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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

Table I. Comparison of table of contents between the Development Safety Update Report (DSUR) proposed by the International Conference on Harmonisation (ICH) E2F draft guideline and the current Periodic Safety Update Report (PSUR) for marketed drugs[a] (reproduced by kind permission of the Council for International Organizations of Medical Sciences.[1] © CIOMS)

Proposed contents of the DSUR[2]	Corresponding contents of the PSUR[3]
Title page	Title page
Executive summary	Executive summary
Table of contents	Table of contents
1. Introduction	1. Introduction
2. Worldwide marketing authorization status	2. Worldwide market authorization status
3. Update on actions taken in the reporting period for safety reasons	3. Update of regulatory authority or MAH actions taken for safety reasons
4. Changes to reference safety information	4. Changes to reference safety information
5. Status of clinical trials ongoing and completed during the reporting period	7. Studies 7.1 Newly analysed company-sponsored studies 7.2 Targeted new safety studies planned, initiated or continuing during the reporting period 7.3 Published safety studies
6. Estimated exposure 6.1 Cumulative subject exposure in clinical trials (phase I–IV) 6.2 Patient exposure from marketed setting	5. Patient exposure
7. Presentation of safety data from clinical trials 7.1 General considerations 7.2 Interval line listings of serious adverse reactions (SARs) 7.3 Cumulative summary tabulations 7.4 Deaths in the reporting period 7.5 Subjects who dropped out in association with any adverse event in the reporting period	6. Presentation of individual case histories 6.1 General considerations 6.2 Cases presented as line listings 6.3 Presentation of the line listing 6.4 Summary tabulations 6.5 MAH's analysis of individual case histories
8. Significant findings from clinical trials during the reporting period 8.1 Completed trials and any interim analyses 8.2 Ongoing clinical trials 8.3 Other therapeutic use of investigational drug 8.4 New safety data related to combination therapies	7. Studies 7.1 Newly analysed company-sponsored studies 7.2 Targeted new safety studies planned, initiated or continuing during the reporting period 7.3 Published safety studies
9. Relevant findings from non-interventional studies	
10. Relevant findings from other studies	
11. Safety findings from marketing experience	Included in point 6. 'Presentation of individual case histories'
12. Other information 12.1 Non-clinical data 12.2 Long-term follow-up 12.3 Literature 12.4 Other DSURs 12.5 Significant manufacturing changes 12.6 Lack of efficacy 12.7 Phase I protocol modifications	8. Other information 8.1 Efficacy-related information 8.2 Late-breaking information
13. Late-breaking information	
14. Overall safety assessment 14.1 Evaluation of the risks 14.2 Benefit-risk considerations 14.3 Conclusions	8. Other information 8.3 Risk management programmes 8.4 Benefit-risk analysis report 9. Overall safety evaluation 10. Conclusion
15. Summary of important risks	Not explicitly covered by PSUR according to ICH E2C (R1)

a Contents are numbered according to the applicable ICH guidelines.

MAH = Marketing Authorization Holder.

Table II. Comparison regarding expected audience of Development Safety Update Reports (DSURs) and separation from Periodic Safety Update Reports (PSURs) for the postmarketing phase

Reports and guidelines	Ethics committee and trial investigators as recipients of DSUR	DSUR as a separate document from PSUR
CIOMS VII report[1]	Executive summary provided where national legislation requires periodic submission of safety information on an investigational drug to ethics committees, institutional review boards or investigators, and a full document delivered upon request	Ultimate goal is to implement an integrated life-cycle periodic safety report covering the scope of the DSUR and PSUR, but current recommendation is to create two stand-alone documents – one for investigational drugs during development (DSUR) and one for postmarketing (PSUR)
ICH E2F draft guideline[2]	Executive summary only for submission to ethics committees and other stakeholders, if required by local regulations No description on full report	No description for integration with the PSUR Create two stand-alone documents – one for investigational drugs during development phase (DSUR) and one for postmarketing (PSUR)
Our proposal	Executive summary submitted to all ethics committees and participating investigators across the board A full report readily available upon request to trial investigators and ethics committees	Introduce a single, life-cycle periodic safety report pertaining to both development and postmarketing as soon as possible Require update of outdated PSUR guidelines to comply with most recent concept of risk management

ICH = International Conference on Harmonisation.

point appears to have been reached, considering ''the significant and complex challenges a unified safety update report would present, such as requiring changes to existing practices and requirements'', presumably the current, long-standing PSUR practice. Thus, the temporal focus of the CIOMS VII Working Group is a stand-alone DSUR in a step-by-step approach towards their ultimate goal.[1] In contrast, the draft ICH E2F guideline included no suggestion regarding an integrated DSUR-PSUR report. We consider the above points as being of high relevance to effective risk communication and rational use of resources. In this current opinion article, we discuss two proposals regarding DSUR recipients and the DSUR as a separate document from the PSUR.

2. Proposals

2.1 Ethics Committees and Investigators as Development Safety Update Report (DSUR) Recipients

The CIOMS VII Working Group considers that ''the DSUR is intended for submission exclusively to regulatory authorities. However, where national legislation requires periodic submission of safety information on an investigational drug to Ethics Committees, Institutional Review Boards, or investigators, the CIOMS VII Working Group recommends that only the DSUR Executive Summary be provided, with a full DSUR available upon request''.[1] Furthermore, the ICH E2F draft guideline recommends that ''where local authorities ask for periodic submission of safety information on an investigational drug to ethics committees, institutional review boards, or investigators, the DSUR executive summary should suffice, supplemented with line listings of serious adverse reactions (SAEs) as warranted''.[2] Thus, even though they are primarily responsible for managing the safety of trial participants, not all the ethics committees and trial investigators around the world receive the executive summary, and a full report might be available only if requested.

Currently, safety information regarding an investigational drug can be relayed to investigators and ethics committees in several ways, namely as an IB and an expedited individual case summary report (ICSR).[5] Recently, the CIOMS VI Working Group proposed periodic reporting with interval line listings of SUSARs, as a substitute for a barrage of expedited ICSRs.[4] Safety risk communication in clinical trials should be established by maintaining transparency of safety data, rapidity and consistency of assessment, and periodicity and clarity of messages throughout all

development programmes. However, whether the current communication tools satisfy all of these criteria is unclear.

An IB is a comprehensive compilation of findings on an investigational drug, and is submitted to an ethics committee when seeking approval to begin a new trial. It is developed and reviewed for update annually according to Good Clinical Practice standards, and updated as significant new information becomes available by sponsors, although the requirements for annual updating is subject to local regulations.[4] However, a revised IB does not necessarily contain the latest safety information from ongoing clinical trials, because such results are not declared as 'locked'. A complete set of results from a clinical trial is included in the revised IB only after the data has been validated and analysed. Occasionally, annual revision may thus be delayed until analysis completion or 'when significant results become available' (figure 1), reducing the periodicity of IBs. Furthermore, this 'dictionary' contains information accumulated from early developmental stages; too much to be efficiently processed. Readers struggle to identify important updates in safety information and the relevant risk assessments. Thus, an IB lacks periodicity in communicating newly emerging risks associated with an investigational drug, and clarity in effectively conveying the sponsor's perspective on those risks. Nonetheless, an IB is submitted annually to ethics committees for continuing review of clinical trial activities, despite the above disadvantages. In fact, submission of revised IBs to regulatory authorities during an ongoing study is not necessarily required.

When a SUSAR case associated with an investigational drug is reported to the sponsor, an expedited ICSR is issued according to existing ICH standards.[5] The report is delivered to

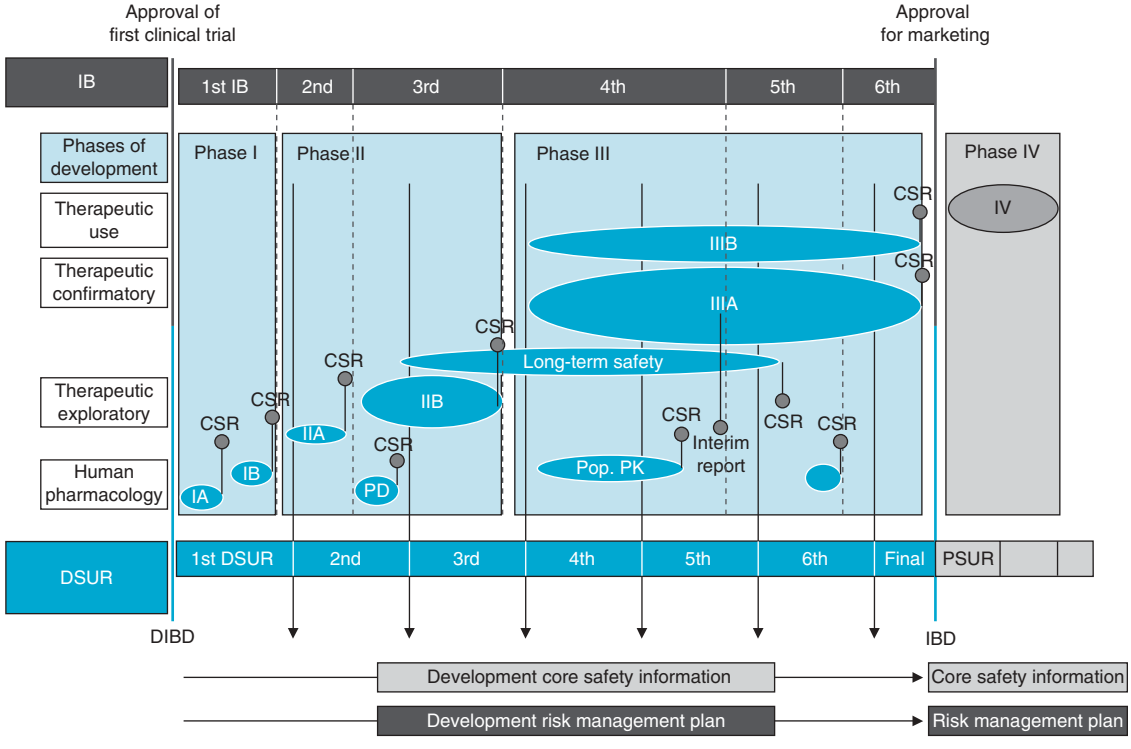

Fig. 1. Periodicity of Development Safety Update Reports (DSURs) and Investigators' Brochures (IBs) in a model development programme. Vertical dotted lines indicate data-lock points for IB revisions, and vertical solid lines indicate data-lock points for each DSUR. **CSR** = Clinical Study Report; **DIBD** = Development International Birth Date; **IBD** = International Birth Date; **PD** = pharmacodynamics; **PSUR** = Periodic Safety Update Report; **Pop. PK** = population pharmacokinetics.

regulators, trial investigators, and ethics committees within a locally determined timeframe. As reported by the CIOMS VI Working Group,[4] in this era of global multi-tiered and parallel development, ethics committees and trial investigators are overwhelmed with paperwork for processing ICSRs for various investigational drugs dispatched one after another from pharmaceutical companies. The original intent to expeditiously convey important risk information is lost, and investigators may overlook relevant safety findings. The CIOMS VI Working Group proposed replacing sporadic ICSRs with periodic interval line listings of unblinded SUSAR cases, along with a brief summary from the sponsor on the up-to-date safety profile.[4] This appears to improve upon current practices with regard to reducing the burden on investigators and ethics committees to process a large quantity of ICSRs while keeping trial investigators and ethics committees abreast of recent unblinded SUSAR cases, but remains to be implemented with a new global consensus on harmonization.

An ICSR also fails to serve as a common tool with global integrity that provides a sponsor's safety assessment on one particular case. Expectedness of adverse events varies depending on the reference documents adopted by local regulations in each country, including an IB, a Summary of Product Characteristics and a package insert. In a multinational study, this difference may result in regulators in different countries receiving ICSRs with different expectedness for a particular case, or even no report at all. To address this issue, the CIOMS VI Working Group proposed using a single reference safety information document for expectedness assessment, namely a Development Core Safety Information (DCSI), which is comparable to company core safety information for postmarketing. The CIOMS VII Working Group report and ICH draft guideline also recommend appending a DCSI to DSURs, and describing any significant changes occurring during the reporting period in the DSUR. Furthermore, by attaching the DCSI to IBs, the recency of IBs may be enhanced because of the more frequent, prompt and independent updates required of DCSIs.[4,6]

The current safety communication tools described above lack either reporting periodicity, data transparency, clarity or risk message integrity. In contrast, a DSUR has accurate periodicity because of the predetermined annual data lock and efficiency in documenting a sponsor's latest comprehensive and integrated perspective on the safety of an investigational drug while focusing on relevant recent data showing any changes from the previous knowledge. The recency of a DSUR would be ensured by its completeness in listing recent SUSAR cases from ongoing clinical trials reported during the covered period in the cumulative tabulation of SAE incidences once the case files are closed, without having to wait for the data lock of the concerned trial. In addition, the focus on interval safety in a DSUR, in contrast to an IB, would be preferable to continuing review of ongoing development activities, and therefore we argue for its submission to all ethics committees and participating investigators across the board (table II).

Transparency in safety communication may be undermined by providing only an executive summary, because of the summary's inherent lack of supporting evidence on which the safety assessments are based. This limitation may be overcome by making relevant information (namely the remaining periodic reports) available to not only clarify events occurring during the interval, but also to bestow a sense of easy access to relevant materials. In the EU, both the ethics committees and regulatory authorities are the target audience of annual safety reports under the applicable regulation. DSURs are developed as replacements for annual safety reports and there would therefore be no definitive reason to stop distributing the equivalent to ethics committees in those countries. It is true that an executive summary may be sufficient during initial review to allow ethics committees to judge whether or not further discussion is necessary. When the committees regard further discussion on the sponsor's recommended actions as necessary, a full DSUR can provide immediate access to the supporting data. Moreover, such reference information on important risks and similar event cases may greatly aid investigators in the early

and appropriate management of adverse event cases and in enhancing their sensitivity to usually overlooked but significant non-SAEs. Objections to distributing full reports stem mainly from the additional burden that reviewing a new voluminous report would pose on investigators. We therefore suggest that sponsors make full DSURs readily available upon request during the conduct of clinical trials via methods such as web distribution under appropriate security control and electronic documentation with hyperlinking, which ensures quick retrieval of documents as the need arises, and easy access from the executive summary to supporting data in the main body of the DSUR without a significant increase in paperwork. Additionally, to further improve development risk communications, it may be worthwhile to conduct a survey on the receptivity and usefulness of DSURs for safety management at study sites after the start of DSUR distribution to reflect feedback from trial investigators and study sites.

It should be noted that the objective of the above-mentioned periodic line listings proposed by the CIOMS VI Working Group, which consist of only expeditiously-reported, unblinded SUSAR cases along with brief updates on the emerging safety profile, differs from that of DSURs. Although DSURs present a transparent overview of interval safety findings for an investigational drug, the CIOMS VI Working Group's proposed line listings lack content essential to ensuring the transparency of a periodic safety report, such as information regarding all SUSAR cases occurring during the period, and tabulated cumulative incidences of SAEs, available safety analyses by study from ongoing or completed clinical trials and information on risk management during the relevant period; these important elements are all available in DSURs.

In summary, we recommend that executive summaries of DSURs should be distributed to all participating study sites around the world on the grounds that they are the most effective tool for strengthening risk communication, and that sponsors should make full DSURs readily available upon request. Further discussion on the role and structure of IBs is required if DSURs are to be submitted to ethics committee review sessions.

2.2 A Single, Life-Cycle Periodic Safety Report Format Pertaining to Development and Post-Authorization Phases

The ICH E2F draft guideline states that "some overlap is expected between the DSUR and PSUR" and contains no description of a single model of periodic safety reporting throughout the life-cycle of a drug (table II).[2] In contrast, the CIOMS VII Working Group presents their goal of "the eventual development and implementation of a single, integrated life-cycle safety report that incorporates the scope of the current DSUR and PSUR, and avoids duplication of information, unnecessary burden and confusion for both sponsors and regulators".[1] We strongly agree with the CIOMS VII Working Group's perspective and further suggest that integrated reporting throughout development and postmarketing be implemented as soon as possible when the periodic safety reports during the development phase start.

Collection of safety data starts before human exposure to an investigational drug and continues into the postmarketing phase. The nature and quantity of available data evolve depending on the developmental stages. All relevant safety-related data should be evaluated within a continual and comprehensive context throughout the life-cycle of the drug, considering the differences in data sources and clinical stages to relate a simple, specific and clear message to all concerned parties. From the perspective of continuing and consistent safety assessment, separating periodic safety reporting by authorization status would not be of great significance as the status varies by country and marketing authorization would be nothing but a landmark during the life-cycle of the drug. Safety data can be collected concurrently from clinical trials and postmarketing experiences for a fair amount of time after the initial marketing authorization. In this peri-approval period, the content of PSURs in any country will be similar to that expected for DSURs in other countries where clinical trials are still ongoing. Both reports deal with a large amount of information from pre-approval clinical trials, along with a comparable portion from emerging postmarketing experiences. The proposed

DSURs and the current PSURs differ with regard to items, order and headings due to differences in applicable guidelines (table I).[1] If a sponsor must create a DSUR in parallel with a PSUR for the same reporting interval, cross-validate them and submit these reports on different schedules according to local regulatory requirements in the recipient countries, inefficiency is inescapable. In addition, it may be undesirable and confusing for a regulatory body to receive two periodic safety reports regarding the same medicinal agent in countries where clinical trials are ongoing after the initial market launch. Therefore, a single, common, integrated periodic update report for each active substance should be pursued to relate a simple, specific and clear safety message with global consistency.

With the effort of the CIOMS VII Working Group, the proposed DSUR format is modelled after the current PSUR format to promote smooth transition to PSURs during the peri-approval period, contributing to the discussion on a common format for integrated report. The CIOMS VII Working Group also expressed their strong belief in the efficiency and utility provided by integration of DSURs and PSURs, and provided the framework for a model integrated periodic safety report, which could accommodate the presentation of both elements for early development compounds, such as non-clinical or clinical pharmacological data, and elements for postmarketing, such as interval line-listings of SUSAR cases for approved indications (table III).[1] As specifying the data sources and authorization status would ensure that readers appropriately understand the significance and quality of various safety findings, refinement in this regard may be necessary for implementation. Thus, we recommend that the international regulatory community should make every effort to realize harmonized life-cycle reporting as soon as possible, rather than maintain parallel production of a separate DSUR and PSUR. In case a sponsor restarts a new development programme for an approved product for an additional indication, for which the development programme has terminated, it would be much more efficient and prudent to use a single integrated periodic

Table III. Proposed table of contents for a model integrated periodic safety report (reproduced by kind permission of the Council for International Organizations of Medical Sciences.[1] © CIOMS)

Title page
Table of contents
Executive summary
Introduction
Worldwide marketing authorization status
Update of regulatory authority, trial sponsor or MAH actions taken for safety reasons (actions taken during the reporting period)
Changes to reference safety information (DCSI and CCSI when relevant)
Patient exposure
market use
clinical trials
Individual case histories from marketing experience (excluding clinical trials)
clinically significant individual case histories
line listings (only for special types of reports, such as SUSARs, and by exception)
summary tabulations (including spontaneous and solicited reports)
Clinical studies
inventory and status of worldwide interventional clinical trials (all phases; approved and non-approved indications, dosage forms, populations)
results from interventional clinical trials
completed (synopsis of results)
approved uses
unapproved uses
ongoing (synopsis of results if interim analysis conducted during reporting period)
approved uses
unapproved uses
line listing (only for SUSARs)
summary tabulations (all serious adverse events from interventional clinical trials; cumulative)
observational and epidemiological studies (including use of registries)
completed
ongoing
targeted new safety studies
completed
ongoing
planned
Other information
efficacy-related information
chemistry, manufacturing and formulation issues

Continued next page

Table III. Contd

non-clinical findings
literature sources
Late-breaking information
Overall safety evaluation
discussion on (i) marketed use experience; and (ii) investigational use
Summary of important issues (problem list; update of those previously identified and any new ones)
identified risks
potential risks
important missing data (needed to resolve outstanding issues/risks)
New actions recommended
Conclusions
Appendices

CCSI = Company Core Safety Information; **DCSI** = Development Core Safety Information; **MAH** = Marketing Authorization Holder; **SUSAR** = Suspected Unexpected Serious Adverse Reaction.

report than compiling two different but similar reports in parallel, to communicate a single, consistent safety message. The cost of inefficiency and redundancy from having both reports would ultimately fall on consumers and society, and therefore we believe that such duplication should be avoided in line with the ICH's objective of "a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health".[7] Therefore, we believe that the international regulatory community would be better off undertaking the new initiative for integrated periodic safety reporting immediately.

3. Main Points to Consider

3.1 Preparing for Distribution of DSURs

Several important points regarding the contents of DSURs should be discussed before distribution to ethics committees and investigators. First, concern exists regarding presenting unblinded SUSAR cases in DSURs in terms of statistical validity. We agree with the CIOMS VI recommendation that all SUSAR cases should be unblinded[4,5] and presented in DSURs. In fact, with the aid of adequate allocation methods, disclosing treatment information regarding isolated SUSAR cases would rarely affect the statistical validity of the results from comparative studies. To ensure unbiased comparison of safety results, cumulative incidences of SAEs should be tabulated by treatment arms, including unblinded placebo cases in DSURs.[1,2]

The second point concerns aggregate safety review from clinical trial data. When designing a development plan for an investigational drug, a prospectively planned aggregate safety review within the sponsoring company should be discussed from the perspective of safety risk management.[4] The ICH E2F draft guideline showed the summary tabulation of SAEs across the programme using a simple summation of cases across studies in its appendix.[2] To obtain more useful statistics for early identification of emerging safety risks, we suggest incorporating into the development plan a carefully planned, prospective meta-analysis, which should be performed at a timing to yield sufficient power to effectively detect important safety signals. Drug exposure, doses and characteristics of populations studied should be considered whenever appropriate.[4,8] The results of these meta-analyses should be reported and discussed within the context of overall safety evaluation in a DSUR when available, ultimately aiding in assessing individual case reports and in interpreting results from each clinical trial.[9] Thus, DSURs include the results of periodic assessment of aggregate safety data, and any subsequent changes to the reference safety information should be reflected in the DCSI. Consequent actions taken for risks are determined in the Development Risk Management Plan, ensuring appropriate risk management throughout the development programme (figure 1).

3.2 Preparing for Integrated Periodic Safety Reports

Some established practices will be challenged by introducing an integrated DSUR/PSUR model.[1] It may take more years to realize integrated

periodic safety reports, considering the possible difficulties discussed below and the time needed for the DSUR guidelines to reconcile EU Annual Safety Reports and US Investigational New Drug annual reports. The likely barriers to establishing the new processes for integrated safety reports include the need for further harmonization in the relevant local regulations and international guidelines regarding postmarketing safety, and the need to fix the existing chasm in evaluation processes between the departments responsible for development and those for postmarketing safety within the regulatory agencies.[10] Should the regulatory community stop advancing further simplification and improvement of periodic safety reporting processes once the new regulation on separate DSURs is set in place; however, the consequence would predictably be costly, as discussed in section 2.2. Introduction of globally harmonized DSURs will also challenge Japanese regulators and commercial sponsors, in particular, as no annual reports during clinical development phases are currently in place in Japan, and post-approval local periodic safety reports are required to have a harmonized PSUR attached in English. To avoid further burdening sponsors with its unique requirements, Japan's peculiar regulatory system must be harmonized before DSUR implementation.[1]

Postmarketing safety risk management was publicly introduced with the implementation of the 2005 ICH E2E guideline, *Pharmacovigilance Planning*.[11] However, the most recent working PSUR guideline [ICH E2C(R1), 2003] is obsolete in current practice because of its insufficiency in specific instructions regarding contents for risk management.[3] In contrast, the draft DSUR guideline provides detailed instructions for several risk-related sections, particularly as provided under the headings "Overall Safety Evaluation" and "Summary of Important Risks" (table I).[2] When the outdated PSUR guideline is updated, its contents will be expanded to convey important risk information in a globally harmonized manner

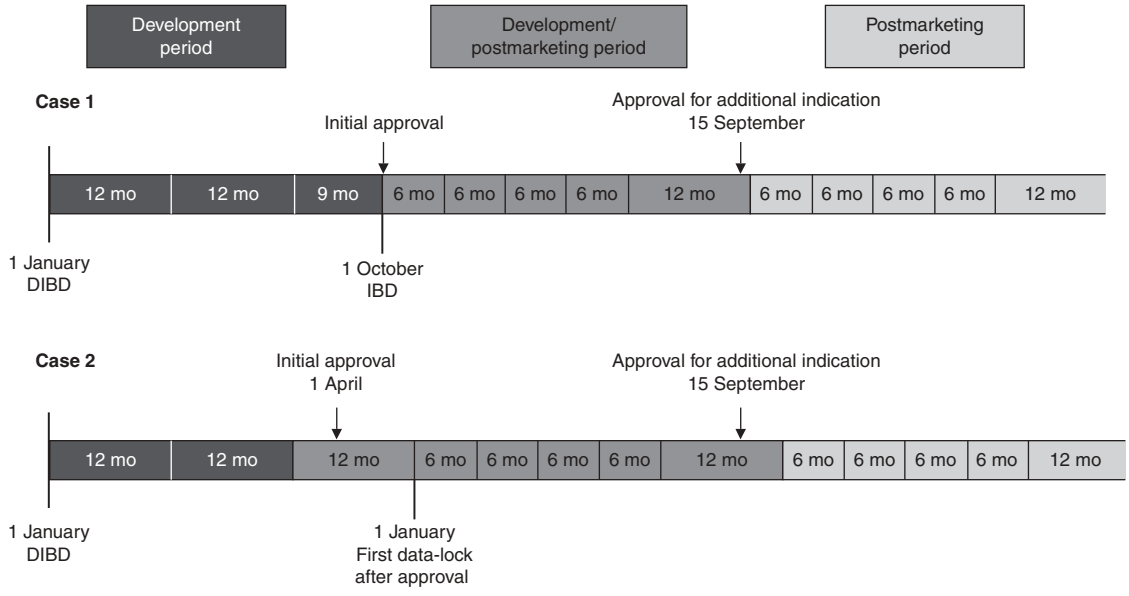

Fig. 2. Data-lock points and intervals in a model transition from development phase to postmarketing for a single, life-cycle periodic safety report. Case 1: When the first marketing approval is granted within 6–12 months after the last Drug Safety Update Report (DSUR) data-lock point, the data-lock point for subsequent integrated periodic safety reports after the first approval is changed to the date of first marketing approval, namely the International Birth Date (IBD). Case 2: When the first marketing approval is granted within 6 months after the last DSUR data-lock point, the data-lock point for the subsequent integrated periodic safety reports after the first approval remains as the date of approval of the first clinical trial, namely the DIBD (Development International Birth Date).

at the latest level of regulatory science, as indicated in the model integrated periodic safety reports proposed by the CIOMS VII Working Group (table III).[1] This expectation also supports the concept of a single integrated periodic report.

Synchronization of reporting intervals represents another outstanding issue. We recommend simple alignment of reporting intervals for integrated reports with the current PSUR intervals of 6 months for the 2 years immediately following approval of a new indication, and with those stipulated by the applicable local regulations thereafter (figure 2). Considering the current PSUR intervals and the suggestion for DSURs by the ICH E2F guideline, keeping intervals to less than 12 months would be necessary for the effective periodic evaluation of the flood of postmarketing information immediately after first launch.[2] The model transition from DSUR to PSUR in the CIOMS VII Working Group report permits a maximum interval of 18 months for a DSUR in the peri-approval period,[1] but this duration appears too long for integrated reports to efficiently convey emerging safety information immediately after launch. We also suggest that use of the Development International Birth Date and International Birth Date as a data-lock point for integrated reports should be determined as a matter of convenience, rather than being bounded by the convention of the existing PSUR regulations, to permit a 6-month to 1-year interval in transitioning from a pure DSUR-type report to a DSUR/PSUR-type report (figure 2). Allocation of a sponsor's resources to an approved product during this peri-approval period would typically cover the anticipated workload for frequent reporting.

4. Conclusions

The DSUR is a comprehensive and concise document fit for communicating risk information of investigational drugs, including safety-related data and actions for patient protection. Distributing the executive summary of DSURs and ensuring immediate accessibility of full reports to all ethics committees and trial investigators worldwide is strongly encouraged as it may strengthen the clarity of current risk communication and enhance risk mitigation actions by providing a rationale. On taking into consideration both the challenges of introducing an integrated periodic safety report and the anticipated unnecessary burden and confusion likely to arise from simultaneously having two similar kinds of periodic reports for one medicinal agent, we believe that pursuing an approach to a single, life-cycle integrated periodic safety report is worthwhile. Additionally, updating the outdated PSUR guideline to the latest regulatory scientific level following the concept of risk management is introduced is urged.

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