



Overview of ICH E2F – Development Safety Update Report (DSUR)

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Suuggest addition of guideline title.

Note also that apparently "ICH M3(R2)" is not mentioned in the official version of the final step 2 document that I have.

bl; 29/07/2008



Overview

- Concept of Development Safety Update Report (DSUR);
- Periodic Safety Reports – Opportunities for Improvement;
- History of ICH E2F – DSUR;
- General Principles of the DSUR;
- Table of Contents of the DSUR;
- Specific sections of DSUR Guideline;
- Conclusion



Concept of a DSUR

- CIOMS VI – Management of Safety Information from Clinical Trials (2005)
 - Annual report;
 - Cover entire development programme of investigational drug;
 - Common international birth date
- CIOMS VII – The Development Safety Update Report: Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials (2006)
 - Details of format, content and scheduling of annual reports;
 - Single DSUR for Investigational Drug – complete picture of evolving safety profile;
 - Example DSURs.



Periodic Safety Reports

- US 'IND Annual Report'
 - 21 CFR 312.33;
- EU 'Annual Safety Report'
 - Directive 2001/20/EC and ENTR/CT3 Sec. 5.2;
- Japan 'Investigational Product Serious/Infection Case Periodical Report' – 6 monthly
 - Pharmaceutical Affairs Law, Enforcement Regulations: revisions PFSB 0229011 Feb 08 & 1001005 Oct 08;
- ICH documents are guidelines, and cannot impose new regulatory requirements;
- DSUR should replace existing annual reporting requirements in US, EU and Japan;
 - Therefore, DSUR needs to incorporate all current regulatory components of those reports.



Opportunities for Improvement

Rationale for ICH DSUR:

- Contents of current periodic safety reports differ;
- Analyses of safety data are not comprehensive;
- Reports focus on regulatory compliance instead of benefit-risk analysis;

Benefits of harmonisation.

- Consistent regulatory terminology;
- Defined reference safety information;
- Co-ordinated periodicity of reports;
- Same scope and content for same trials in different regions.



History of ICH E2F EWG

Preparation of DSUR Guideline ICH E2F.

- Final Concept Paper: September 20, 2006
- 1st ICH Meeting: Oct 2006 (Chicago)
- 2nd ICH Meeting: Oct/Nov 2007 (Yokohama)
- 3rd ICH Meeting: Jun 2008 Step 2 document (Portland)
- Step 3 – consultation/comment period: June – December 2008;
- 4th ICH Meeting: Jun 2009, incorporate EU comments;
- ICH Teleconferences: Jun 2009-present, incorporate US comments and prepare Step 4 document;
- Step 4 document : Mid 2010?
- 80+ Versions; 40+ teleconferences



Framework of DSUR Guideline

- Introduction:
 - Objectives, Scope, Relation to PSUR, Recipients;
 - General Principles:
 - Single DSUR, Periodicity, Data lock point, Duration of submissions, Responsibilities for preparation and submission, Combination therapies, Reference Safety Information, Format and Presentation.
 - Guidance on Contents of DSUR;
 - Appendices to the DSUR;
 - Appendices to the Guideline: glossary of terms, example tables and headings, examples of summary of important risks;
- [Example DSUR for (a) commercial development programme and (b) for investigator initiated trials.]



Objectives of the DSUR

The DSUR is an annual review & evaluation of safety information to assure regulators that sponsors are adequately monitoring and evaluating the safety profile of the investigational drug.

It reports:

- Safety information obtained by the sponsor during the current review period;
- Analyses of the new information based on previous knowledge of the product's safety, including:
 - New safety issues that may impact the overall programme or specific clinical trials;
 - Current understanding and management of known and potential safety risks to patients;
 - Changes in the product's safety profile; and
 - Status of the clinical development programme.



Single DSUR & Scope

Format: Whenever practicable the sponsor should prepare a single DSUR. This includes:

- Sponsors with multiple clinical trials;
- Multiple Sponsors in formal co-development agreements;
- Combination Products (Fixed Combination drug, Multidrug regimen trials).

Scope: The DSUR should include:

- Safety data from all clinical trials conducted with the investigational drug for:
 - All indications;
 - All dosage forms;
 - All intended populations.



Periodicity & Relation to PSUR

- An annual report with the data lock point based on the Development International Birth Date (DIBD);
- DIBD: the date of the first authorization to conduct an interventional clinical trial in any country;
- When clinical trials continue after receiving market approval, both DSUR and PSUR are needed separately;
- DSUR data lock point (DIBD) should coincide with the marketing International Birth Date (IBD).



Duration & Responsibilities for Submissions

Sponsor Responsibilities:

- Submit DSURs in accordance with national or regional laws and regulations; e.g. in EU – 60 days from data lock point;
- Indicate that DSUR is final annual report in a country or region;
- May delegate preparation of DSUR to a third party;
- Arrange with co-sponsors to submit a single DSUR;
- Agree in writing how data will be exchanged and responsibilities for preparation of DSUR with co-sponsors.



Reference Safety Information

- Reference Safety Information = Investigators Brochure (IB) in effect at the start of the period;
- When IB is not required by national or regional laws and regulations the appropriate local product label may serve as the Reference Safety Information;
- Usually a single document but exceptionally more than one reference document may be appropriate, e.g., investigational drug used as a combination product as well as monotherapy;
- When IB has been revised during the reporting period, sponsor should submit the current version with the DSUR.



Table of Contents of DSUR

- Title page;
- Executive Summary;
- Table of Contents:
 - 1. Introduction;
 - 2. Worldwide Marketing Approval Status;
 - 3. **Actions Taken in the Reporting Period for Safety Reasons ;**
 - 4. Changes to Reference Safety Information;
 - 5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period ;
 - 6. Estimated Cumulative Exposure;
 - 6.1 Cumulative Subject Exposure in the Development Programme;
 - 6.2 Patient Exposure from Marketing Experience
 - 7. Data in Line Listings and Summary Tabulations :
 - 7.1 Reference Information;
 - 7.2 Line Listings of Serious Adverse Reactions during the Reporting Period;
 - 7.3 Cumulative Summary Tabulations of Serious Adverse Events;...



Table of Contents of the DSUR

- 8. Significant Findings from Clinical Trials During the Reporting Period:
 - 8.1 Completed Clinical Trials;
 - 8.2 Ongoing Clinical Trials;
 - 8.3 Long-term Follow up;
 - 8.4 Other Therapeutic Use of Investigational Drug;
 - 8.4 New safety data related to combination therapies;
- 9. Safety Findings from Non-Interventional Studies;
- 10. Other Clinical Trial/Study Safety Information;
- 11. Safety findings from marketing experience;
- 12. Non-clinical data;
- 13. Literature;
- 14. Other DSURs;
- 15. Lack of Efficacy;
- 16. Region Specific Information;...



Table of Contents of the DSUR

- 17. Late-Breaking Information;
- 18. Overall Safety Assessment:
 - 18.1. Evaluation of the risks;
 - 18.2. Benefit-risk considerations;
- 19. Summary of important risks;
- 20. Conclusions.

Possible Appendices to the DSUR

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



Actions Taken for Safety Reasons

- Rationale and description of significant actions related to safety in the reporting period:
 - Taken by sponsor, regulators, DSMB, IEC, e.g., refusal to authorise or suspension of a clinical trial;
 - Due to safety with the marketed drug e.g, refusal of marketing approval for an indication being tested; and/or
 - To implement advice from regulatory authorities that involves a constraint on development, e.g., additions of a special safety reporting requirement;
- Resulting changes to the Reference Safety Information should be discussed separately.



Additional Clinical Sources of Safety Data

- Safety Findings from Non-interventional Studies
 - Observational studies;
 - Epidemiological studies;
 - Registries; and
 - Active surveillance programmes.
- Other Clinical Trial/Study Safety Information, such as:
 - Pooled or meta analysis of randomised clinical trials;
 - Safety information provided by co-development partners;
 - Investigator-initiated trials.
- Safety Findings from Marketing Experience, such as:
 - Changes to Summary of Product Characteristics, informed consent document or amendments to the risk management plan;
 - Includes off-label use, administration to special populations, medication errors, overdose and abuse.



Overall Safety Assessment

- This section should be an integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information in relation to previous knowledge of the investigational drug, such as:
 - Changes in previously identified risks;
 - New safety issues;
 - Newly and previously identified clinically significant toxicities e.g, hepatotoxicity, QT prolongation;
 - Drug-drug and other interactions;
 - Specific at-risk populations, e.g., pregnancy;
 - Important non-clinical safety findings;
- Benefit-risk considerations:
 - Any changes in the balance since previous DSUR.



Summary of Important Risks

- Issue-by-issue list of important identified and potential risks (narrative or tabular format), i.e.:
 - Those that might lead to warnings, precautions, or contraindications in labeling, such as:
 - Toxicities related to a drug class or molecular structure;
 - Safety concerns from accumulating clinical or non-clinical data;
- New information should be highlighted;
- Each risk should be re-evaluated annually, including:
 - Ongoing risks; and
 - Fully addressed and resolved risks.



Conclusion

The conclusion should briefly describe:

- Any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR;
- Actions that have been or will be taken to address emerging safety issues in the clinical development programme.



Executive Summary

- Serves as a “stand-alone” document for submission to stakeholders (e.g., Ethics Committees)
- Summarises the important information contained in the DSUR
- Including:
 - Introduction;
 - Information on investigational drug;
 - Estimated cumulative exposure;
 - Marketing approval status;
 - Summary of overall safety assessment;
 - Summary of important risks;
 - Actions taken for safety reasons including changes to IB;
 - Conclusion.



Region-Specific Information

- Used to comply with national and regional laws and regulations and can be provided in appendices, such as:
 - Cumulative summary tabulation of serious adverse reactions;
 - List of subjects who died during the reporting period;
 - List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period;
 - Significant Phase I protocol modifications;
 - Significant manufacturing changes;
 - Description of the general investigation plan for the coming year with respect to the US IND;
 - Log of outstanding business with respect to the US IND.



Summary

- Current procedures for periodic reporting in ICH regions should be harmonised to save resources;
- The focus should be on evaluation of safety and benefit-risk rather than compliance with regulations;
- The DSUR will provide thorough periodic evaluation of safety of an investigational medicinal product and should help to:
 - Improve patient safety;
 - Identify safety issues early;
 - Allow safety issues to be better managed and monitored;
 - Prevent continuation of trials with safety issues that cannot be managed;
 - Provide the basis for appropriate warnings, contraindications and/or changes to the protocol.

