
Guidance for Industry

E2F Development Safety Update Report

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**August 2011
ICH**

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E2F Development Safety Update Report

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1)²

The development safety update report (DSUR) proposed in this guidance is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. U.S. and European Union (EU) regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the U.S. investigational new drug application (IND) annual report and the EU annual safety report, respectively, and can therefore take the place of these existing reports.³ This guidance defines the recommended content and format of a DSUR and provides an outline of points to be considered in its preparation and submission.

Definitions of the technical terms used in the guidance are included in a glossary (Appendix A); the first mention of a term in the guidance is identified with an asterisk (*).

¹ This guidance was developed within the Efficacy Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, August 2010. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

² Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, August 2010.

³ Japan will consider existing regulations on periodic safety reporting in implementing the DSUR.

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A. Background (1.1)

During the clinical development of an investigational drug,⁴ periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects.^{5,6} It is also important to inform regulators and other interested parties (e.g., ethics committees) at regular intervals about the results of such analyses and the evolving safety profile of an investigational drug, and apprise them of actions proposed or being taken to address safety concerns. Currently, laws and regulations of some ICH countries and regions require submission of a periodic report to regulatory authorities to provide this information. However, significant differences in the content, format, and timing of these reports highlight the importance of a common standard report in promoting consistency and enhancing efficiency. Some national and regional laws and regulations also require a periodic report that describes the status of ongoing individual investigations, manufacturing changes, and overall development status and plans. To be broadly useful, the DSUR should also include this information, in addition to safety-related information. The harmonization of the content, format, and timing of periodic safety reports will help to ensure that regulators in the three ICH regions receive a uniform, high-quality, comprehensive report.

B. Objectives (1.2)

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

- (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
- (2) describing new safety issues that could have an impact on the protection of clinical trial subjects;
- (3) summarizing the current understanding and management of identified and potential risks;^{*} and
- (4) providing an update on the status of the clinical investigation/development program and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

⁴ The term *investigational drug* is used in this guidance to indicate only the experimental product under study or development.

⁵ For detailed discussion see *The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials: Report of CIOMS Working Group VII*, Council for International Organizations of Medical Sciences (CIOMS), Geneva 2006.

⁶ ICH E6 Good Clinical Practice: Consolidated Guidance, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>.

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C. Scope of the DSUR (1.3)

The main focus of the DSUR is data and findings from interventional clinical trials* (hereafter referred to as *clinical trials*) of drugs and biologicals that are under investigation, whether or not they have a marketing approval. Because clinical development of a drug frequently continues following marketing approval,⁷ relevant information from postmarketing studies should also be included in the DSUR. The DSUR should concentrate primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects.

The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

- Clinical trials using an investigational drug (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase 1–3));⁸
- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase 4));
- Therapeutic use of an investigational drug (e.g., expanded access programs, compassionate use programs, particular patient use, single patient INDs, and treatment INDs); and
- Clinical trials conducted to support changes in the manufacturing process of medicinal products.

The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:

- Observational or epidemiological studies;
- Nonclinical studies (toxicological and in vitro studies);
- Related DSURs, if applicable to the investigational drug;
- Manufacturing or microbiological changes;
- Studies recently published in the literature;
- Clinical trials with results indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life-threatening);
- Any other source of relevant safety findings for products in the same therapeutic class;
- Clinical trials conducted by a co-development partner, if permitted by the contractual agreement.

D. Relation of the DSUR to the Periodic Safety Update Report (1.4)

At present, some ICH countries and regions accept submission of a periodic safety update report (PSUR) to fulfill national and regional requirements for periodic reporting on the safety of approved drugs. Although the focus of the DSUR is on investigational drugs, there can be

⁷ For the purposes of this document, we use the terms *authorization* or *authorized* to refer to approvals of clinical trials and *approved* or *marketing approval* to refer to marketing authorizations.

⁸ For classification of clinical trials, see ICH E8 *General Considerations for Clinical Trials*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073132.pdf>.

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overlap between the content of the DSUR and PSUR, and some repetition is expected. For example, information from marketing experience (reported in the PSUR) might be relevant to clinical development, and therefore reported in the DSUR. Safety findings from clinical trials conducted using marketed drugs would be included in the DSUR, but would also be pertinent to postmarketing safety and would be reported in the PSUR. Both the DSUR and PSUR should be comprehensive and stand alone as they focus on different subject matter and have differing periodicities and recipients.

E. Recipients of the DSUR (1.5)

The DSUR is intended to serve as an annual report to regulatory authorities. Where national or regional laws or regulations require submission of an annual safety report on an investigational drug to ethics committees/institutional review boards, the DSUR Executive Summary might be appropriate, supplemented with line listings of serious adverse reactions⁹ (SARs) as warranted.

II. GENERAL PRINCIPLES (2)

A. Single DSUR for an Active Substance (2.1)

In order to promote a comprehensive analysis and presentation of the safety profile of the investigational drug, a sponsor should prepare a single DSUR with data pertinent to all dosage forms and strengths, all indications, and all patient populations under study with the investigational drug, wherever feasible. If this is not possible (e.g., when the data are not available to the sponsor), an explanation should be provided in the introduction section of the DSUR.

If more than one sponsor is involved in drug development, particularly in a co-development or other contractual agreement, a single DSUR can be submitted (see section II.D.2 (2.4.2)).

B. Periodicity and DSUR Data Lock Point* (2.2)

The Development International Birth Date* (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.

When the sponsor's first clinical trial is conducted in a country without a formal authorization process, the sponsor should designate an appropriate date linked to the commencement of the first clinical trial. Where clinical trials are ongoing in one country and are later initiated in another country, the original DIBD should be maintained and used for all countries in preparing the DSUR.

⁹ *Serious adverse reaction, serious adverse event, and adverse drug reaction* are defined in ICH E2A *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073087.pdf>.

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The data lock point of the DSUR should be the last day of the one-year reporting period. For administrative convenience, if desired by the sponsor, the data lock point of the DSUR can be designated as the last day of the month prior to the month of the DIBD.

When clinical development of a drug continues following a marketing approval in any country worldwide, both a PSUR and a DSUR should be submitted as specified by national or regional laws or regulations. If desired by the sponsor, a DSUR can be prepared based on the PSUR International Birth Date (IBD) so that the DSUR and the PSUR can be synchronized. In synchronizing the data lock points for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.

The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR data lock point.

C. Duration of DSUR Submissions (2.3)

DSURs should continue to be submitted for as long as indicated by national or regional laws or regulations.¹⁰ When submission of an annual report is no longer required in an individual country or region, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug in that country or region. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

D. Responsibilities for Preparing and Submitting a DSUR (2.4)

1. Sponsor's Responsibilities (2.4.1)

The sponsor* of a clinical trial is considered responsible for the preparation, content and submission of a DSUR. The sponsor can delegate the preparation of the DSUR to a third party (e.g., a contract research organization).

In situations where the sponsor does not have access to the information to be included in specific sections (e.g., sponsor-investigators* might not have information on manufacturing issues, nonclinical data, and marketing status), this should be stated in the DSUR.

2. Responsibilities of Multiple Parties (2.4.2)

When there is more than one sponsor of a clinical trial or drug development program, the parties should arrange to prepare a single DSUR, if possible. This includes situations where a sponsor is in a formal co-development or licensing relationship with one or more partners, or where individual clinical trials or a drug development program involve collaboration with public or private institutions, business partners, or other parties. Written agreements should be in place specifying how data will be exchanged and detailing the responsibilities for preparation and submission of the DSUR.

¹⁰ For example, in the United States, sponsors might keep an IND open even if no clinical trials are ongoing or planned. Annual reports are submitted for as long as the IND remains open.

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When a single DSUR cannot be arranged, multiple sponsors can agree to prepare separate DSURs for the same investigational drug. This can occur where different indications, routes of administration, or formulations are being investigated by different parties. In this situation, the rationale for separate DSURs should be provided in each report.

E. DSURs for Combination Therapies (2.5)

Given the potential complexities of clinical development involving combination therapies, it is not possible to provide guidance that addresses all such situations. The sponsor should select the most appropriate option based on judgment, taking into account patient population, indication, formulation, etc., as well as the circumstances in which the clinical trials are being conducted and national or regional laws or regulations. The rationale for this decision should be provided in the report.

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e., a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual component(s) of the fixed combination product, separate DSUR(s) should be submitted for each component. Relevant findings from each DSUR should be summarized in section 8.5 of the other DSUR(s).

For trials involving multi-drug therapy, i.e., combinations of drugs that are not fixed, the sponsor can prepare either:

- (1) a DSUR for the multi-drug therapy, or
- (2) DSUR(s) for one or more of the individual components; in this case information on the multidrug therapy trials can be included in the DSURs of one or all of the components.

The following table provides examples of strategies for preparation of DSURs for multi-drug therapies.

Multi-drug therapy used in clinical trial(s)	DSUR
Investigational drug (A) + marketed drug(s) (X, Y, Z)	Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy
Two investigational drugs (A) + (B)	Either a single DSUR focusing on (A + B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy
Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)	A single DSUR focusing on the multi-drug therapy (X + Y + Z)

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F. Reference Safety Information (2.6)

The Investigator's Brochure (IB) in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. Section 7.1 of the DSUR should clearly indicate the version number and date of the IB used for this purpose. When an IB is not required by national or regional laws or regulations, the applicable national or regional product label¹¹ should serve as the reference safety information.

Usually, a single document should serve as the reference safety information. However, in certain circumstances, it might be appropriate to use more than one reference document to support the DSUR (e.g., for a DSUR providing information on an investigational drug used in combination and as monotherapy).

If the IB has been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the current version of the IB as an attachment to the DSUR.

G. Format and Presentation of DSUR (2.7)

1. Format (2.7.1)

The recommended format and content of the DSUR, including table of contents, section numbering, and content of each section, is outlined below. For each heading where information is available, the information should be presented concisely; when no information is available or a DSUR section is not applicable, this should be stated.

If a sponsor intends to submit a DSUR in eCTD format, the sponsor should consult with the relevant regulatory authority regarding the appropriate placement of the DSUR in the eCTD structure.

2. Presentation (2.7.2)

The recommended table of contents, including section numbering, for the DSUR is provided below:

Title page
Executive Summary
Table of Contents
1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

¹¹ In the EU, this would be the Summary of Product Characteristics (SmPC); in Japan, this would be the Japanese Package Insert; and in the United States, this would be the U.S. Package Insert.

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6. Estimated Cumulative Exposure
 - 6.1 Cumulative Subject Exposure in the Development Program
 - 6.2 Patient Exposure from Marketing Experience
 7. Data in Line Listings and Summary Tabulations
 - 7.1 Reference Information
 - 7.2 Line Listings of Serious Adverse Reactions During the Reporting Period
 - 7.3 Cumulative Summary Tabulations of Serious Adverse Events
 8. Significant Findings from Clinical Trials during the Reporting Period
 - 8.1 Completed Clinical Trials
 - 8.2 Ongoing Clinical Trials
 - 8.3 Long-term Follow-up
 - 8.4 Other Therapeutic Use of Investigational Drug
 - 8.5 New Safety Data Related to Combination Therapies
 9. Safety Findings from Noninterventional Studies
 10. Other Clinical Trial/Study Safety Information
 11. Safety Findings from Marketing Experience
 12. Nonclinical Data
 13. Literature
 14. Other DSURs
 15. Lack of Efficacy
 16. Region-Specific Information
 17. Late-Breaking Information
 18. Overall Safety Assessment
 - 18.1 Evaluation of the Risks
 - 18.2 Benefit-risk Considerations
 19. Summary of Important Risks
 20. Conclusions
- Appendices to the DSUR

III. GUIDANCE ON CONTENTS OF A DSUR (3)¹²

All sections should be completed; when no information is available, this should be stated.

Title page

The title page of the DSUR should include the following information:

- DSUR number (reports should be numbered sequentially)
- Investigational drug(s)
- Reporting period
- Date of the report
- Sponsor(s) name(s) and address(es)

¹² Headings in this section on guidance on the contents of a DSUR are numbered to correspond to the numbering of an actual DSUR.

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- Statement on the confidentiality of the information included in the DSUR
- A cautionary statement that the DSUR includes unblinded information, if applicable

Executive Summary

This section should provide a concise summary of the important information contained in the report. Together with the title page, it can serve as a stand-alone document suitable for submission to ethics committees and other stakeholders, if required by national or regional laws or regulations. The following information should be included in the Executive Summary:

- Introduction — report number and reporting period
- Investigational drug(s) — mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s)
- Estimated cumulative exposure of clinical trial subjects
- Marketing approval(s)? (yes/no) — If yes, number of countries
- Summary of overall safety assessment (based on section 18 of the DSUR)
- Summary of important risks (based on section 19 of the DSUR)
- Actions taken for safety reasons including significant changes to IB
- Conclusions

Table of Contents

1. Introduction (3.1)

This section should include:

- DIBD or IBD (as applicable)
- Reporting period and sequential number of the report
- Investigational drug(s) — mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- A brief description of the indication(s) and population(s) being studied
- A short summary of the scope of the clinical trials covered by the report (e.g., all trials with the investigational drug, indication-specific trials, trials with combination products)
- A brief description and explanation of any information that has not been included in the DSUR (e.g., when written agreements with a partner company do not provide for exchange of all safety data)
- The rationale for submission of multiple DSURs for the investigational drug, if applicable

2. Worldwide Marketing Approval Status (3.2)

This section should provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable.

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3. Actions Taken in the Reporting Period for Safety Reasons (3.3)

This section should include a description of significant actions related to safety that have been taken during the reporting period by the sponsor, regulators, data monitoring committees* (DMC) or ethics committees that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.* The reason(s) for each action should be provided if known. Relevant updates to previous actions should also be summarized in this section (e.g., resumption of a clinical trial after suspension).

Changes to the Investigator's Brochure should be discussed separately in the "Changes to Reference Safety Information" (see section III.4 (3.4)).

Examples of significant actions taken for safety reasons include:

Actions related to investigational drugs:

- Refusal to authorize a clinical trial for ethical or safety reasons
- Partial¹³ or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy (see section III.15 (3.15))
- Recall of investigational drug or comparator
- Failure to obtain marketing approval for a tested indication including voluntary withdrawal of a marketing application
- Risk management activities, including:
 - Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration)
 - Restrictions in study population or indications
 - Changes to the informed consent document relating to safety issues
 - Formulation changes
 - Addition by regulators of a special safety-related reporting requirement
 - Issuance of a communication to investigators or healthcare professionals
 - Plans for new studies to address safety issues

Actions related to marketed drugs:

- Failure to obtain a marketing approval renewal
- Withdrawal or suspension of a marketing approval
- Risk management activities including:
 - Significant restrictions on distribution or introduction of other risk minimization measures
 - Significant safety-related changes in labeling documents that could affect the development program, including restrictions on use or population treated
 - Communications to health care professionals
 - New postmarketing study requirement(s) imposed by regulators

¹³ *Partial suspension* might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another and/or suspension of a particular dosing regimen in a trial but continuation of other doses).

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This section should also summarize requests from regulatory authority(ies) that place a specific limitation on current or future development (e.g., a request to conduct long-term animal studies before initiating a long-term clinical trial, specification of a maximum dose to be evaluated, a request for specific safety data before initiating trials in pediatric subjects). A cumulative listing of such requests from regulatory authorities should be provided, including any updates if applicable. This can be provided as a table, in an appendix, or in this section.

4. Changes to Reference Safety Information (3.4)

This section should list any significant safety-related changes to the IB or other reference safety information within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest,* interactions, and any important findings from nonclinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.

5. Inventory of Clinical Trials Ongoing and Completed During the Reporting Period (3.5)

This section should provide a brief overview of the clinical trials ongoing* and completed* by the sponsor in the reporting period, with detailed information presented in a table as an appendix (see examples in Appendix B, Table 1 of this guidance). Separate tables can be provided by indication, formulation, and study population, if appropriate. In addition, where required by national or regional laws or regulations, similar information should be provided for other therapeutic use of an investigational drug in the reporting period. The table(s) should include the following information for each clinical trial:

- Study ID (e.g., protocol number or other identifier)
- Phase (1, 2, 3, or 4)
- Status:
 - Ongoing (clinical trial has begun; has begun but is currently on hold; has concluded but clinical study report has not been finalized)
 - Completed (clinical study report is finalized)
- Countries/regions where there is at least one investigational site for the protocol
- Abbreviated study title
- Design (uncontrolled, controlled, open, single blind, double blind, parallel, cross-over, etc., including treatment arms)
- Dose and regimen of investigational drug and any comparators
- Study population as appropriate (age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment)
- Date of clinical trial start (as defined by the sponsor, e.g., first visit of first patient (FVFP))

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- Planned enrollment for study as a whole
- Estimates of cumulative numbers of exposed subjects for each treatment arm, where available. The actual enrollment numbers for open or completed trials, and/or an estimate based on the randomization scheme for blinded trials, should be provided.

Appendix B, Table 1 of this guidance provides an example of the column headings for such tables.

6. Estimated Cumulative Exposure (3.6)

Sections 6.1 and 6.2 of the DSUR should provide information on cumulative exposure in clinical trials and the marketed setting, respectively.

An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events (SAEs) and the overall assessment of safety. The accuracy of the estimation of clinical trial exposure might be limited because of a number of factors, including the rapidity of subject enrolment and the number of ongoing trials where treatment assignment remains blinded.

The optimal method of data presentation will depend on a number of factors, and the following general points should be considered in the preparation of the estimated exposure for the DSUR:

- Data should be presented in tabular format.
- When there are important differences among trials in dose, route of administration, or patient population, these differences can be noted in the tables, or separate tables can be considered.
- If the summary tabulations of SAEs are presented by indication, the exposure data should also be presented by indication, when available.
- When there are substantial differences in time of exposure between subjects randomized to the investigational drug and comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure data in subject-time (subject-days, -months, or -years).
- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, particularly when volunteers are exposed to only a single dose. Such data can be presented separately with explanation, when appropriate.
- For marketed drugs that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data (e.g., when the drug has been marketed for a number of years and/or has many indications). In these circumstances, the sponsor should provide an explanation.

6.1. Cumulative Subject Exposure in the Development Program (3.6.1)

This section should include the following information, in tabular format (see Appendix B, Tables 2-4 of this guidance for examples):

- The cumulative number of subjects from ongoing and completed clinical trials; the number exposed to the investigational drug, placebo, and/or active comparator(s) since

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the DIBD (Note: When treatment assignment is blinded, numbers of subjects can be estimated based on the randomization scheme.)

- Cumulative number of subjects exposed to the investigational drug from ongoing and completed clinical trials, subgrouped by age range, sex, and racial group for the development program when the data are available
- Demographic characteristics for a single trial if the trial is of particular importance (e.g., a pivotal Phase 3 trial).

The specific categorization of age might be dependent on the subject population and indication.

This section should also include an explanation of the sponsor's rationale for selecting the method to estimate subject exposure, and the limitations of that method, based on the points above.

6.2. Patient Exposure From Marketing Experience (3.6.2)

If the investigational drug is marketed by the sponsor, the DSUR should include an estimate of the cumulative patient exposure in the marketed setting, based on the information provided in the most recent PSUR or other suitable data source, with an explanation of the method(s) used to determine the estimate.

7. Data in Line Listings and Summary Tabulations (3.7)

Sections 7.1-7.3 of the DSUR should present important clinical safety information through:

- Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and
- Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

Although causality assessment is generally useful for the evaluation of individual rare adverse drug reactions (ADRs) and for making decisions regarding expedited reporting, individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations in a DSUR should include all SAEs and not just SARs for the investigational drug and comparators.

The line listings and tabulations should include blinded and unblinded clinical trial data. Unblinded data might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors should not unblind data for the specific purpose of preparing the DSUR.

At the sponsor's discretion, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

If the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level should be presented in the line listings and summary tabulations.

In general, the tabulation(s) of SAEs should include only those terms that were used in defining the case as serious; they should not include nonserious events.

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Certain adverse events can be excluded from the line listings and summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database, and those that are integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

7.1. Reference Information (3.7.1)

This section of the DSUR should specify the version(s) of the coding dictionary used. If applicable, it should also specify the document and version used as Reference Safety Information for determining expectedness for the tabulations, where required by national or regional laws or regulations.

7.2. Line Listings of Serious Adverse Reactions During the Reporting Period (3.7.2)

This section of the DSUR should summarize how case reports were selected for inclusion in the line listings. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be provided in an appendix (see Appendix B, Table 5 of this guidance).

The line listings should provide key information on all SARs (blinded and unblinded) reported from the sponsor’s clinical trials during the reporting period. The data should be organized by trial and then by System Organ Class (SOC).

Where possible the line listing(s) should include each subject only once regardless of how many SAR terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom, or diagnosis), as judged by the sponsor. It is possible that the same subject could experience different SARs on different occasions (e.g., weeks apart during a clinical trial). Under such circumstances, the SARs can be listed separately, and a single subject can be included in a line listing more than once.

The following information should be included in the line listings:

- (a) Study identification number and EudraCT number¹⁴ as applicable
- (b) Subject clinical trial identification number
- (c) Sponsor’s adverse reaction case reference number
- (d) Country in which case occurred
- (e) Age and sex of trial subject
- (f) Treatment group; identified as “blinded” if the blind has not been broken
- (g) Dose and dosing interval of investigational drug (and, when relevant, dosage form and route of administration)
- (h) Date of onset and/or time to onset of the most serious adverse reaction
- (i) Dates of treatment and/or best estimate of treatment duration
- (j) Serious adverse reaction(s); when MedDRA is used, the Preferred Term should be presented

¹⁴ The EudraCT number is the unique identifier for trials authorized in the European Economic Area.

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- (k) Outcome (e.g., resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- (l) Comments, if relevant (e.g., causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available)

Appendix B, Table 5 of this guidance provides an example of the headings for a line listing.

7.3. Cumulative Summary Tabulations of Serious Adverse Events (3.7.3)

This section should refer to an appendix that provides a cumulative summary tabulation of SAEs reported in the sponsor's clinical trials, from the DIBD to the data lock point of the current DSUR. The sponsor should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years or for products acquired through a business merger). The tabulation(s) should be organized by SOC, for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo, and treatment unknown due to blinding) used in the program. Data can be integrated across the program. Alternatively, when useful and feasible, tabulations of SAEs can be presented by protocol, indication, route of administration, or other variables.

This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix B, Table 6 of this guidance provides an example.

8. Significant Findings from Clinical Trials During the Reporting Period (3.8)

The information in this section can be provided by indication, when appropriate, and should address the following topics, when applicable:

8.1. Completed Clinical Trials (3.8.1)

This section of the DSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting period. This information can be presented in narrative format or as a synopsis.¹⁵ It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.*

¹⁵Examples of synopses are provided in ICH E3 *Structure and Content of Clinical Study Reports*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073113.pdf> and CIOMS VII.

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8.2. Ongoing Clinical Trials (3.8.2)

If the sponsor is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarize the issue(s). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

8.3. Long-Term Follow-up (3.8.3)

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products, and tissue engineered products). When the development program is completed and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.

8.4. Other Therapeutic Use of Investigational Drug (3.8.4)

This section of the DSUR should include clinically important safety information from other programs conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access programs, compassionate use programs, particular patient use, single patient INDs, and treatment INDs).

8.5. New Safety Data Related to Combination Therapies (3.8.5)

If the DSUR is for an investigational drug that is also under development as a component of a fixed combination product or a multi-drug regimen, this section should summarize important safety findings from the combination therapy DSUR.

Conversely, if this DSUR is for a multi-drug therapy or fixed combination product, this section should summarize important safety information arising from trials on the individual components.

Alternatively, the information specific to the combination can be incorporated into a separate section(s) of the DSUR for one or all of the individual components of the combination.

General Principles, section II.E (2.5), provides additional guidance on preparation of DSURs for combination products.

9. Safety Findings From Noninterventional Studies (3.9)

This section should summarize relevant safety information from noninterventional studies* that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries,* and active surveillance programs).

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10. Other Clinical Trial/Study Safety Information (3.10)

This section should summarize relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

11. Safety Findings From Marketing Experience (3.11)

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and that became available to the sponsor during the reporting period, particularly if the findings resulted in changes to the product labeling, Investigator's Brochure, or informed consent document or amendments to the product's risk management plan. This includes not only safety findings relating to approved use but also off-label use, administration to special populations (e.g., pregnant women), medication errors, overdose and abuse.

12. Nonclinical Data (3.12)

This section should summarize major safety findings from nonclinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting period. Implications of these findings should be discussed in the Overall Safety Assessment (see section III.18 (3.18) of this guidance).

13. Literature (3.13)

This section should summarize new and significant safety findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug that the sponsor became aware of during the reporting period. This section should include information from nonclinical and clinical studies and, if relevant and applicable, information on drugs of the same class. It should also summarize significant new safety information presented at a scientific meeting and published as an abstract; the sponsor should provide a copy of the abstract, if possible.

14. Other DSURs (3.14)

A sponsor should prepare a single DSUR for a single investigational drug. However, if a sponsor prepares multiple DSURs for a single investigational drug (e.g., covering different indications, development programs, or formulations), this section should summarize significant findings from the other DSURs if they are not presented elsewhere within this report.

When available, the sponsor should summarize significant findings from DSURs provided by other sponsors conducting clinical trials with the same investigational drug during the reporting period.

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15. Lack of Efficacy (3.15)

Data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for investigational drugs intended to treat serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to clinical trial subjects and should be summarized in this section.

16. Region-Specific Information (3.16)

The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR. Sponsors should refer to national or regional requirements to determine which of the following sections should be included, as well as the scope of clinical trials that should be covered by these sections. Examples include:

- Cumulative summary tabulation of serious adverse reactions

This cumulative summary tabulation of all SARs should specify the number of SARs by: (a) SOC, (b) adverse reaction term, and (c) treatment arm, if applicable. Unexpected adverse reaction terms should be identified.

- List of subjects who died during the reporting period

The list of subjects who died during participation in the clinical trials should include the following information at a minimum: case number, assigned treatment (could still be blinded), and cause of death of each subject. Any safety issues identified from a review of these deaths should be addressed in section 18 of the DSUR as appropriate.

- List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period

This list should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not thought to be drug-related. Any safety issues identified from a review of these withdrawals should be addressed in section 18 of the DSUR as appropriate.

- Significant Phase 1 protocol modifications

This section should describe significant Phase 1 protocol modifications made during the reporting period, if not previously submitted as a protocol amendment, as described in the U.S. Code of Federal Regulations.

- Significant manufacturing changes

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This section should include a summary of significant manufacturing or microbiological changes during the reporting period and discuss potential safety issues arising from these changes in section 18 of the DSUR, if applicable.¹⁶

- Description of the general investigation plan for the coming year

This section should outline an investigational plan to replace that submitted for the previous year. U.S. IND holders should refer to the U.S. Code of Federal Regulations.¹⁷

- Log of outstanding business with respect to the U.S. IND

If desired by the sponsor, this section can provide a log of any outstanding business with respect to the U.S. IND for which the sponsor requests or expects a reply, comment, or meeting.

17. Late-Breaking Information (3.17)

This section should summarize information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings, and any action that the sponsor, a DMC, or a regulatory authority has taken for safety reasons. The Overall Safety Assessment (see section III.18 (3.18)) should also take these new data into account.

18. Overall Safety Assessment (3.18)

The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, nonclinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant postmarketing data. It should not summarize or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development program. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation and/or indication.

18.1. Evaluation of the Risks (3.18.1)

In evaluating the risks, particular emphasis should be placed on interpretation of data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Relevant points to consider include (where applicable):

¹⁶ In addition U.S. IND holders should refer to FDA guidance for industry, *INDs for Phase 2 and Phase 3 Studies — Chemistry, Manufacturing and Controls Information* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf>

¹⁷ U.S. Code of Federal Regulations 21 CFR 312.23(a)(3)(iv); revised April 2009, at <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi>

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- newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions)
- meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)
- symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:
 - hepatotoxicity
 - cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies
 - bone marrow toxicity
 - pulmonary toxicity
 - renal toxicity
 - central nervous system toxicity
 - immunogenicity and hypersensitivity
- deaths that are an outcome of an adverse event
- study drug discontinuations because of adverse events, including abnormal laboratory values or investigations
- drug–drug and other interactions
- important nonclinical safety findings
- manufacturing issues that could affect risk
- lack of efficacy where this would place trial participants at risk
- any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at-risk groups (e.g., slow or fast metabolizers)
- pregnancy and lactation exposure and outcomes
- safety findings arising from experience with long-term treatment
- evidence of clinically significant medication errors
- evidence of lack of patient compliance
- experience with overdose and its treatment
- occurrences of drug misuse and abuse
- any safety issues resulting from procedures required by the protocol (e.g., bronchoscopy, biopsy, central line insertion) or associated with the conduct or design of a particular study (e.g., inadequate subject monitoring schedule, excessive period without active treatment) and
- potential impact of significant new safety issues identified with another drug in the same class

18.2. Benefit-Risk Considerations (3.18.2)

This section should provide a succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits* and should note whether there have been any changes in this balance since the previous DSUR. This section is not intended to be a full benefit-risk assessment of the investigational drug.

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19. Summary of Important Risks (3.19)

This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks* (e.g., those that might lead to warnings, precautions, or contraindications in labeling). Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating nonclinical or clinical data. Each risk should be re-evaluated annually and re-summarized as appropriate, based on the current state of knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained, the information on each risk might be less detailed.

The information in this section could provide the basis for the safety specification of a risk management plan (*ICH E2E Pharmacovigilance Planning*).

Risks that have been fully addressed or resolved should remain in the summary and be briefly described, e.g., findings from toxicology studies or early clinical trials that were not borne out by later clinical data.

The information can be provided in either narrative or tabular format (see examples of both in Appendix C of this guidance).

20. Conclusions (3.20)

The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR. The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development program.

Appendices to the DSUR

The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:

1. Investigator's Brochure (if required by national or regional laws or requirements)
2. Cumulative Table of Important Regulatory Requests
3. Status of Ongoing and Completed Clinical Trials
4. Cumulative Summary Tabulations of Demographic Data
5. Line Listings of Serious Adverse Reactions
6. Cumulative Summary Tabulation of Serious Adverse Events
7. Scientific Abstracts (if relevant)

The DSUR should also be accompanied by the following Regional Appendices, as appropriate (see section III.16 (3.16)):

- Cumulative summary tabulation of serious adverse reactions

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- List of subjects who died during the reporting period
- List of subjects who dropped out of studies during the reporting period
- Significant Phase 1 protocol modifications with respect to a U.S. IND
- Significant manufacturing changes
- Description of the general investigation plan for the coming year with respect to a U.S. IND
- Log of outstanding business with respect to a U.S. IND

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IV. APPENDICES TO THIS GUIDANCE

APPENDIX A — Glossary

Throughout this guidance the Working Group has used terms previously defined by ICH and other groups (e.g., CIOMS). Generally, the definitions of terms that were previously defined in ICH documents are not repeated in this glossary. However, the glossary includes several ICH terms of particular importance to the DSUR, as well as terms defined by CIOMS and other groups.

Adverse event of special interest: An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. (Based on CIOMS VI)

Anticipated efficacy/benefit: Efficacy/benefit that has not yet been established for the investigational drug, but which is anticipated based on knowledge of the class of drugs or data from previous clinical trials or nonclinical studies. (Based on wording of CIOMS VI definition of anticipated risk)

Clinical development program: This refers to all clinical trials being conducted with the same investigational drug, regardless of indication or formulation. (ICH E2F)

Completed clinical trial: Study for which a final clinical study report is available. Note: For purposes of the DSUR, any clinical trial for which enrolment has begun, but for which a final clinical study report is not available, is considered to be ongoing (see *ongoing clinical trial* definition). (CIOMS VII)

Data lock point: The date (month and day) designated as the cut-off for data to be included in a DSUR. It is based on the Development International Birth Date (DIBD). (CIOMS VII)

Data Monitoring Committee (synonyms: Independent Data Monitoring Committee, Data and Safety Monitoring Board): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. (ICH E6)

Development International Birth Date: Date of first approval (or authorization) for conducting an interventional clinical trial in any country. (CIOMS VII)

Identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. (Volume 9A Rules Governing Medicinal Products in the EU)

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Examples of identified risks include:

- an adverse reaction adequately demonstrated in nonclinical studies and confirmed by clinical data
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions

Important identified risk; important potential risk: An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health. (Volume 9A Rules Governing Medicinal Products in the EU)

Interventional clinical trial: An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (e.g., preventive care, drugs, surgical procedures, behavioral treatments, etc.) to evaluate their effects on health-related outcomes. (CIOMS VII)

Investigational drug: The term investigational drug is used in this guidance to indicate only the experimental product under study or development. Note: This term is more specific than “investigational medicinal product” which includes comparators and placebos. (CIOMS VII)

Noninterventional clinical study: A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data. (EU Directive 2001/20/EC on Clinical Trials)

Ongoing clinical trial: Trial where enrolment has begun, whether a hold is in place or analysis is complete, but without a final clinical study report available. (CIOMS VII)

Potential risk: An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. (Volume 9A Rules Governing Medicinal Products in the EU)

Examples of potential risks include:

- Nonclinical safety concerns that have not been observed or resolved in clinical studies
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship
- A signal arising from a spontaneous adverse reaction reporting system

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- An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product

Registry: A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Commentary: Exposure (drug) registries collect information over time on populations exposed to drugs of interest and/or specific populations. Patients can be included in a cohort study to collect data on adverse events using standardized questionnaires. They can be useful for signal amplification, particularly of rare outcomes. (ICH E2E)

Signal: A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. (CIOMS VI)

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (ICH E6 (R1))

Sponsor-investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (ICH E6)

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APPENDIX B — Examples of Tables and Table Headings for Clinical Trial Listings

Table 1. Status of Ongoing and Completed Clinical Trials

Overview of Ongoing Studies [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP†	Planned enrolment	Subject exposure‡

† FVFP = first visit first patient

‡ Based upon total number of patients recruited as of [date] and applied randomization schemes

Overview of Studies Completed During the DSUR Period [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Subject/patient patient exposure per treatment arm (M/F)

Table 2. Estimated Cumulative Subject Exposure

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomization schemes for ongoing trials.

Treatment	Number of subjects
drug	
comparator	
placebo	

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Table 3. Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex*

	Number of subjects		
Age range	Male	Female	Total

* Data from completed trials as of [date]

Table 4. Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group*

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

* Data from completed studies as of [date]

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Table 5. Examples of Headings for Interval Line Listings of Serious Adverse Reactions

Interval Line Listings of Serious Adverse Reactions

Study ID EudraCT number	Case ID/ Subject number†	Country Sex Age	Serious adverse drug reactions (SARs)	Outcome	Date of onset‡ Time to onset‡	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
	-----	-----	-----	-----	-----	-----	-----	-----	-----

† Study/center/patient

‡ ‘Primary’ SAR only

Table 6. Examples of Cumulative Tabulations of Serious Adverse Events

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

<u>System Organ Class</u> Preferred Term	Total up to 31-Dec-09			
	[Study drug]	Blinded	Active comparator	Placebo
<u>Investigations</u>	18	4	7	2
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
<u>Nervous System Disorder</u>	2	2	4	7
Syncope	2	2	4	7

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APPENDIX C — Examples of the Summary of Important Risks

This appendix depicts fictitious examples of the Summary of Important Risks, prepared in three consecutive years, from 2012 to 2014. The Summary of Important Risks can be provided in either narrative (Appendix C1) or tabular (Appendix C2) format.

APPENDIX C1: Narrative Format

DSUR 2012

19 Summary of Important Risks

New or updated risks are denoted with an asterisk.

1. Nephrotoxicity

Drug Z is a para-aminoglycolate that bears structural similarities to aminoglycosides, currently under development for amelioration of angina pectoris in patients with stable coronary artery disease. Other members of this class are known to be nephrotoxic, and there was evidence of nephrotoxicity in both rats and rabbits at doses of 20 and 60 mg/kg/d, respectively.

In Phase 1 trials in healthy volunteers, 2 of 30 subjects (6.7%) who received the highest dose of drug Z (100 mg po qd for 7 days) exhibited transient increases in serum creatinine associated with proteinuria: subject 0127 had an increase in creatinine from 0.9 mg/dL at baseline to 1.8 mg/dL at Day 7; subject 0139 had an increase from 1.0 mg/dL at baseline to 1.9 mg/dL at Day 7. Both subjects had mild proteinuria (2+ by dipstick, 24-hour urinary protein not quantified). Urinalyses of both subjects were unremarkable (minimal cells; no casts). By Day 21, serum creatinine had returned to baseline in both subjects, and proteinuria had resolved (see sections 8.2 and 18.1 for details). None of the other 28 healthy subjects who received drug Z 100 mg qd, and none of the 119 subjects who received drug Z at lower doses (50 mg or less, including 72 subjects with coronary artery disease), experienced proteinuria or significant increases in creatinine.

The increases in creatinine in the healthy volunteers who received the highest dose of drug Z (100 mg QD) were thought likely to be drug-related, in part because of the known nephrotoxicity of the drug class. It was decided, therefore, to reduce the maximum dose of drug Z in the Phase 2 trials to 50 mg. In addition, subject monitoring was intensified: serum creatinine, eGFR, albumin/creatinine ratios, blood urea nitrogen, and urinalysis are now performed at baseline, Weeks 1, 2, 4, 8, 16, and 24. Twenty-four-hour urinary protein excretion will be determined for any subject who develops proteinuria by dipstick. Study drug will be discontinued in subjects with creatinine increases of 0.5 mg/dL, a 30% rise in creatinine, or a 25% decrease in eGFR (repeated 2 times over a 3-day period). The protocol, informed consent document, and Investigator's Brochure have been revised accordingly.

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2. Hepatotoxicity

In rat study KR-102, 2 of 8 rats in the highest dose group (60 mg/kg/d) developed hepatic injury, with centrilobular necrosis. None of the rats that received lower doses had evidence of hepatotoxicity, and no hepatotoxicity was evident in rabbits at doses as high as 60 mg/kg/d.

One (1) subject (102-037) with coronary artery disease in study 102 who received 50 mg po qd drug Z developed moderate elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on Day 14 (2.7 and 2.3 x the upper limits of normal, respectively), without increases in alkaline phosphatase or bilirubin (see sections 8.2 and 18.1 for details). Drug Z was discontinued on Day 16, and transaminases returned to normal by Day 28. The subject denied alcohol consumption, and all serology was negative. The subject had been receiving drugs X and Y concomitantly on a chronic basis for >2 years prior to enrolment. Neither drug was suspected of causing the elevation in transaminases. Both were continued during the adverse event, making it very unlikely that they were the cause of the transaminase elevations. Of note, subject 102-037 was found to have concentrations of drug Z (C_{max}) approximately 8-fold higher than the mean of the 50 mg cohort, suggesting an inability to metabolize drug Z. This possibility remains under investigation. An additional 148 subjects were exposed to drug Z in the Phase 1 program, and none exhibited transaminase elevations.

In light of the rat findings and the transaminase elevations in subject 102-037, more frequent monitoring has been implemented for the Phase 2 study. Assessments at Weeks 4 and 16 have been added, so that subjects now undergo assessment of ALT, AST, bilirubin, and alkaline phosphatase at baseline, Weeks 1, 2, 4, 8, 16, and 24. The protocol, informed consent document, and Investigator's Brochure have been revised accordingly.

DSUR 2013

19 Summary of Important Risks

New or updated risks are denoted with an asterisk.

1. Nephrotoxicity*

Drug Z is a para-aminoglycolate, one of a class of drugs bearing structural similarities to aminoglycosides, and known to be nephrotoxic. Two of 30 healthy volunteers (6.7%) in the Phase 1 program who had received drug Z 100 mg PO qd developed transient increases in serum creatinine associated with mild proteinuria (by dipstick), and the 100 mg dose was dropped from further development. In the completed Phase 2 trial of drug Z in patients with coronary artery disease and stable angina pectoris (Study 201), increases in creatinine >1.25 but ≤1.5 times baseline were observed in 5 of 60 subjects (8.3%) in the 50 mg group, 5 of 62 subjects (8.1%) in the 25 mg group, and 3 of 59 subjects (5.1%) in the 10 mg group, versus 6 of 61 subjects (10%) in the placebo group. For all of these subjects, the study drug was continued (per protocol), and serum creatinine returned to baseline within 2 weeks. Increases in creatinine >1.5 times baseline were observed in 1 of 60 subjects (1.7%) in the 50 mg group,

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0 of 62 subjects in the 25 mg group, and 1 of 59 subjects (1.7%) in the 10 mg group, versus 2 of 61 subjects (3.3%) in the placebo group. The study drug was discontinued in all of these subjects (per protocol), and serum creatinine returned to baseline within 2 weeks. As explained in sections 8.2 and 18.1, the “recovery” of creatinine to normal (i.e., the slope of the creatinine vs. time relationship) was the same in subjects who continued and discontinued the study drug, suggesting that this was not a specific drug effect. Of note, 3 of the 4 drug Z-treated subjects who developed creatinine elevations were taking concomitant diuretics. In ongoing studies 202 and 204, serum creatinine, eGFR, blood urea nitrogen, and urinalysis continue to be monitored at baseline, Weeks 1, 2, 4, 12, 24, and 48. Twenty-four-hour urinary protein excretion is determined in any subject who develops proteinuria by dipstick.

2. Hepatotoxicity*

Drug Z caused centrilobular necrosis at the highest dose tested (60 mg/kg/d) in rats (although there was no evidence of liver damage at this dose in rabbits). One (1) of 149 subjects (0.7%) in the Phase 1 program developed unexplained elevations of ALT and AST approximately 2.5 x the upper limit of normal on Day 14; which resolved on discontinuation of the drug. Two drug Z-treated subjects in the completed Phase 2 study #201 (2/181, 1.1%) had transaminase elevations (see section 8.2), but these were mild and transient, and one subject in the placebo group (1/61, 1.6%) had more severe elevations. Based on this information, the present monitoring plan seems appropriate, and no changes have been made to the protocol, Investigator’s Brochure, or informed consent document. Of note, one subject with elevated transaminases (102-037) had been thought to have had an unusually high C_{max}; however, this was subsequently determined to be a laboratory error.

3. Syncope*

Drug Z is thought to be a mild nitric oxide (NO)-dependent vasodilator, which could be partly responsible for its anti-anginal effect. During this period there were 2 reports of syncope (2/81, 1.1%) from study #201 that were considered by investigators to be causally-related to drug Z (subjects 201-119 and 201-212). The subjects had been receiving 10 and 25 mg of drug Z, respectively. Although both subjects were predisposed to syncope (one was apparently very dehydrated; the other had a long history of syncope), there is mechanistic plausibility and we will continue to focus on syncope as a possible drug-related side effect. No specific changes have been made to the monitoring plan as a result of these adverse events.

DSUR 2014

19 Summary of Important Risks

New or updated risks are denoted with an asterisk.

1. Nephrotoxicity*

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Drug Z is a para-aminoglycolate, one of a class of drugs bearing structural similarities to aminoglycosides, and known to be nephrotoxic. A 100 mg dose, studied in Phase 1, was dropped from further development because of increases in creatinine and proteinuria in normal volunteers. In the Phase 2 program, increases in creatinine >1.25 but <1.5 times baseline were observed in 7.8%, 6.8%, and 5.8% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 6.3% in the placebo group. Increases in creatinine >1.5 times baseline were observed in 1.5%, 0.5%, and 1.9% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 2.7% in the placebo group. As noted in sections 8.2 and 18.1, increases in creatinine seem to be associated with dehydration and diuretic use. In addition, a number of the subjects with increases in creatinine of more than 50% from baseline have had unusually low baseline values (i.e., ≤ 0.6 mg/dL). The clinical meaning of this is unclear.

In the ongoing Phase 3 trial (301), serum creatinine, eGFR, blood urea nitrogen, and urinalysis are monitored at baseline, Weeks 1, 4, 12, and 48. Twenty-four-hour urinary protein excretion is determined in any subject who develops 3+ or greater proteinuria by dipstick.

2. Hepatotoxicity*

Drug Z caused centrilobular necrosis at the highest dose tested in rats. There was frequent monitoring of ALT, AST, alkaline phosphatase, and bilirubin in the Phase 1 and 2 trials, and no consistent pattern of laboratory abnormalities has emerged suggestive of liver injury.

In the ongoing Phase 3 study (301), the above laboratory tests of liver injury are monitored at baseline, Weeks 1, 4, 12, and 48.

3. Syncope*

Drug Z is thought to be a nitric oxide (NO)-dependent vasodilator, which could be partly responsible for its anti-anginal effect. There have been 21 reports of syncope in drug Z-treated subjects thus far in the development program (21/632, 3.3%), versus 3 (1.4%) in placebo. Most of the cases were orthostatic, and/or associated with coadministration of nitrates or vasodilators. In the Phase 3 program, subjects are advised against concurrent administration of vasodilators (e.g., nitrates, dihydropyridine calcium channel blockers), and given general precautions regarding orthostatic dizziness. The protocol, informed consent document, and Investigator's Brochure have been revised to include this risk.

4. Pancreatitis*

Three case reports of pancreatitis have been reported from subjects in the completed Phase 2 and ongoing Phase 3 trials (see sections 8.1 and 8.2, respectively). Although there were plausible alternative explanations for each case, evidence of pancreatitis will be carefully sought thorough laboratory monitoring: all subjects enrolled in the Phase 3 trial (301) undergo screening evaluations of lipase and amylase, with repeat evaluations at Weeks 1 and 4.

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APPENDIX C2: Tabular Format

19 Summary of Important Risks

This section summarizes the important identified or potential risks that have been recognized during the conduct of the Drug Z clinical development program. At present, all are considered as potential risks, with none characterized as identified risks associated with the administration of drug Z.

The following have been recognized as important potential risks during the reporting period:

- Nephrotoxicity
- Hepatotoxicity
- Syncope
- Pancreatitis

Additional details are provided in Table X, below:

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Table X Summary of Important Risks

New or updated risks are denoted with an asterisk.

Risk	Nonclinical data	Clinical data	Actions
Nephrotoxicity*	Nephrotoxicity in rats and rabbits at doses of 20 and 60 mg/kg/d, respectively	<p>Drug Z is a para-aminoglycolate, in drug class structurally similar to aminoglycosides. Nephrotoxicity well known.</p> <p>Phase 1: A 100 mg dose was dropped from further development because of increases in creatinine and proteinuria in normal volunteers.</p> <p>Phase 2: Increases in creatinine >1.25 but <1.5 times baseline were observed in 7.8%, 6.8%, and 5.8% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 6.3% in the placebo group.</p> <p>Increases in creatinine >1.5 times baseline were observed in 1.5%, 0.5%, and 1.9% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 2.7% in the placebo group.</p> <p>Increases in creatinine seem to be associated with dehydration and diuretic use. In addition, a number of the subjects with increases in creatinine of more than 50% from baseline have had unusually low baseline values (i.e., ≤0.6 mg/dL). The</p>	<p>In Phase 3 trial (301), serum creatinine, eGFR, blood urea nitrogen, and urinalysis monitored at baseline, Weeks 1, 4, 12, and 48.</p> <p>24-hour urinary protein excretion is determined in subjects who develop >2+ or proteinuria by dipstick.</p>

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Risk	Nonclinical data	Clinical data	Actions
		clinical meaning of this is unclear. See sections 8.2 and 18.1, i	
Hepatotoxicity*	Rat study KR-102: 2 of 8 rats in the highest dose group (60 mg/kg/d) developed centrilobular necrosis. At lower doses, no rats had evidence of hepatotoxicity. No hepatotoxicity seen in rabbits at doses \leq 60 mg/kg/d.	With frequent monitoring of ALT, AST, alkaline phosphatase, and bilirubin in the Phase 1 and 2 trials, no consistent pattern of laboratory abnormalities emerged suggestive of liver injury.	Routine monitoring in ongoing Phase 3 study (301): ALT, AST, alkaline phosphatase, and bilirubin monitored at baseline, Weeks 1, 4, 12, and 48.
Syncope*	Published studies: drug Z is a nitric oxide (NO)-dependent vasodilator in canine models.	21 reports of syncope in drug Z-treated subjects to date in the development program (21/632, 3.3%), versus 3 (1.4%) in placebo. Most cases orthostatic, and/or associated with coadministration of nitrates or vasodilators.	In Phase 3 program, subjects advised against concurrent administration of vasodilators; given precautions regarding orthostatic dizziness. Protocol, informed consent, and Investigator's Brochure revised to include this risk.
Pancreatitis*	No findings.	3 cases of pancreatitis reported from subjects in the completed Phase 2 and ongoing Phase 3 trials. Causal relationship with drug Z not determined - plausible alternative explanations for each case.	Subjects in the Phase 3 trial (301) undergo screening evaluations of lipase and amylase, with repeat evaluations at Weeks 1 and 4.