Final Concept Paper
E2F: Development Safety Update Report
dated 7 September 2006
Endorsed by the ICH Steering Committee on 20 September 2006

Type of Harmonization Action Proposed

It is proposed that ICH develop a guideline on periodic reporting of safety information from clinical trials. This guideline would define the preferred content, format, and timing of such reports. The CIOMS VI Working Group referred to this type of report as a Development Safety Update Report (DSUR). The DSUR would be used by industry to regularly inform appropriate stakeholders of new safety data and the evolving safety profile of drugs, vaccines, and therapeutic biologic products before they are marketed, and also when new indications, formulations, etc. are being studied for marketed products. The objective of the proposed DSUR for clinical trials would be similar to that of the Periodic Safety Update Report (PSUR) that is commonly used for marketed pharmaceutical products.

Statement of the Perceived Problem

Until recently, very few countries required periodic reports on investigational compounds. The US FDA has required IND Annual Reports for quite some time, but this report is a general update on the progress of the clinical development program, and is not focused strictly on safety. The recently implemented EU Clinical Trial Directive also requires an Annual Safety Report, but its content, format, and timing are quite different than that required by FDA. As the provisions of the Clinical Trial Directive are being incorporated into regulation by each Member State, it is becoming obvious that interpretation of its provisions varies among regulatory authorities, and different regulators are requiring different report formats, content, and/or timeframes for the same compounds. This not only leads to a duplication of effort on the part of study sponsors, but could also lead to inconsistency in the information each regulatory authority receives regarding the safety of the investigational compounds. In addition, even where there is a single standard for the content of periodic reports, such as in the US, the information provided varies considerably from one sponsor to another.

Since most global companies conduct multi-country studies during product development, a standard safety report with defined content, format, and timing would improve the business efficiency of both industry and regulators. An ICH Guideline on DSURs would serve to define expectations for these reports; provide practical and useful guidance regarding provision of meaningful information to regulators; and facilitate consistency among sponsors and regulators. This would promote a focus on high value activities, such as data interpretation, and regulatory authorities worldwide would have access to the same data in the same timeframes.

Issues to be Resolved

The CIOMS VI Working Group introduced the concept of a DSUR in their report on Management of Safety Information from Clinical Trials, but did not define the content or format, or propose timing for such a report. The Working Group did suggest establishment of an international birth date to be used in setting timeframes for the DSUR. The CIOMS VII Working Group has continued the work of CIOMS VI, and their report (currently in draft)

provides recommendations regarding the general principles behind a DSUR, as well as an example of a model DSUR.

In addition to issues related to content and format of the report, additional issues to be addressed by an ICH guidance document include the following, many of which are also addressed in the CIOMS VII report. It is envisioned that the CIOMS VII report will form the starting point for the ICH EWG discussions and guideline.

- Scope of the DSUR (e.g., entire clinical program, indication-specific, protocol-specific, etc.);
- Relationship between a DSUR and PSUR for the same compound, when clinical studies continue after it is marketed; or when a compound is in pre-marketing development in one region, and marketed in another;
- When it might be appropriate to initiate a DSUR for a marketed product that has a PSUR, but no DSUR (e.g., when a new IND is filed for a new indication), and how these reports are linked;
- Relationship of the DSUR to the Development Core Safety Information (DCSI);
- Periodicity (e.g., always annual, or dependent on stage of development, type/length of trials, etc.);
- Timing of the first DSUR;
- Scope of the DSUR (i.e. should a DSUR cover only the current report period, or should some (or all) of it include cumulative data?);
- Target audience for the report (e.g., regulatory authorities, investigators, IRBs/ECs, etc.);
- Presentation of data (blinded versus unblinded, active (including comparators) versus placebo, need for differentiation by study type, geographic region, etc.);
- Content/format of overall benefit/risk assessment based on available data;
- Issues related to reporting for combination products that were also developed individually;
- Guidance related to what non-clinical study information should be included;
- Definitions and guidance for content items, for example:
    - which studies qualify as clinical trials for DSUR reporting purposes (e.g., only company-sponsored studies, or also investigator-sponsored studies, cooperative group-sponsored studies, etc.);
    - how reports from published literature, patient registries, regulatory authority databases are handled;
    - inclusion of non-interventional studies, as well as other programs that solicit safety data, but are not truly “studies” (e.g., patient support programs, disease management programs, etc.);
    - inclusion criteria for adverse event cases (e.g., only serious cases, serious adverse events, serious adverse reactions, should any non-serious cases be included, would there be any consideration of investigator or company causality assessments in determining which events are included, etc.);
    - inclusion criteria for spontaneous reports.

Background to the Proposal

The recent implementation of the EU Clinical Trial Directive has accelerated the need for global harmonization of annual safety reporting for developmental programs. Harmonization is necessary to stem the emergence of technical variations across different regulatory jurisdictions that will have a great impact on resource, but little impact on the public health. An ICH consensus effort would complement that of CIOMS; the concept of a DSUR was introduced by the CIOMS VI Working Group, and the CIOMS VII Working Group was established to produce additional detail for DSURs. Timelines for issuance of recommendations from the CIOMS VII Working Group are such that they can be incorporated into the ICH Step 2 document. When more fully developed, the ICH guidance document for DSURs will describe the relationships with stakeholders, including CIOMS and the EU Clinical Trials Facilitation Group, and will provide background on the experience with PSURs.

Type of Expert Working Group, Remit, and Deliverables

A. Working Group
An Expert Working Group should be established in September 2006. The EWG should include one or two experts from each of the ICH Parties and Observers and other interested parties. Members should include experts in pharmacovigilance with experience in both pre-market and post-market clinical safety and risk management. In addition, the EWG should include representatives with experience in clinical research. Ideally, one or more members of the EWG should be members of the CIOMS VII Working Group.

B. Remit
The primary remit of the proposed EWG would be to develop, for global use, uniform standards in the form of a guideline that would be used for periodic reports of safety data from clinical trials. The standard would need to accommodate the needs of those to whom such reports are sent (e.g., regulatory authorities, investigators, IRBs/ECs, etc.).

C. Process and Deliverables
The established ICH processes and procedures should be followed. If an acceptable Detailed Concept Paper and draft Business Plan are agreed in September 2006, it is expected that the work of the EWG will be completed within this general schedule:

Step 2 guideline: November 2007
Step 4 guideline: November 2008

Most work will be conducted via teleconferences and email; face-to-face meetings are contemplated twice per year from October 2006 through November 2007 and then in November 2008. A 12-month interval is anticipated between the Step 2 and Step 4 documents to allow the usual consultation and also for stakeholders to consider implications of electronic exchange of the DSUR. It is likely that this working group will liaise with the E2B(M), M2, and M5 EWGs when necessary for consultation on topics related to technical aspects of data exchange, including development of electronic reporting standards for the DSUR.

Next Steps

This Detailed Concept Paper will be presented to the Steering Committee during the September 2006 teleconference. If progress with informal discussions is satisfactory, it is expected that the Steering Committee will endorse formation of an EWG to begin work via quarterly teleconferences, with its first face-to-face meeting during the ICH meeting in Chicago, in October 2006.