in parallel (or shortly thereafter) should be used.

The MHRA has announced that after the EU-CTR transition phase (January 31, 2022, to January 31, 2025) they will publish United Kingdom (UK) specific guidance to clarify whether elements of the EU-CTR will apply also for the UK.

For the time being, sponsors will have to decide whether to follow ICH E2F and at the same time fulfil the MHRA's request for using the RSI in effect at the beginning of the reporting period, or to concur with the logic of the CTFG and EU-CTR instructions and use the RSI version that was most recently approved. One view that was brought up at the Meet & Share event was that it makes sense that the data cut-off for the DSUR and the RSI are the same. This is an argument in favour of using the latest RSI version approved, because it is the one that was submitted with the previous DSUR, with analyses performed at the same level of knowledge and using the same data status. The RSI version in effect at the start of the DSUR reporting period has a data cut-off that is one year older.

We continue to see a contradiction between "in effect at the start of the reporting period" and "the version of the RSI most recently approved", even after many discussions and continuous efforts to find the logic in equating the one with the other, as is done in CTFG and EU-CTR.

MHRA, HC, and EU-CTR on safety signals

The RSI topic caused extensive discussions and continues to do so. Two further topics that are included in a guidance document released by the MHRA and HC[5] and that are also included in the new EU-CTR, are likely less controversial, but will also have visible implications for the DSUR. Sponsors are requested to transparently describe their safety review process,[3,5] i.e., they should "explain how they performed their due diligence during the reporting period".[5] This description, as per EU-CTR, should provide information on "their surveillance processes for reviewing and identifying potential new safety signals and updating existing safety signals, including but not limited to how often data is reviewed and by whom, what type of data source/format is reviewed, and what potential action may arise as a result of the surveillance process".[3] Additionally, the criteria used for adding or deleting expected terms in the RSI should be described. All of this should be included in a region-specific appendix (EU-CTR)[3] or in the region-specific information section of the DSUR (MHRA/HC).[5] The EU-CTR and MHRA/HC also require that the outcome of the signal process is presented in the DSUR, and for both the format used in the PBRER is acceptable, but not mandatory. The EU-CTR even acknowledges that signal evaluation for clinical trials may not always be possible or appropriate, and that a justification for not including this information should in such a case be provided instead.[3]

EU CTR on study ID, case ID, and subject ID in the DSUR

One more change for the DSUR will come with the new EU-CTR for those sponsors that so far included the subject ID in the document. The DSUR appendices contain listings and tabulations, like the interval and cumulative SARs, cumulative SAEs, a list of fatal cases, or of subjects who dropped out of a trial because of adverse events. Some of these data appendices use identifiers for the cases that are presented. So far, depending on the processes and systems established and used by a sponsor, these identifiers would be study ID, case ID, and/or subject ID. To ensure that patient's rights are protected, the new EU-CTR now clarifies that the subject ID should not be used for this purpose: "[…] SARs in the line listing should be identified by case ID and study ID without including subject ID in this document".[3] For the DSUR as well as for any potential investigation any authority will initiate, for example on a specific SAR, sponsors are asked to provide the corresponding data in anonymised manner and without revealing the subject ID.

Conclusion

As we have seen, there is quite some change on the horizon and the appearance of the DSUR will most visibly change by the additional signal presentation, with an additional regional appendix required for this purpose. But once the safety review process is described and the description transferred into template boilerplates, this will cause no additional work for future DSURs, and neither will the presentation of the actual signals, at least for those drugs that are on the market and for which a PBRER is available, from which this can be copied. It is the seemingly small changes, like avoiding the subject ID in line listings, that can cause quite some technical effort or can require substantial process changes, depending on a sponsor's database and established processes. And the presentation of expectedness in the cumulative SAR tabulation by applicable RSI version can be a tricky task – remember, it should be the one that was in effect at the start of the DSUR reporting period and the latest one approved, and only experience (and authority feedback) will show whether this indeed is the contradiction we perceive it to be.

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