ICH Public Meeting
E2F: The DSUR

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

The ICH E2F Guideline: The Development Safety Update Report (DSUR)

- An annual summary of safety information for any drug, including biologics and vaccines, undergoing clinical trials
- Analogous to the PSUR (Periodic Safety Update Report; ICH E2C Guideline) which exists for licensed drugs and biologics

Background / History

Council for International Organizations of Medical Sciences:

- CIOMS VI Working Group - *Management of Safety Information from Clinical Trials (2005)*
  - Proposed an annual, internationally harmonized clinical trial safety report suitable for all regulators
- CIOMS VII Working Group -*The Development Safety Update Report: Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials* (2006)
  - Developed a detailed model for the DSUR

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: June 2009 (planned)

Existing Clinical Trial Periodic Safety Reports (ICH Regions)

- US IND Annual Report (AR)
  - 21 CFR 312.33
- EU Annual Safety Report (ASR)
  - Directive 2001/20/EC and ENTR/CT3 Sec. 5.2
- Japan - no annual safety report currently – regulatory requirement being introduced

DSUR - Important Constraints and Principles

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

Current Situation – Opportunities for Improvement

- Current reports focus more on regulatory compliance than on benefit vs. risk analysis;
- Confusing regulatory terminology;
- Inconsistent reference safety information;
- Uncoordinated periodicity of reports;
- Different scope and content of annual reports for same trials in different regions;
- Burden on IRBs / Ethics Committees lacking expertise.

Purpose and Scope of the DSUR

The DSUR presents an annual review & evaluation of safety information collected during the period, including:

- Presentation by trial sponsor (commercial and non-commercial) of information reported during the period, and analysis based on previous knowledge of the product's safety;
- Description of new safety issues that may impact the overall drug development program or specific clinical trials;
- Summary of current understanding and management of known and potential safety risks to exposed patients / subjects;
- Examination of changes in the product's safety profile;
- An update on the status of the clinical development program.

Benefits of DSUR - 1

- Harmonization of format, content and scheduling of annual reports in 3 regions:
  - Also harmonizes with other ICH Guidelines: E2C (PSUR), E2A, and E2E
  - Single DSUR for one Investigational Drug (wherever possible) – yields complete picture of drug's evolving safety profile
  - Improved consistency among trial sponsors
  - Decrease in number of reports generated
  - Regulators receive the same information at the same time

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Benefits of DSUR - 2

- Comprehensive, thoughtful annual review
- Increased assurance of protection for trial subjects
- *Summary of Important Risks* section – highlights issues to monitor (for industry and regulators)
- Summary of advice rendered by regulators that constrains development
- May facilitate work sharing (regulators)

Recipients of DSUR

- The DSUR is designed primarily for regulators
- The *Executive Summary* of the DSUR is recommended for other pertinent stakeholders, e.g. Ethics Review Committees (ERCs), DSMBs, Investigators
- A complete DSUR could be provided to DSMBs and to ERCs, as required or if requested
- Proprietary information may be redacted

The Future

- The Step 2 E2F Guideline is currently undergoing regulatory consultation in the three ICH regions, with deadlines for comments in November and December, 2008.
- Because submission of comments will be ongoing, the E2F Expert Working Group (EWG) will not be meeting at the November 2008 ICH Meeting in Brussels.
- Following the deadline for comments and after receipt of input from all three regions, the Group will revise the draft Guideline in accord with the comments and responses.
- The EWG is currently aiming to complete this by the end of the ICH meeting in Yokohama in June 2009, so that the Step 4 document can be completed at that time.

The Future - 2

- The E2F EWG has been holding monthly teleconferences since August, 2008, with a major focus on developing model DSURs for both commercial and non-commercial sponsors.
- The Group has also been working on a communication plan, which includes webinars, an invited article on the DSUR for a major pharmaceutical journal, and a presentation at the 45th Annual Meeting of the Drug Information Association in San Diego, California, in June 2009.

For further information:

http://www.ich.org/cache/compo/276-254-1.html

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

DEVELOPMENT SAFETY UPDATE REPORT
E2F

Current *Step 2* version
dated 5 June 2008

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.