Final Business Plan
E2F: Development Safety Update Report
dated 21 August 2006
Endorsed by the ICH Steering Committee on 20 September 2006

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

  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 (25 possible formats), 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. In addition, even where there is a single standard for the content of periodic reports such as in the US, the lack of clear, useful guidance results in variation from one sponsor to another with regard to the type and quality of information provided.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

  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. Lack of harmonization will not only lead 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.

2. Planning

- *What are the main deliverables?*

  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 and CIOMS VII Working Groups refer to this type of report as a Development Safety Update Report (DSUR). The DSUR would be used by industry to regularly inform appropriate stakeholders, including health authorities and others to be defined in the guideline, of new safety data placed in the context of the evolving safety profile of drugs, vaccines, and therapeutic biologic products before they are marketed. In addition, the DSUR would contain clinical trial

information on new indications, formulations, etc. 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.

The CIOMS VII Working Group expects to have a "near final" draft of their report available for review by the ICH Informal Working Group by the end of August 2006. This document will form the basis for the ICH WG discussions and guideline.

- *What resources (financial and human) would be required?*

  An Expert Working Group should be established. 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. EWG members' sponsoring organizations would need to provide financial resources for periodic face-to-face meetings (twice/year).

- *What is the time-frame of the project?*

  Summer 2006 through late 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.

  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.

- *What will be the key mile-stones?*

  The established ICH processes and procedures should be followed. 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

3. The impacts of the project

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

  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, and would promote a focus on high value activities, such as data interpretation. 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. In addition, regulatory authorities worldwide would have access to the same data in the same timeframes.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

  Applicable regulations and guidelines in the various regions would need to be amended to accept the DSUR, similar to the process required for revising the regulations and guidelines for post-marketing periodic reporting to accept the ICH PSUR.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*

  The results will be evaluated by:

  - Implementation of local regulations and/or guidance documents in line with the final Guidance.
  - Ad hoc feedback from interested parties.