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Development Safety Update Reports and Proposals for Effective and Efficient Risk Communication

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Abstract

The periodic safety reporting to regulatory authorities is globally harmonized for postmarketing medicinal products by the International Conference on Harmonisation (ICH) guidelines, and is being extended for investigational drugs. To facilitate effective safety risk communication regarding investigational drugs, and to reduce duplicate periodic reporting to the US and EU by sponsors during development programmes, standardized Development Safety Update Reports (DSURs) are to be implemented in the near future.

In this current opinion article, after extensively reviewing the relevant report from the CIOMS VII Working Group and the ICH draft guideline regarding DSURs, we discuss an effective and efficient approach to its application. To ensure effective risk communication, we recommend that DSURs be made available to all the ethics committees and participating investigators around the world for the purpose of continuing review during ongoing clinical trials.

Furthermore, in order to maintain the consistency and integrity of safety information throughout the life-cycle of a drug, we believe it would be substantially more prudent and efficient to start a single, integrated, life-cycle periodic safety report covering both development and postmarketing, as proposed by the CIOMS VII Working Group, rather than maintain separate DSURs and Periodic Safety Update Reports, which can overlap considerably in content. To this end, we believe that the international regulatory community should undertake the new initiative for integrated periodic reporting immediately.

1. Periodic Safety Reporting during Drug Development

1.1 Safety Risk Communication for Investigational Drugs

Risk communication with regulatory bodies, investigators and ethics committees regarding an investigational drug is carried out during development programmes using several internationally well established tools, including the investigators' brochure (IB) and expedited reporting of suspected unexpected serious adverse reactions (SUSARs). Additionally, regulatory bodies in the EU and US require different annual reporting on investigational drugs from sponsors under local regulations, namely the EU Annual Safety Report

and the US FDA Investigational New Drug Annual Report. These reports overlap slightly in content but differ substantially in purpose, scope and timing of data-lock points, creating costly inefficiency and redundant work for sponsors. Because of the gap in reporting periods and the difference in purposes between these annual reports, it has been pointed out that, for example, EU regulators might receive different safety messages regarding a particular investigational drug at different timepoints from FDA regulators.[1,2]

These issues prompted a new initiative by CIOMS for developing a unique, standardized content and format for periodic safety reports on investigational drugs. In August 2006, the CIOMS VII Working Group published *The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials*.[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) step 2 consensus guideline (E2F) on the DSUR, based on the CIOMS proposals, was issued for public comment in June 2008.[2]

In this present current opinion article, while we argue for the significance of harmonized periodic safety reports during development phases, we present extensive discussion on the draft ICH E2F guideline and the CIOMS VII Working Group report to help improve the current, malfunctioning risk communication and to promote safety risk management during clinical development programmes. In particular, we discuss the following subjects:

- effective use of DSURs to improve the current risk communication system;
- efficiency brought about by introduction of integrated periodic safety reporting throughout the life-cycle of a drug.

Furthermore, we hope that our discussion will attract greater public attention to the regulatory system on drug development safety, and trigger wider discussion among the international regulatory community as well as the representatives of trial investigators and ethics committees, on the basis that although these parties are primarily responsible for managing the safety of individual patients, they have thus far rarely been involved with the bigger picture.

1.2 Comparison between the Report of the CIOMS VII Working Group and the Draft International Conference on Harmonisation (ICH) E2F Guideline

DSURs are intended to be a common standard report to ''notify regulators and other interested parties (e.g. ethics committees) at regular intervals of the evolving safety profile of an investigational drug and actions proposed or being taken to address safety concerns'' during clinical development.[2] The CIOMS VII Working Group further stated that ''by design, [DSURs] will enable a seamless transition for communicating safety information to relevant stakeholders, starting at the early clinical development stage and […] continuing throughout the post-approval period''. The DSUR table of contents was developed in alignment with that of established PSURs for marketed drugs (table I).[2,3] Where possible, commonalities in the table of contents between the proposed DSUR and the PSUR were retained. Furthermore, the concept of safety risk management during development is fully reflected in the detailed instructions in the proposed DSUR guideline, in accordance with the proposal by the CIOMS VI Working Group, 'Management of Safety Information from Clinical Trials'.[4]

Several recommendations made by the CIOMS VII Working Group were not reflected in the draft ICH E2F guideline (table II). For example, both the CIOMS VII Working Group and the draft ICH E2F guideline recognize the value of providing an executive summary of a DSUR to ethics committees and trial investigators where the local legislation requires, although only the CIOMS VII Working Group suggests disclosure of the full report upon request. Additionally, one chapter of the CIOMS VII Working Group report is devoted to the goal of a single periodic safety report covering the lifecycle of a drug from development to post-launch, and incorporating the current PSURs within its scope. However, a compromise on this