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

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Agenda

- Background Information
- Development Safety Update Report: Existing Situation – Opportunities for Improvement
- General Principles of the DSUR
- Anticipated Challenges in Implementing DSURs

Background Information

- CIOMS VI – Management of Safety Information from Clinical Trials (2005)
  - Annual
  - Cover entire development program
  - Common international birthdate
- CIOMS VII – The Development Safety Update Report: Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials (2006)
  - Defined detail of contents, format, timing
  - General principles re: administrative matters, technical content
  - Example DSURs

ICH E2F Expert Working Group

Timelines

- Final Concept Paper: September 20, 2006
- 1st ICH Meeting: Oct 2006 (Chicago)
- 2nd ICH Meeting: Oct/Nov 2007 (Yokohama)
- Step 2 document: June 2008 (Portland)
- Step 3 – consultation/comment period: June – December 2008
- Step 4 document: August 2010

Some Constraints/Principles

- ICH documents are guidelines, and cannot impose new regulatory requirements.
- DSUR should replace existing annual reporting requirements in US and EU
  - Therefore, DSUR needs to incorporate all current regulatory components of those reports

Existing Situation – Opportunities for Improvement

Rationale for DSUR:

- Current periodic safety reports differ, analyses of safety are not comprehensive;
- Benefits of harmonization.

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 - no annual safety report when E2F Expert Working Group convened

Comparison: US versus EU

Subject	US IND Annual Report	EU Annual Safety Report
Data Lock Point (DLP)	Effective Date of IND	EU DIBD→ IBD
Recipients	FDA	Member State Competent Authority(ies), Independent Ethics Committees
Purpose	IND progress report	Clinical trial safety report

Comparison: US v EU

Subject	US IND Annual Report	EU Annual Safety Report
Short-term trials	≤ 1year from end of study	≤ 90 days from end of trial
Regulator feedback	On request	Not specified
Adverse events included	All SAEs	All SARs
Expectedness	IB or package insert	IB or Summary of Product Characteristics

US IND Annual Report Content

Individual studies:

Status of each study:

- identification – title, protocol number;
- purpose,
- patient population: (by age, sex, race)
  - planned;
  - included;
  - completed;
  - drop-outs.

US IND Annual Report Content

Summary Information:

- Narrative or tabular summary of most frequent and most serious adverse experiences by body system;
- Summary of all IND safety reports;
- List of subjects who died with cause of death;
- List of drop-outs due to adverse events;
- Pharmacodynamic/pharmacokinetic information;
- List of pre-clinical studies;
- Summary of significant manufacturing/ microbiological changes;
- Other: e.g., Investigational plan for coming year; changes to IB; Phase I protocol changes.

EU Annual Safety Report Content

Individual clinical trials:

- Analysis on the subjects safety in the trial:
  - All new and relevant findings in the period;
- A line listing of all suspected SARs in the period;
- Cumulative summary tabulation of SARs;
  - Numbers of SAR reports by:
    - ADR term;
    - Body system;
    - Treatment arm;
    - Identification of unexpected ADR terms.

EU Annual Safety Report Content

Summary Information: ***individual and multiple trials***

- Concise safety analysis and benefit-risk evaluation;
- Description and critical analysis of all new safety findings related to Investigational Drug;
- Results of non-clinical studies;
- Other studies likely to affect subjects' safety;
- Measures to minimise risks;
- Rationale – updating protocol, consent form, Patient Information Leaflet, IB;
- Implications for trial subjects and tested IMP based on all available clinical data;

Opportunities for Improvement

- Focus on regulatory compliance instead of benefit vs. risk analysis;
- Confusing regulatory terminology;
- Inconsistent reference safety information;
- Uncoordinated periodicity of reports;
- Different scope and content for same trials in different regions;
- Burden on IRB/IECs lacking expertise.

Benefits of DSUR

- Harmonization of format, content and scheduling of annual reports in 3 regions:
  - Harmonizes with ICH E2A and E2E
  - Single DSUR for Investigational Drug – complete picture of evolving safety profile
  - Improved consistency among companies
  - Decrease in number of reports generated
  - Regulators receive the same information at the same time

Benefits of DSUR

- Comprehensive, thoughtful annual review
- Increased assurance of protection for trial subjects
- New concept in Section 19 – Summary of Important Risks – highlights issues to monitor (industry and regulators)
- New concept in Section 3 – advice rendered by regulators that places specific limitation(s) on current or future development
- Facilitates work sharing (regulators)

Framework of DSUR Guideline

- Introduction
- Guidance
  - When, Who, How should DSUR be prepared?
- DSUR Format/Table of Contents
- Guidance on Contents of DSUR
- Appendices to DSUR
- Glossary

Objective of the DSUR

The DSUR presents an annual review & evaluation of safety information:

- Information reported during the current review period and analysis based on previous knowledge of the product's safety;
- Description of new issues that may impact the overall program or specific clinical trials;
- Summarization of current understanding and management of known and potential safety risks to exposed patients;
- Examine changes in the product's safety profile; and
- Provide an update on the status of the clinical development program.

Scope of the DSUR -1

DSUR focuses on:

- Clinical trials of investigational drugs (including vaccines and biologics)
- Other findings that impact the safety and welfare of clinical trial subjects (e.g., non-clinical studies, observational studies)

Scope of the DSUR - 2

DSUR should:

- focus on the investigational drug, providing information on comparators where relevant to the safety of trial participants;
- be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the safety profile of the investigational drug.

Single DSUR

A single DSUR including safety data from all clinical trials conducted with the drug should be prepared for an investigational drug:

- All indications
- All dosage forms
- All intended populations

This includes:

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

Periodicity

- 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

DSUR and PSUR

- When clinical trials continue after receiving market approval, both DSUR and PSUR are needed separately.
- DSUR data lock point (DIBD) can coincide with the International Birth Date (IBD) if desired by sponsor

Recipients of DSUR

- Regulatory Authorities: DSUR; within 60 days from the DIBD
- EC/IRB, if required: Executive Summary (plus line listing of SADRs)
- Final DSUR in a Territory: will be notified with a cover letter.

Reference Safety Information

- Single document containing reference safety information to assess the changes in the safety profile of investigational drug.
- Reference Safety Information = Investigators Brochure in effect at the start of the period.
- Local product label should be used as Reference Safety Information when IB is not required.

Content of DSUR (1 of 2)

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
6. Estimated Cumulative Exposure
7. Data in Line Listings and Summary Tabulations
8. Significant Findings from Clinical Trials
9. Safety Findings from Non-interventional Studies

Content of DSUR (2 of 2)

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
17. Late-Breaking Information
18. Overall Safety Assessment
19. Summary of Important Risks
20. Conclusions

Executive Summary

- Summary of the important information contained in the DSUR
- Serve as a “stand-alone” document for submission to stakeholders (e.g., Ethics Committees)
- Includes:
  - Introduction
  - Investigational drug
  - Estimated clinical trial exposure (cumulative)
  - Marketing authorization status
  - Summary of overall safety assessment
  - Summary of important risks
  - Actions taken for safety reasons including changes to IB
  - Conclusion

Actions Taken for Safety Reasons

- Description of significant actions related to safety in the reporting period
  - taken by sponsor, regulators, DSMB, IEC, etc.
  - could have an impact on the conduct of clinical trial(s)
  - including significant actions due to safety with the marketed drug
  - including advice from regulatory authorities that involves a constraint on development
- Changes to the Reference Safety Information should be discussed separately

Presentation of Safety Data

- Interval SAR Line listings
- Cumulative SAE Summary Tabulations

Other Information

Include relevant findings from:

- Non-interventional, observational and epidemiologic studies
- Marketing experience
- Other sources/data:
  - Non-clinical data
  - Long-term follow-up
  - Literature
  - Other DSURs
  - Lack of efficacy

Region-specific Information

- Cumulative summary tabulation of serious adverse reactions
- List of subjects who died during reporting period
- List of subjects who dropped out of clinical trials in association with an adverse event
- Significant Phase I protocol modifications
- Significant manufacturing changes
- General investigation plan for the coming year
- Log of outstanding business with respect to US IND

Overall Safety Assessment

- Evaluation of the risks
  - Changes in previously identified risks
  - New safety issues
  - Interactions
  - Experiences during pregnancy
  - Other risks
- Benefit Risk considerations
- Conclusions

Summary of important risks

- Cumulative summary list of important identified and potential risks – those that might lead to Warnings, Precautions, or Contraindications in labeling, including:
  - Ongoing risks
  - Fully addressed or resolved risks
- This information could provide the basis for the Safety Specification of a risk management plan (ICH E2E).