Comparison of DSUR Guidelines to AR CFR Requirements

DSUR GUIDELINES	AR CFR REQUIREMENTS
Title page • DSUR number • Investigational agent(s) • Reporting period • Date of report • Sponsor(s) name(s) and address(es) • Confidentiality statement • A cautionary statement that the DSUR includes unblinded information, if applicable	Not in CFR but inclusion is understood
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 the IB • Conclusions	NA
Table of Contents	Not in CFR but inclusion is understood

1.0 Introduction • Date of Clinical Trial Authorisation approval, Development International Birth Date of drug or International Birth Date of Drug as appropriate • Reporting period and sequential number of the report • Investigational drug(s) – mode(s) of action, therapeutic class (es), indication(s), 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.	21CFR 312.33 (b)(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
2.0 Worldwide Marketing Approval Status This section should provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable.	21CFR 312.33 (f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.
3.0 Actions Taken in the Reporting Period for Safety Reasons 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 committee or ethics committee that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme. 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).	NA

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 paediatric 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.	
4.0 Changes to Reference Safety Information This section should list any significant safety-related changes to the Investigator's Brochure (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 non-clinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.	21CFR 312.33 (d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

5.0 Inventory of Clinical Trials Ongoing and Completed during the Reporting Period
 	
This section should provide a brief overview of the clinical trials ongoing and completed by the sponsor during the reporting period, with detailed information presented in a table as an appendix (see examples from DSUR guidance at the end of this document, Table 1). The tables 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
	21CFR 312.33 (a) *Individual study information.* A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:
	
	• 21CFR 312.33 (a)(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.
	
	• 21CFR 312.33 (a)(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

• 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) • 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.	
6.0 Estimated Cumulative Exposure **6.1 Cumulative Subject Exposure in the Development Programme** **6.2 Patient Exposure from Marketing Experience** 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, 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. See also Tables 2, 3, and 4 (Estimated Cumulative Subject Exposure; by Age & Sex; and by Race) in examples of Appendices provided in Guidance.	21CFR 312.33 (a)(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

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 an explanation should be provided.	
7.0 Data in Line Listings and Summary Tabulations Sections 7.1 – 7.3 of the DSUR should present important clinical safety information through: • Interval line listings of the Serious Adverse Reactions that were reported during the period covered by the DSUR; and • If appropriate, cumulative summary tabulations of serious adverse events that have been reported since the Developmental International Birth Date of the drug. 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 reasons (e.g., expedited reporting), if applicable. Data should not be unblinded for the specific purpose of preparing the DSUR. **7.1 Reference Information** This section should specify the version of the medical coding dictionary used. If applicable, it should also specify the document and version used as Reference Safety Information for determining expectedness (e.g., IB, Summary of Product Characteristics). **7.2 Line Listings of Serious Adverse Reactions during the Reporting Period** This section 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). Where possible the line listings should include each subject only once regardless of how many SAR items are reported for the case. If there is more than one reaction, they should all be mentioned by the case should be listed under the most serious or primary adverse reaction. It is possible that the same subject could experience different SARs on different occasions (e.g., weeks apart). Under such circumstances, the SARs can be listed separately and a single subject can be included in the line listing more than once.	21CFR 312.33 (b)(2) A summary of all IND safety reports submitted during the past year. (covers only part of what is recommended in this DSUR section)

7.3 Cumulative Summary Tabulations of Serious Adverse Events See Appendix A, Table 3 in DSUR for an example of the headings for the line listing.	
8.0 Significant Findings from Clinical Trials during the Reporting Period 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** Should provide a brief summary of clinically important emerging efficacy and safety findings from clinical trials completed during the reporting period. **8.2 Ongoing Clinical Trials** Should provide details of clinically important safety 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). **8.3 Long-term Follow-up** Where applicable, this section should provide information from long-term follow up of subjects from clinical trials of investigational drugs. **8.4 Other Therapeutic Use of Investigational Drug** This section should include clinically important information from other programmes conducted by the same sponsor or co-sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access programs, compassionate use programs, particular patient use, sing patient INDs, and treatment INDs). **8.5 New Safety Data Related to Combination Therapies** If this 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-therapy drug or fixed combination product, this section should summarize important safety information arising from trials on the individual components.	21CFR 312.33 (b) *Summary information.* Information obtained during the previous year's clinical and nonclinical investigations. 21CFR 312.33 (a)(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

9.0 Safety Findings from Non-interventional Studies This section should summarize relevant safety information from sponsored or co-sponsored non-interventional studies that becomes available during the reporting period (e.g., observational studies, epidemiological studies, active surveillance programmes).	NA
10.0 Other Clinical Trial/Study Safety Information This section should summarize relevant safety information from any other sponsored or co-sponsored clinical trial/study sources that becomes available during the reporting period (e.g., results from pooled analyses or meta analyses of randomised clinical trials).	NA
11.0 Safety Findings from Marketing Experience 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.	NA
12.0 Non-clinical Data This section should summarize major safety findings from non-clinical *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 (Section 18).	21CFR 312.33 (b)(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
13.0 Literature This section should summarize new and significant findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug during the reporting period. This section should include information from non-clinical and clinical studies and, if relevant an 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; a copy of the abstract should be provided, if possible.	21CFR 312.33 (b)(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

14.0 Other DSURs One single DSUR should be prepared for all trials being undertaken on one investigational drug. However, if multiple DSURs are to be prepared for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarize significant findings from other DSURs if not presented elsewhere in the report.	NA
15.0 Lack of Efficacy 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 the clinical trial subjects and should be summarized in this section.	21CFR 312.33 (a)(3) If the study has been completed, or if interim results are known, a brief description of any available study results.
16.0 Region-Specific Information The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR. Should a DSUR be required for a country other than U.S., determine the requirements for that country. (See appendices.)	NA
17.0 Late-Breaking Information 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 or co-sponsors, data monitoring committee, or a regulatory authority has taken for safety reasons. Section 18 should also take account of this new data as appropriate.	NA
18.0 Overall Safety Assessment This section should be a concise, integrated evaluation of all new relevant clinical, non-clinical, and epidemiological information obtained during the reporting period relative to the previous knowledge of the investigational drug. This assessment should consider cumulative experiences, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data.	NA

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.	
19.0 Summary of Important Risks This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks, e.g., those that might lead to warning, precautions, or contraindications on labelling. Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating non-clinical or clinical data. Each risk should be re-evaluated annually and re-summarized as appropriate, based on the current state of the knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of the 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.	NA
20.0 Conclusions This section should briefly describe any changes to the previous knowledge or efficacy and safety resulting from information gained since the last DSUR. The conclusions should outline the actions that have been or will be taken to address emerging safety issues.	NA

Appendices to the DSUR The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:	NA
1. Investigators Brochure	21CFR 312.33 (d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.
2. Cumulative Table of Important Regulatory Requests	NA
3. Status of Ongoing and Completed Trials	21CFR 312.33 (a)(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed. 21CFR 312.33 (a)(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.
4. Cumulative Summary Tabulations of Demographic Data	21CFR 312.33 (a)(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.
5. Line Listings of Serious Adverse Reactions	21CFR 312.33 (b)(2) A summary of all IND safety reports submitted during the past year.
6. Cumulative Summary Tabulation of Serious Adverse Events	NA
7. Scientific Abstracts (if relevant)	NA
R1 – Cumulative summary of data for ongoing trial	21CFR 312.33 (b) *Summary information.* Information obtained during the previous year's clinical and nonclinical investigations.
R2 – List of subjects who died during the reporting period	21CFR 312.33 (b)(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

R3 – List of subjects who dropped out during the reporting period	21CFR 312.33 (a)(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. 21CFR 312.33 (b)(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.
R4 – Significant protocol modifications	21CFR 312.33 (e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.
R5 – Most serious and most frequent adverse events	21CFR 312.33 (b)(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.
R6 – Significant manufacturing changes	21CFR 312.33 (b)(7) A summary of any significant manufacturing or microbiological changes made during the past year.
R7 – Description of the general investigational plan for the coming year with respect to a US IND	21CFR 312.33 (c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under 312.23(a)(3)(iv).