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USE

DRAFT CONSENSUS GUIDELINE

DEVELOPMENT SAFETY UPDATE REPORT
E2F

Current *Step 2* version
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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

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DEVELOPMENT SAFETY UPDATE REPORT

Draft ICH Consensus Guideline

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DEVELOPMENT SAFETY UPDATE REPORT

1. INTRODUCTION

1.1 Objective of the Guideline

The periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects during the clinical development of an investigational drug.^{1,2,3} It is also important to notify regulators and other interested parties (e.g., ethics committees) at regular intervals of the evolving safety profile of an investigational drug and actions proposed or being taken to address safety concerns. Currently, regulations in some countries or regions require submission of a periodic report to regulatory authorities to address these issues. However, significant differences in the content and format of these reports highlight the importance of a common standard to promote a consistent approach, and enhance efficiency. The Development Safety Update Report (DSUR) proposed in this guideline is intended to be the common standard for annual clinical trial safety reporting among the ICH regions and can be submitted instead of existing reports including the US IND Annual Report and the EU Annual Safety Report. This comprehensive, thoughtful annual review can provide an additional level of assurance of protection for subjects in clinical trials. In addition, by harmonising the format, content and timing of annual safety reports, regulators in the three ICH regions can receive the same information at the same time, thereby reducing the number of reports generated.

The main objective of a DSUR is to present an annual review and evaluation of pertinent safety information collected during the reporting period to: (1) summarise the current understanding and management of identified and potential risks; (2) describe new safety issues that could have an impact on the protection of clinical trial subjects; (3) examine whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the product's safety; and (4) provide an update on the status of the clinical investigation/development programme. This guideline defines the content and format of a DSUR and provides an outline of points to be considered in its preparation and submission.

1.2 Scope of the DSUR

The main focus of the DSUR is data from interventional clinical trials (referred to in this document as “clinical trials”) of investigational drugs including biologicals, with or without a marketing approval, whether conducted by commercial or non-commercial sponsors. However, other findings that impact the safety and welfare of clinical trial subjects, (e.g., significant safety findings from non-clinical studies, safety findings from clinical trials conducted by a co-development partner in a licensing agreement, or relevant findings from non-interventional studies/compassionate use) should also be

¹ The term investigational drug is used in this guideline to indicate only the experimental product under study or development.

² For detailed discussion see: The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials: Report of CIOMS Working Group VII, Geneva 2007.

³ ICH Topic E6(R1) Guideline for Good Clinical Practice
<http://www.ich.org/LOB/media/MEDIA482.pdf>

included where appropriate. Some of the information contained in the DSUR, such as safety findings, inclusion of serious adverse reactions in line listings, and discussion of relevant articles from published literature can also be provided in Periodic Safety Update Reports (PSURs) for marketed products that are the subject of ongoing clinical trials. Therefore, some overlap is expected between the DSUR and PSUR because of the different periodicities for submission and objectives.

The DSUR should provide safety information from all ongoing clinical trials that the sponsor is conducting or has completed during the review period including:

- clinical trials conducted using an investigational drug whether with or without a marketing approval, i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III);⁴
- clinical trials conducted using marketed drugs in approved indications, i.e., therapeutic use trials (Phase IV);
- other therapeutic use of an investigational drug; and
- comparability trials conducted to support changes in the manufacturing process of medicinal products.

The DSUR should focus primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects. A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the safety profile of the investigational drug. It should not contain initial notification of any significant new safety issues, as these should have been communicated to regulatory authorities via expedited reporting.

2. GUIDANCE

2.1 When Should a DSUR be Prepared?

A sponsor overseeing more than one clinical trial of a single investigational drug should prepare one DSUR for that drug with a single data lock point (DLP) wherever possible. If this is not possible, an explanation should be provided in the covering letter.

2.2 Periodicity and DSUR Data Lock Point

The DSUR is intended to be an annual report that should be submitted to regulatory authorities, as appropriate, for as long as the sponsor conducts clinical trials with the investigational drug, or for as long as appropriate to satisfy local requirements. Where local authorities ask for periodic submission of safety information on an investigational drug to ethics committees, institutional review boards, or investigators, the DSUR Executive Summary should suffice, supplemented with line listings of serious adverse reactions as warranted.-

The DSUR should be submitted no later than 60 calendar days from the DSUR data lock point. The data lock point of the DSUR should be based on the date of the sponsor's first authorisation to conduct a clinical trial in any country. This date is termed the "Development International Birth Date" (DIBD).⁵ For administrative convenience, if

⁴ For classification of clinical trials see ICH E8 General considerations for clinical trials.

⁵ This is analogous to the International Birth Date (IBD) for a PSUR, defined as the date of first marketing approval worldwide.

desired by the sponsor, the DIBD can be designated as the last day of the month of authorisation.

Where clinical trials are ongoing in one country and are later initiated in another country(ies), one DSUR based on the same DIBD should be used for all countries.

2.3 Change of DSUR Data Lock Point

Once a drug has received a marketing approval⁶ in any country or region, and clinical trials continue or are initiated, both a PSUR and a DSUR should be prepared in accordance with directions from local authorities. The sponsor should change the DSUR data lock point to coincide with the International Birth Date (IBD) so that the DSUR and the PSUR can be synchronised. In synchronising the data lock points for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.

2.4 Interruption or Discontinuation of Clinical Trials

A DSUR should be prepared and submitted as indicated by local authorities, even when the clinical trials are interrupted or discontinued. If the sponsor has not collected any further data pertinent to the clinical development programme in the period of the DSUR, a letter stating this can replace the DSUR.

2.5 Final DSUR

When an annual report of clinical trials is no longer required in an individual country or region, the DSUR should be accompanied by a cover letter indicating that the report serves as the final DSUR for the investigational drug in that country or region. The letter should also indicate whether or not clinical trials are continuing elsewhere.

2.6 Responsibilities for Preparing and Submitting a DSUR

2.6.1 Sponsor's Responsibilities

The sponsor of a clinical trial, whether commercial or non-commercial, should be responsible for the preparation, content and submission of a DSUR.

2.6.2 Shared Responsibilities

Where individual clinical trials or a drug development programme involve collaboration with public or private institutions, business partners or other parties, a written agreement should be in place clearly detailing the responsibilities for preparation and submission of the DSUR. The same principle applies in situations where the sponsor delegates the preparation of the DSUR to a third party, e.g., a contract research organisation.

2.6.3 Non-Commercial Sponsor Responsibilities

Non-commercial sponsors should be responsible for the preparation of the DSURs for the clinical trials they conduct, in accordance with local requirements. Sections of the DSUR

⁶ For the purposes of this document, we use the term “authorisation/ authorised” to refer to approvals of clinical trials, and “approved/ marketing approval” to refer to marketing authorisations.

that are not applicable to non-commercial sponsors (e.g., manufacturing issues, non-clinical data, and marketing status) should be identified as such.

2.6.4 Responsibilities of Multiple Sponsors in Formal Agreements

When there is more than one sponsor, e.g., when a sponsor is in a formal co-development or licensing relationship with one or more partners, or more than one partner is a sponsor of a clinical trial(s) of the investigational drug, the parties should arrange to prepare a single DSUR whenever possible. Written agreements should be in place specifying how safety data will be exchanged so that a single DSUR can be produced by one sponsor on behalf of all parties.

When unavoidable, multiple sponsors can agree in writing to prepare separate DSURs for the same investigational drug. This can include situations where different indications, routes of administration, or formulations are being investigated. The rationale for separate DSURs should be provided in each report.

2.7 DSURs for Combination Products

Given the potential complexities of clinical development involving combination therapies, it is not possible to provide guidance that addresses all such situations. The sponsor should select the most appropriate option based on judgement, taking into account patient population, indication, formulation etc., as well as the circumstances in which the clinical trials are being conducted and local regulatory requirements. The rationale for this decision should be provided in the report.

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product.

For trials involving drug combinations that are not fixed, it can be appropriate to prepare a stand-alone DSUR. Alternatively, information on the multidrug regimen trials can be included in the DSUR of one or all of the components.

Although medical devices are outside the scope of the DSUR, specific local regulations can require a DSUR for certain drug-device combinations, depending upon whether the principal therapeutic effect is achieved by the drug or the device.

2.8 Reference Safety Information

A single document containing the reference safety information should be used to assess whether the safety information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.

The Investigator's Brochure (IB) in effect at the start of the reporting period should serve as the reference safety information for the DSUR for an investigational drug whether or not the drug has a marketing approval. The report should clearly indicate the version number and date of the IB used for this purpose. If the IB has been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the revised version of the IB as an attachment to the DSUR. When an IB is not required for the trial by local regulations (e.g., non-commercial

sponsors conducting a clinical trial with a marketed product) the applicable local product label⁷ or another suitable document should be used as the reference safety information.

2.9 Format and Presentation of DSUR

2.9.1 Format

The format and content of the DSUR should follow the table of contents below. For each heading where information is available, the information should be presented concisely; when no information is available, this should be stated. Guidance on the content of each section is provided below. Note that the section numbers below reflect the numbering in the DSUR.

2.9.2 Table of Contents

Title page

Executive Summary

Table of Contents

1. Introduction
2. Worldwide Marketing Authorisation Status
3. Update on Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Status of Clinical Trials Ongoing and Completed During the Reporting Period
6. Estimated Exposure
 - 6.1 Cumulative subject exposure in clinical trials (Phase I-IV)
 - 6.2 Patient exposure from marketed setting
7. Presentation of Safety Data from Clinical Trials
 - 7.1 General considerations
 - 7.2 Interval line listings of Serious Adverse Reactions (SARs)
 - 7.3 Cumulative summary tabulations
 - 7.4 Deaths in the reporting period
 - 7.5 Subjects who dropped out in association with any adverse event in the reporting period
8. Significant Findings from Clinical Trials During the Reporting Period
 - 8.1 Completed trials and any interim analyses
 - 8.2 Ongoing clinical trials
 - 8.3 Other therapeutic use of investigational drug

⁷ In the EU this would be the Summary of Product Characteristics (SmPC); in Japan this would be the Japanese Package Insert; and in the US this would be the US Package Insert.

- 8.4 New safety data related to combination therapies
 9. Relevant Findings from Non-Interventional Studies
 - 10 Relevant Findings from Other Studies
 11. Safety findings from marketing experience
 12. Other Information
 - 12.1 Non-clinical data
 - 12.2 Long-term follow-up
 - 12.3 Literature
 - 12.4. Other DSURs
 - 12.5 Significant manufacturing changes
 - 12.6 Lack of efficacy
 - 12.7 Phase I protocol modifications
 13. Late-Breaking Information
 14. Overall Safety Assessment
 - 14.1. Evaluation of the risks
 - 14.2 Benefit-risk considerations
 - 14.3 Conclusions
 15. Summary of important risks
- Appendices to the DSUR

2.10 Guidance on Contents of DSUR

Title Page

The title page of the DSUR should include the following information:

- DSUR number (reports should be numbered sequentially);
- Investigational drug(s);
- Reporting period;
- Date of the report;
- Sponsor name and address;
- Confidentiality statement; and
- Note regarding the inclusion of unblinded information in the DSUR.

Executive Summary

This section should provide a concise summary of the important information contained in the report. Together with the title page, it should serve as a “stand-alone” document suitable for submission to ethics committees and other stakeholders, if required by local regulations. Information on the following should be included in the Executive Summary:

- Introduction – report version and reporting period;
- Investigational drug – mode of action, class, indications, dose, route of administration;
- Estimated cumulative clinical trial exposure;
- Marketing authorisation(s)? (yes/no) – If yes, number of countries;
- Summary of overall safety assessment;
- Summary of important risks (based on Section 15 of the DSUR);
- Actions taken for safety reasons including significant changes to IB;
- Conclusion.

All sections should be completed; when no information is available, this should be stated.

Table of Contents

1. Introduction

This section should include:

- Reporting period and sequential number of the report;
- Brief description of the drug, e.g., therapeutic class, mode of action, route of administration, formulation;
- Whether the report covers a development programme or a single clinical trial. This section should also note the scope of the trials covered by the report (e.g., all trials with the investigational drug, or indication-specific trials);
- A brief description of the indications and populations being studied;
- A brief description and explanation of any information that has been excluded (e.g., when written agreements with a partner company do not provide for exchange of all safety data).

2. Worldwide Marketing Authorisation Status

This section should be completed only if a marketing application for the product has been submitted in one or more countries/regions. Cumulative information should be provided where available, usually in the form of a table that provides the status of each application. The content and format for this table is the same as that recommended for PSURs, as outlined in ICH E2C, Table 1.

3. Update on Actions Taken in the Reporting Period for Safety Reasons

This section should include a description of significant actions related to safety that have been taken by the sponsor, regulators, Data and Safety Monitoring Boards or independent ethics committees that could have an impact on the conduct of a specific trial or the whole clinical development programme. Any relevant updates to previous actions should also be summarised in this section. Changes to the Investigator's Brochure should be discussed separately in the "Changes to Reference Safety Information", see Section 4.

Examples of significant actions relating to safety issues include:

- Refusal of authorisation of a clinical trial for ethical or safety reasons;
- Partial⁸ or complete clinical trial suspension or early termination of a clinical trial due to lack of efficacy or safety issues;
- Resumption of a clinical trial after suspension;
- Failure to obtain marketing approval for a tested indication;
- Risk management activities, including:
 - Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion criteria, intensification of monitoring);
 - Restrictions in study population or indications;
 - Changes to the informed consent document relating to safety issues;
 - Formulation changes for safety reasons;
 - Addition of a special reporting requirement;
 - Issuance of a communication to investigators or healthcare professionals;
 - Plans for new safety trials.
- Important specific advice for safety reasons from a regulatory authority that involves a constraint on development (e.g., requirement to conduct long-term animal studies before initiating a long-term clinical trial; need for thorough QT/QTc study prior to Phase III clinical trials). In addition a cumulative listing of advice from regulatory authorities should be provided as a table in an appendix.

In addition to the above, for drugs with a marketing approval, examples of significant actions due to safety reasons include:

- Failure to obtain a marketing approval renewal;
- Marketing approval withdrawal or suspension for safety reasons;
- Risk management activities including:
 - Significant restrictions on distribution or introduction of risk minimisation measures;
 - Significant changes in labelling documents that could affect the development programme, e.g., restrictions to indication or population or a new warning;
 - Communications to health care professionals as a result of the above actions; and
 - New postmarketing study requirement(s) imposed by regional authorities.

4. *Changes to Reference Safety Information*

This section should list any significant safety-related changes to the IB within the reporting period. This includes information relating to contraindications, warnings, precautions, serious adverse drug reactions, adverse reactions of special interest, interactions, and any important findings from non-clinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.

⁸ “Partial suspension” may include several actions – e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another and/or suspension of a particular dosing regimen in a trial but continuation of other doses.

5. *Status of Clinical Trials Ongoing and Completed During the Reporting Period*

This section should refer to an appendix that presents a listing of each clinical trial in progress and each clinical trial completed during the reporting period. Separate tables can be provided by indication, formulation, and study population if appropriate. In addition, where required by local authorities, similar information should be provided for other therapeutic use of an investigational drug in the reporting period e.g., compassionate use or expanded access.

The table(s) should include the following information for each trial:

- Protocol number or other trial identifier;
- Clinical trial phase (I, II, III, or IV);
- Status:
 - Ongoing (study has begun; study has begun but is currently on hold; study is completed, but final clinical study report is not yet available);
 - Completed (final clinical study report is available).
- Countries/regions where there is at least one investigational site for the protocol;
- Abbreviated study title ;
- Study design (uncontrolled, controlled, open, single blind, double blind, parallel, cross-over, etc., including treatment arms);
- Dose and regimen of study drug and any comparators;
- Subject population as appropriate (age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment);
- Date of first visit for first patient;
- Planned enrolment for study as a whole;
- Estimates of cumulative numbers of exposed subjects where available for each treatment arm. The actual enrolment numbers for open or completed trials, and/or an estimate based on the randomisation scheme for blinded trials should also be provided.

An example of the column headings for this listing is provided in Table 1.

6. *Estimated Exposure*

The sponsor should clearly explain in the DSUR the method used to estimate subject/patient exposure.

6.1 *Cumulative Subject Exposure in Development Programme*

Data on subject exposure to the investigational drug and placebo/active comparators should be included in the DSUR. The DSUR should provide summary tables including estimates of the overall numbers of subjects exposed as of the DSUR data lock point, using either number of trial subjects or patient-time, as appropriate.

When the data are available, the DSUR should provide cumulative exposure data giving the number of trial subjects by age group, gender, and ethnic origin⁹ for the development programme. Tabulation of demographic characteristics for a single trial can be useful if the trial is of particular importance, e.g., a pivotal phase III trial.

See Table 2 for examples of these tables.

These exposure tables provide context for the cumulative summary tabulations of serious adverse events (SAEs). Therefore, if the summary tabulations are presented by indication, the exposure data should also be presented by indication where available.

6.1 Patient Exposure from Marketing Experience

If the investigational product is marketed, the commercial sponsor should provide the estimated patient exposure in the marketed setting based on the information provided in the PSUR for that product or other suitable data source.

7. Presentation of Safety Data from Clinical Trials

The DSUR should contain both cumulative and interval (periodic) safety information relating to the investigational drug. This section of the report should present important clinical safety information through interval line listings of the serious adverse reactions that arose during the period covered by the DSUR, and cumulative tabulations of serious adverse events that have been reported to the sponsor since the DIBD. If MedDRA is used for coding the adverse event/reaction terms, the Preferred Term level should be presented in the line listings and summary tabulations.

In general, the tabulation(s) of serious adverse events should include only those terms that were used in defining the case as serious. Non-serious and incidental findings should not be included.

If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained.

Certain adverse events can be excluded from the summary tabulations and line listings, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database, and those that are integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint or disease progression in cancer trials).

⁹ Ethnic factors are defined as those factors relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population as described in ICH E5(R1): Ethnic Factors in the Acceptability of Foreign Clinical Data.

7.1 General Considerations

This section of the DSUR should include the version of the coding dictionary used, and the document and version used as Reference Safety Information for determining expectedness for the tabulations, where required by regional authorities.

7.2 Interval Line Listings of Serious Adverse Reactions (SARs)

This section of the DSUR should include general information about the content of the line listings, the criteria for inclusion, and reference to appropriate appendices.

The line listings should provide key information on all blinded and unblinded SARs reported during the reporting period, organised by System Organ Class (SOC). They can integrate data from all the trials being conducted with an investigational drug. Alternatively, when useful and feasible, SARs can be listed by protocol, indication, or other variables.

Where possible the line listing(s) should include each subject only once regardless of how many SAR terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis), as judged by the sponsor. It is possible that the same subject could experience different SARs on different occasions (e.g., weeks apart during a clinical trial). Such experiences can be treated as separate reports. Under such circumstances, the same subject can be included in a line listing more than once, and the line listings should be cross-referenced when possible.

The format and content of the line listings described in ICH E2C can be used with appropriate modifications (e.g., addition of the clinical trial identification number). An example of the headings for a line listing is provided in Table 3.

7.3 Cumulative Summary Tabulations

This section of the DSUR should include general information about the content of the tabulations, the criteria for inclusion, and reference to appropriate appendices.

Summary tabulations should present cumulative safety data from the DIBD to the data lock point of the current DSUR. The summary tabulations in a DSUR should include the number of serious adverse events,¹⁰ organised by SOC, for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo, and treatment unknown due to blinding) used in the programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by protocol, indication, or other variables.

An example is provided in Table 4.

¹⁰ For DSURs to be submitted to an EU Member State, a regional appendix should be provided. It should contain a summary tabulation of all SARs, specifying the number of SARs by: a) SOC, b) reaction term and c) treatment arm, if applicable. Unexpected adverse reaction terms should be identified.

7.4 Deaths in the Reporting Period

A list of subjects who died during participation in the investigation should be provided as an appendix to the DSUR if required by regional authorities. The list should include the following information at a minimum: case number, assigned treatment (could still be blinded), and cause of death.

7.5 Subjects who Dropped Out in Association with Any Adverse Event in the Reporting Period

Tabulations and listings of information on drop-outs should be provided as an appendix to the DSUR, if required by regional authorities. Any safety issues identified from a review of these withdrawals should be briefly described.

8. Significant Findings from Clinical Trials During the Reporting Period

The information in this section can be provided by indication, when appropriate, and should address the following topics, when applicable.

8.1 Completed Trials and Any Interim Analyses

The DSUR should provide a brief summary of the clinically important safety findings included in the final study reports from all clinical trials completed and any interim analyses conducted during the reporting period. This information can be in narrative format, or in the study synopsis format provided as Appendix 5 of the Report of CIOMS Working Group VII.

8.2 Ongoing Clinical Trials

The DSUR should provide a concise summary of any preliminary safety findings from ongoing trials, including safety issues that are the same or similar to those previously identified, as well as evidence of new clinically significant safety signals.

8.3 Other Therapeutic use of Investigational Drug

The DSUR should include safety information from expanded access programmes, compassionate use programmes and treatment INDs, because they each follow a specific protocol.

8.4 New Safety Data Related to Combination Therapies

If the sponsor has prepared a separate DSUR for a multidrug regimen or fixed combination product containing the single investigational drug that is the subject of this DSUR, relevant findings from that DSUR should be summarised in this section.

Conversely, if this DSUR is for a multidrug regimen or fixed combination product, important safety information arising from trials on the individual components should be briefly summarised here.

Alternatively, the information specific to the combination can be incorporated into a separate section(s) of the DSUR for one or all of the individual components of the combination.

9. *Relevant Findings from Non-Interventional Studies*

This section of the DSUR should summarise relevant safety information that became available in the reporting period from non-interventional studies, e.g., observational studies, registries, active surveillance programmes or epidemiological studies.

10. *Relevant Findings from Other Sources*

The DSUR should also discuss relevant safety findings from any other available sources (e.g., results from pooled or meta-analyses of randomised clinical trials, lack of efficacy from trials in high morbidity/mortality disease states and trials with vaccines).

11. *Safety Findings from Marketing Experience*

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience during the reporting period, particularly if the findings resulted in changes to the labelling or amendments to the product's risk management plan.

12. *Other Information*

12.1 *Non-Clinical Data*

Major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) initiated or completed during the reporting period should be summarised, and any impact on the clinical safety of the investigational drug should be discussed.

12.2 *Long-Term Follow-Up*

This section of the DSUR should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products and tissue engineered products). This section could be the only information presented in the DSUR when the clinical trials are completed and long-term follow-up is the only ongoing activity generating data for the DSUR.

12.3 *Literature*

The commercial sponsor is expected to review the scientific literature periodically for new safety information. This section should summarise new and significant safety findings from non-clinical studies and clinical trials that have been published during the reporting period. When available, this section should also include relevant new information on drugs of the same class. Significant new safety information published as an abstract for a scientific meeting should be summarised and a copy provided if possible.

12.4 Other DSURs

When available, a commercial sponsor should summarise significant findings from the DSUR provided by another sponsor conducting clinical trials with the investigational drug during the reporting period.

12.5 Significant Manufacturing Changes

When required by regional authorities, this section should include a summary of significant changes to the manufacturing process and/or formulation of an investigational drug during the reporting period and discuss potential safety issues arising from these changes, if applicable.

12.6 Lack of Efficacy

For investigational drugs intended to treat serious or life-threatening illnesses, lack of efficacy could constitute a significant risk to clinical trial subjects. In this setting, data received during the reporting period that indicates lack of efficacy relative to alternative therapies should be summarised.

12.7 Phase I Protocol Modifications

This section should describe significant Phase I protocol modifications not previously reported, as required by regional authorities.

13. Late-Breaking Information

Information on potentially important safety findings that present while the DSUR is in preparation after the data lock point should be included in this section. Examples include clinically significant new case reports, important follow-up data, and clinically relevant toxicological findings. Any action that the sponsor, a Data and Safety Monitoring Board, or regulatory authority has taken for safety reasons should also be included.

14. Overall Safety Assessment

The overall safety assessment should be a concise, integrated assessment of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information, and its implications for the clinical trial population. If appropriate, separate assessments can be provided by therapeutic area and/or indication.

14.1 Evaluation of the Risks

When relevant, the following points should be considered:

- meaningful changes in previously identified reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);
- newly identified safety issues (detailed description of adverse reaction; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions);

- particular emphasis should be placed on symptoms, signs, and laboratory evidence of newly and previously identified, clinically significant:
 - hepatotoxicity;
 - cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies;
 - bone marrow toxicity;
 - renal toxicity;
 - central nervous system toxicity;
 - immunogenicity and hypersensitivity;
 - reactive metabolites.
- deaths that are an outcome of an adverse reaction;
- withdrawals due to safety reasons;
- any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at risk groups (e.g., slow or fast metabolisers);
- positive and negative experiences during pregnancy or lactation;
- overdose and its treatment;
- drug misuse and abuse;
- experience with long-term treatment;
- risks associated with protocol procedures, including administration of the investigational drug and diagnostic procedures;
- evidence of clinically significant medication errors;
- potential impact of significant new safety issues identified with another drug in the same class; and
- drug–drug and other interactions.

The overall safety assessment should also discuss other relevant findings such as: non-clinical research, manufacturing issues, lack of efficacy and lack of patient compliance, when available.

14.2 Benefit-Risk Considerations

This section is not meant to be a full benefit-risk assessment but should be a succinct statement on the balance between the theoretical benefits and the identified risks, focusing particularly on whether there have been any changes in this balance since the previous DSUR. If there has been a change, the sponsor should provide an assessment of the impact on the clinical development programme.

14.3 Conclusions

The section should present a brief conclusion, addressing any changes to the previous knowledge of safety and risks resulting from information gained since the last DSUR. Finally, the conclusion should describe how risks have been managed in the trials and any additional actions that should be taken to address emerging safety issues.

15. *Summary of Important Risks*

This section should provide a concise cumulative list of important identified and potential risks (e.g., those that might lead to warnings, precautions, or contraindications in labelling). The information in this section could provide the basis for the Safety Specification of a risk management plan (ICH E2E). The list should be continuously evaluated and updated from DSUR to DSUR and include risks that require further evaluation, as well as safety concerns that have been fully addressed or resolved.

Appendices to the DSUR

The following are appendices that might accompany the DSUR:

- 1 Investigator's Brochure (if required);
- 2 Cumulative Table of Important Regulatory Advice;
- 3 Status of Ongoing and Completed Clinical Trials;
- 4 Cumulative Summary Tabulations of Demographic Data;
- 5 Line Listings of Serious Adverse Reactions (SARs);
- 6 Cumulative Summary Tabulation of Serious Adverse Events (SAEs);
- 7 Scientific Abstracts (if relevant).

Regional Appendices (as required by regional regulatory authority):

- 1 Drop-outs in Association with Adverse Events;
- 2 Deaths;
- 3 Summary Tabulations of SARs.

3. APPENDICES TO THE GUIDELINE

Appendix A Glossary

Appendix B Tables 1-4

APPENDIX A - GLOSSARY

Throughout this guideline the Working Group has used terms previously defined by ICH and other groups e.g., CIOMS. Those terms that were previously defined in ICH documents are not repeated in this glossary. However, the glossary includes terms defined by CIOMS and other groups.

| Item | Glossary Term | Source of Definition | Definition/Commentary |
|------|--|--|---|
| 1. | Adverse event of special interest | Based on CIOMS VII | An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. |
| 2. | Clinical Trial Authorisation | Based on EU Clinical Trials Directive 2001/20/EC | The authorisation in writing by the relevant regulatory authority of a clinical trial(s) described in a valid application. <u>Commentary</u> : In this guideline the term "authorisation" is used to refer to permission to conduct a clinical trial and the term "approval" is used to refer to permission to place a medicine on the market. |
| 3. | Other therapeutic use of an investigational drug <u>Synonym</u> : Expanded Access Compassionate Use | | Therapeutic use of an investigational drug under a protocol. This can include Expanded Access Programmes, Compassionate Use, and Treatment IND. <u>Expanded Access Programme</u> : IND-based programme in the US that allows a sponsor to supply an investigational drug to patients with an indication for which benefit has been demonstrated. <u>Compassionate Use Programme</u> : A programme in the EU to supply an investigational product to patients with an indication for which benefit has been demonstrated. <u>Treatment IND</u> : Allows the supply of an investigational drug to treat patients with serious or |

| Item | Glossary Term | Source of Definition | Definition/Commentary |
|------|---|--|--|
| | ‘Treatment IND’ | | <p>immediately life-threatening disease for whom no satisfactory alternative is available.</p> <p><u>Commentary:</u> This term does not include “particular patient”, “named patient” prescribing which do not require a protocol.</p> |
| 4. | Data lock point | CIOMS VII | <p>The date (month and day) designated as the cut-off for data to be included in a DSUR.</p> <p><u>Commentary:</u> It is based on the Development International Birth Date (DIBD) and should usually be in twelve-monthly increments.</p> |
| 5. | Development International Birth Date | CIOMS VII Glossary | <p>Date of first approval (or authorisation) for conducting an interventional clinical trial in any country.</p> |
| 6. | Identified risk | Volume 9A Rules Governing Medicinal Products in the EU | <p>An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.</p> <p>Examples of identified risks include:</p> <ul style="list-style-type: none"> - an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data; - an adverse reaction observed in well designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance or unexposed group) on a parameter of interest suggests a causal relationship; - an adverse reaction suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions. |
| 7. | Important identified risk; Important potential risk. | Volume 9A Rules Governing Medicinal Products in the EU | <p>An identified risk or potential risk that could impact on the risk-benefit balance of the product or have implications for public health.</p> |
| 8. | Investigational | | <p>The term investigational drug is used in this guideline to indicate only the experimental product</p> |

| Item | Glossary Term | Source of Definition | Definition/Commentary |
|------|-----------------------------------|--|--|
| | drug | | under study or development. |
| 9. | Non-commercial sponsor | | For the purposes of this guideline, examples of non-commercial sponsors include the following: (a) university, (b) healthcare centre, (c) a public scientific organisation, (d) a non-profit institution, (e) a patient organisation, and (f) an individual researcher who is responsible for the design, initiation, conduct, recording and publishing of the clinical trial. |
| 10. | Non-interventional clinical study | Based on EU Directive 2001/20/EC on Clinical Trials | A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data. |
| 11. | Potential risk | Volume 9A Rules Governing Medicinal Products in the EU | <p>An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.</p> <p>Examples of potential risks include:</p> <ul style="list-style-type: none"> • Non-clinical safety concerns that have not been observed or resolved in clinical studies; • Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship; • A signal arising from a spontaneous adverse reaction reporting system; • An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product. |
| 12. | Registry | ICH E2E | A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information |

| Item | Glossary Term | Source of Definition | Definition/Commentary |
|-------------|----------------------|-----------------------------|---|
| | | | using standardised questionnaires in a prospective fashion. |

APPENDIX B

Table 1 - Examples of Table Headings for Clinical Trial Status Listings

STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS

OVERVIEW OF ONGOING [study drug] STUDIES

| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Study population | FVFP* | Planned enrollment | Subject exposure** |
|----------|-------|---------|-------------|--------------|----------------|------------------|-------|--------------------|--------------------|
| | | | | | | | | | |

* FVFP = first visit first patient

** based upon total number of patients recruited as of [date] and applied randomisation schemes

OVERVIEW OF [study drug] STUDIES COMPLETED DURING THE DSUR PERIOD

| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Subject population | Subject/patient exposure per treatment arm (M/F) |
|----------|-------|---------|-------------|--------------|----------------|--------------------|--|
| | | | | | | | |

APPENDIX B

Table 2 - Examples of Demographic Data Tables

CUMULATIVE SUMMARY TABULATIONS OF DEMOGRAPHIC DATA

Estimated cumulative subject exposure to [study drug] clinical studies by age and gender*

| Number of subjects | | | |
|--------------------|------|--------|-------|
| Age (yr) | Male | Female | Total |
| <16 | | | |
| 16 - 25 | | | |
| 26 - 35 | | | |
| 36 – 45 | | | |
| 46 – 55 | | | |
| 56 – 65 | | | |
| 66 – 75 | | | |
| >75 | | | |
| Total | | | |

* data from completed studies as of [date]

Estimated cumulative subject exposure to [study drug] in all clinical studies by ethnic origin*

| Ethnic origin | Number of subjects |
|----------------------|---------------------------|
| Caucasian | |
| Black | |
| Oriental | |
| Other | |
| Total | |

* data from completed studies as of [date]

APPENDIX B

Table 3 - Examples of Headings for Interval Line Listings of Serious Adverse Reactions

INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARs)

| Study ID EudraCT number | Case ID/ Subject number* | Countr y Gender Age | Serious ADR(s) | Outcome | Date of Onset** Time to Onset** | Suspect Drug | Daily dose Route Formulation | Dates of treatment Treatment duration | Comments |
|--|---|--|-----------------------|----------------|--|-------------------------|---|--|-----------------|
| | | | | | | | | | |
| | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- |

* Study/centre/patient

** 'Primary' SADR only

APPENDIX B

Table 4 - Examples of Cumulative Tabulations of Serious Adverse Events

CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS (SAEs)

| <u>System Organ Class</u> | Total up to 31-Dec-07 | | | | |
|---------------------------------------|-----------------------|--------------|----------|-------------------|----------|
| | Preferred Term | [study drug] | Blinded | Active comparator | Placebo |
| <u>Investigations</u> | | 18 | 4 | 7 | 2 |
| Alanine aminotransferase increased | | 9 | 2 | 4 | 1 |
| Aspartate aminotransferase increased | | 9 | 2 | 3 | 1 |
| <u>Nervous System Disorder</u> | | 2 | 2 | 4 | 7 |
| Syncope | | 2 | 2 | 4 | 7 |