

E2F Development Safety Update Report

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. An alternative approach may be used if such 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.

For questions regarding this draft document contact (CDER) Ellis F. Unger 301-796-2240 or (CBER) Peter F. Bross at 301-827-5102

FDA-2008-D-0386

GDL

1 INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
2 REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
3 USE

4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

ICH HARMONISED TRIPARTITE GUIDELINE

DRAFT

**DEVELOPMENT SAFETY UPDATE REPORT
E2F**

**Current Step 2 version
05 June 2008**

20

21	1	INTRODUCTION	4
22	1.1	OBJECTIVE OF THE GUIDELINE.....	4
23	1.2	SCOPE OF THE DSUR.....	5
24	2	GUIDANCE	6
25	2.1	WHEN SHOULD A DSUR BE PREPARED?.....	6
26	2.2	PERIODICITY AND DSUR DATA LOCK POINT	6
27	2.3	CHANGE OF DSUR DATA LOCK POINT	7
28	2.4	INTERRUPTION OR DISCONTINUATION OF CLINICAL TRIALS.....	7
29	2.5	FINAL DSUR.....	7
30	2.6	RESPONSIBILITIES FOR PREPARING AND SUBMITTING A DSUR	7
31	2.8	REFERENCE SAFETY INFORMATION	9
32	2.9	FORMAT AND PRESENTATION OF DSUR	10
33	2.10	GUIDANCE ON CONTENTS OF DSUR	11
34	3.	UPDATE ON ACTIONS TAKEN IN THE REPORTING PERIOD FOR	
35		SAFETY REASONS.....	13
36	7	PRESENTATION OF SAFETY DATA FROM CLINICAL TRIALS	17
37	8	SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE	
38		REPORTING PERIOD.....	19
39	9	RELEVANT FINDINGS FROM NON-INTERVENTIONAL STUDIES.....	20
40	10	RELEVANT FINDINGS FROM OTHER SOURCES.....	21
41	11	SAFETY FINDINGS FROM MARKETING EXPERIENCE	21
42	12	OTHER INFORMATION.....	21
43	12.1	NON-CLINICAL DATA.....	21
44	12.2	LONG-TERM FOLLOW UP	21
45	12.3	LITERATURE	21
46	12.4	OTHER DSURS	22
47	12.5	SIGNIFICANT MANUFACTURING CHANGES	22
48	12.6	LACK OF EFFICACY.....	22
49	13	LATE BREAKING INFORMATION.....	22
50	14	OVERALL SAFETY ASSESSMENT.....	23
51	14.1	EVALUATION OF THE RISKS	23
52	14.2	BENEFIT-RISK CONSIDERATIONS	24
53	14.3	CONCLUSIONS	24
54	15	SUMMARY OF IMPORTANT RISKS.....	24

55	APPENDICES TO THE DSUR	25
56	16 TABLE OF GLOSSARY TERMS	26

58 1 INTRODUCTION

59 1.1 Objective of the Guideline

60 The periodic analysis of safety information is crucial to the ongoing assessment of
61 risk to trial subjects during the clinical development of an investigational drug.^{1,2,3} It is
62 also important to notify regulators and other interested parties (e.g. ethics
63 committees) at regular intervals of the evolving safety profile of an investigational
64 drug and actions proposed or being taken to address safety concerns. Currently,
65 regulations in some countries or regions require submission of a periodic report to
66 regulatory authorities to address these issues. However, significant differences in the
67 content and format of these reports highlight the importance of a common standard to
68 promote a consistent approach, and enhance efficiency. The Development Safety
69 Update Report (DSUR) proposed in this guideline is intended to be the common
70 standard for annual clinical trial safety reporting among the ICH regions and can be
71 submitted instead of existing reports including the US IND Annual Report and the EU
72 Annual Safety Report. This comprehensive, thoughtful annual review can provide an
73 additional level of assurance of protection for subjects in clinical trials. In addition, by
74 harmonising the format, content and timing of annual safety reports, regulators in the
75 three ICH regions can receive the same information at the same time, thereby
76 reducing the number of reports generated.

77

78 The main objective of a DSUR is to present an annual review and evaluation of
79 pertinent safety information collected during the reporting period to: (1) summarise
80 the current understanding and management of identified and potential risks; (2)
81 describe new safety issues that could have an impact on the protection of clinical trial
82 subjects; (3) examine whether the information obtained by the sponsor during the

¹ The term investigational drug is used in this guideline to indicate only the experimental product under study or development.

² 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, Geneva 2007.

³ ICH Topic E6(R1). Guideline for Good Clinical Practice. <http://www.ich.org/LOB/media/MEDIA482.pdf>
8413dft.doc Page4 of 34

83 reporting period is in accord with previous knowledge of the product's safety; and (4)
84 provide an update on the status of the clinical investigation/development programme.
85 This guideline defines the content and format of a DSUR and provides an outline of
86 points to be considered in its preparation and submission.

87 1.2 Scope of the DSUR

88 The main focus of the DSUR is data from interventional clinical trials (referred to in
89 this document as "clinical trials") of investigational drugs including biologicals, with or
90 without a marketing approval, whether conducted by commercial or non-commercial
91 sponsors. However, other findings that impact the safety and welfare of clinical trial
92 subjects, (e.g. significant safety findings from non-clinical studies, safety findings
93 from clinical trials conducted by a co-development partner in a licensing agreement,
94 or relevant findings from non-interventional studies/compassionate use) should also
95 be included where appropriate. Some of the information contained in the DSUR, such
96 as safety findings, inclusion of serious adverse reactions in line listings, and
97 discussion of relevant articles from published literature can also be provided in
98 Periodic Safety Update Reports (PSURs) for marketed products that are the subject
99 of ongoing clinical trials. Therefore, some overlap is expected between the DSUR
100 and PSUR because of the different periodicities for submission and objectives.

101

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

- 104 • clinical trials conducted using an investigational drug whether with or without a
105 marketing approval, i.e., human pharmacology, therapeutic exploratory and
106 therapeutic confirmatory trials (Phase I – III);⁴
- 107 • clinical trials conducted using marketed drugs in approved indications, i.e.,
108 therapeutic use trials (Phase IV);
- 109 • other therapeutic use of an investigational drug; and
- 110 • comparability trials conducted to support changes in the manufacturing process
111 of medicinal products.

112

⁴ For classification of clinical trials see ICH E8 General considerations for clinical trials.
8413dft.doc

113 The DSUR should focus primarily on the investigational drug, providing information
114 on comparators only where relevant to the safety of trial subjects. A DSUR should be
115 concise and provide information to assure regulators that sponsors are adequately
116 monitoring and evaluating the safety profile of the investigational drug. It should not
117 contain initial notification of any significant new safety issues, as these should have
118 been communicated to regulatory authorities via expedited reporting.

119 2 GUIDANCE

120 2.1 When Should a DSUR be Prepared?

121 A sponsor overseeing more than one clinical trial of a single investigational drug
122 should prepare one DSUR for that drug with a single data lock point (DLP) wherever
123 possible. If this is not possible, an explanation should be provided in the covering
124 letter.

125 2.2 Periodicity and DSUR Data Lock Point

126 The DSUR is intended to be an annual report that should be submitted to regulatory
127 authorities, as appropriate, for as long as the sponsor conducts clinical trials with the
128 investigational drug, or for as long as appropriate to satisfy local requirements.
129 Where local authorities ask for periodic submission of safety information on an
130 investigational drug to ethics committees, institutional review boards, or investigators,
131 the DSUR Executive Summary should suffice, supplemented with line listings of
132 serious adverse reactions as warranted.

133

134 The DSUR should be submitted no later than 60 calendar days from the DSUR data
135 lock point. The data lock point of the DSUR should be based on the date of the
136 sponsor's first authorisation to conduct a clinical trial in any country. This date is
137 termed the "Development International Birth Date" (DIBD).⁵ For administrative
138 convenience, if desired by the sponsor, the DIBD can be designated as the last day
139 of the month of authorisation.

140

⁵ This is analogous to the International Birth Date (IBD) for a PSUR, defined as the date of first marketing approval worldwide.

141 Where clinical trials are ongoing in one country and are later initiated in another
142 country(ies), one DSUR based on the same DIBD should be used for all countries.

143 2.3 Change of DSUR Data Lock Point

144 Once a drug has received a marketing approval⁶ in any country or region, and clinical
145 trials continue or are initiated, both a PSUR and a DSUR should be prepared in
146 accordance with directions from local authorities. The sponsor should change the
147 DSUR data lock point to coincide with the International Birth Date (IBD) so that the
148 DSUR and the PSUR can be synchronised. In synchronising the data lock points for
149 the DSUR and PSUR, the period covered by the next DSUR should be no longer
150 than one year.

151 2.4 Interruption or Discontinuation of Clinical Trials

152 A DSUR should be prepared and submitted as indicated by local authorities, even
153 when the clinical trials are interrupted or discontinued. If the sponsor has not
154 collected any further data pertinent to the clinical development programme in the
155 period of the DSUR, a letter stating this can replace the DSUR.

156 2.5 Final DSUR

157 When an annual report of clinical trials is no longer required in an individual country
158 or region, the DSUR should be accompanied by a cover letter indicating that the
159 report serves as the final DSUR for the investigational drug in that country or region.
160 The letter should also indicate whether or not clinical trials are continuing elsewhere.

161

162 2.6 Responsibilities for Preparing and Submitting a DSUR

163 2.6.1 *Sponsor's responsibilities*

164 The sponsor of a clinical trial, whether commercial or non-commercial, should be
165 responsible for the preparation, content and submission of a DSUR.

166 2.6.2 *Shared responsibilities*

167 Where individual clinical trials or a drug development programme involve
168 collaboration with public or private institutions, business partners or other parties, a

⁶ For the purposes of this document, we use the term "authorisation/ authorised" to refer to approvals of clinical trials, and "approved/ marketing approval" to refer to marketing authorisations

169 written agreement should be in place clearly detailing the responsibilities for
170 preparation and submission of the DSUR. The same principle applies in situations
171 where the sponsor delegates the preparation of the DSUR to a third party, e.g., a
172 contract research organisation.

173 *2.6.3 Non-commercial sponsor responsibilities*

174 Non-commercial sponsors should be responsible for the preparation of the DSURs
175 for the clinical trials they conduct, in accordance with local requirements. Sections of
176 the DSUR that are not applicable to non-commercial sponsors (e.g., manufacturing
177 issues, non-clinical data, and marketing status) should be identified as such.

178

179 *2.6.4 Responsibilities of multiple sponsors in formal agreements*

180 When there is more than one sponsor, e.g., when a sponsor is in a formal co-
181 development or licensing relationship with one or more partners, or more than one
182 partner is a sponsor of a clinical trial(s) of the investigational drug, the parties should
183 arrange to prepare a single DSUR whenever possible. Written agreements should be
184 in place specifying how safety data will be exchanged so that a single DSUR can be
185 produced by one sponsor on behalf of all parties.

186

187 When unavoidable, multiple sponsors can agree in writing to prepare separate
188 DSURs for the same investigational drug. This can include situations where different
189 indications, routes of administration, or formulations are being investigated. The
190 rationale for separate DSURs should be provided in each report.

191

192 **2.7 DSURs for Combination Products**

193 Given the potential complexities of clinical development involving combination
194 therapies, it is not possible to provide guidance that addresses all such situations.
195 The sponsor should select the most appropriate option based on judgement, taking
196 into account patient population, indication, formulation etc., as well as the
197 circumstances in which the clinical trials are being conducted and local regulatory
198 requirements. The rationale for this decision should be provided in the report.

199

200 In general, a single DSUR should be prepared for clinical trials involving a fixed
201 combination product.

202

203 For trials involving drug combinations that are not fixed, it can be appropriate to
204 prepare a stand-alone DSUR. Alternatively, information on the multidrug regimen
205 trials can be included in the DSUR of one or all of the components.

206

207 Although medical devices are outside the scope of the DSUR, specific local
208 regulations can require a DSUR for certain drug-device combinations, depending
209 upon whether the principal therapeutic effect is achieved by the drug or the device.

210 2.8 Reference Safety Information

211 A single document containing the reference safety information should be used to
212 assess whether the safety information received during the reporting period remains
213 consistent with previous knowledge of the safety profile of the investigational drug.

214

215 The Investigator's Brochure (IB) in effect at the start of the reporting period should
216 serve as the reference safety information for the DSUR for an investigational drug
217 whether or not the drug has a marketing approval. The report should clearly indicate
218 the version number and date of the IB used for this purpose. If the IB has been
219 revised during the reporting period and not previously submitted to the relevant
220 regulatory authority, the sponsor should provide a copy of the revised version of the
221 IB as an attachment to the DSUR. When an IB is not required for the trial by local
222 regulations (e.g., non-commercial sponsors conducting a clinical trial with a marketed
223 product) the applicable local product label⁷ or another suitable document should be
224 used as the reference safety information.

⁷ In the EU this would be the Summary of Product Characteristics (SmPC); in Japan this would be the Japanese Package Insert; and in the US this would be the US Package Insert.
8413dft.doc

225 2.9 Format and Presentation of DSUR

226 2.9.1 *Format*

227 The format and content of the DSUR should follow the table of contents below. For
228 each heading where information is available, the information should be presented
229 concisely; when no information is available, this should be stated. Guidance on the
230 content of each section is provided below. Note that the section numbers below
231 reflect the numbering in the DSUR.

232 2.9.2 *Table of Contents*

233 Title page

234 Executive Summary

235 Table of Contents

236 1. Introduction

237 2. Worldwide Marketing Authorisation Status

238 3. Update on Actions Taken in the Reporting Period for Safety Reasons

239 4. Changes to Reference Safety Information

240 5. Status of Clinical Trials Ongoing and Completed During the Reporting
241 Period

242 6. Estimated Exposure

243 6.1 Cumulative subject exposure in clinical trials (Phase I-IV)

244 6.2 Patient exposure from marketed setting

245 7. Presentation of Safety Data from Clinical Trials

246 7.1 General considerations

247 7.2 Interval line listings of Serious Adverse Reactions (SARs)

248 7.3 Cumulative summary tabulations

249 7.4 Deaths in the reporting period

250 7.5 Subjects who dropped out in association with any adverse event in the
251 reporting period

252 8. Significant Findings from Clinical Trials During the Reporting Period

253 8.1 Completed trials and any interim analyses

254 8.2 Ongoing clinical trials

255 8.3 Other therapeutic use of investigational drug

256	8.4	New safety data related to combination therapies
257	9.	Relevant Findings from Non-Interventional Studies
258	10	Relevant Findings from Other Studies
259	11.	Safety findings from marketing experience
260	12.	Other Information
261	12.1	Non-clinical data
262	12.2	Long-term follow-up
263	12.3	Literature
264	12.4.	Other DSURs
265	12.5	Significant manufacturing changes
266	12.6	Lack of efficacy
267	12.7	Phase I protocol modifications
268	13.	Late-Breaking Information
269	14.	Overall Safety Assessment
270	14.1.	Evaluation of the risks
271	14.2	Benefit-risk considerations
272	14.3	Conclusions
273	15.	Summary of important risks
274		Appendices to the DSUR
275		
276	2.10	Guidance on Contents of DSUR
277		<i>Title page</i>
278		The title page of the DSUR should include the following information:
279		• DSUR number (reports should be numbered sequentially);
280		• Investigational drug(s);
281		• Reporting period;
282		• Date of the report;
283		• Sponsor name and address;
284		• Confidentiality statement; and
285		• Note regarding the inclusion of unblinded information in the DSUR.

286 *Executive Summary*

287 This section should provide a concise summary of the important information
288 contained in the report. Together with the title page, it should serve as a “stand-
289 alone” document suitable for submission to ethics committees and other
290 stakeholders, if required by local regulations. Information on the following should be
291 included in the Executive Summary:

- 292 • Introduction – report version and reporting period;
- 293 • Investigational drug – mode of action, class, indications, dose, route of
294 administration;
- 295 • Estimated cumulative clinical trial exposure;
- 296 • Marketing authorisation(s)? (yes/no) – If yes, number of countries;
- 297 • Summary of overall safety assessment;
- 298 • Summary of important risks (based on section 15 of the DSUR);
- 299 • Actions taken for safety reasons including significant changes to IB;
- 300 • Conclusion.

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

303 *Table of Contents*

304 1. *Introduction*

305 This section should include:

- 306 • Reporting period and sequential number of the report;
- 307 • Brief description of the drug, e.g., therapeutic class, mode of action, route
308 of administration, formulation;
- 309 • Whether the report covers a development programme or a single clinical
310 trial. This section should also note the scope of the trials covered by the
311 report (e.g., all trials with the investigational drug, or indication-specific
312 trials);
- 313 • A brief description of the indications and populations being studied;

- 314 • A brief description and explanation of any information that has been
315 excluded (e.g., when written agreements with a partner company do not
316 provide for exchange of all safety data).

317

318 2. *Worldwide marketing authorisation status*

319 This section should be completed only if a marketing application for the
320 product has been submitted in one or more countries/regions. Cumulative
321 information should be provided where available, usually in the form of a table
322 that provides the status of each application. The content and format for this
323 table is the same as that recommended for PSURs, as outlined in ICH E2C,
324 Table 1.

325

326 3. *Update on Actions Taken in the Reporting Period for Safety Reasons*

327 This section should include a description of significant actions related to safety
328 that have been taken by the sponsor, regulators, Data and Safety Monitoring
329 Boards or independent ethics committees that could have an impact on the
330 conduct of a specific trial or the whole clinical development programme. Any
331 relevant updates to previous actions should also be summarised in this
332 section. Changes to the Investigator's Brochure should be discussed
333 separately in the "Changes to Reference Safety Information", see section 4.

334 Examples of significant actions relating to safety issues include:

- 335 • Refusal of authorisation of a clinical trial for ethical or safety reasons;
336 • Partial⁸ or complete clinical trial suspension or early termination of a
337 clinical trial due to lack of efficacy or safety issues;
338 • Resumption of a clinical trial after suspension;
339 • Failure to obtain marketing approval for a tested indication;
340 • Risk management activities, including:

⁸ "Partial suspension" may 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.

- 341 ○ Protocol modifications due to safety or efficacy concerns (e.g., dosage
342 changes, changes in study inclusion criteria, intensification of
343 monitoring);
- 344 ○ Restrictions in study population or indications;
- 345 ○ Changes to the informed consent document relating to safety issues;
- 346 ○ Formulation changes for safety reasons;
- 347 ○ Addition of a special reporting requirement;
- 348 ○ Issuance of a communication to investigators or healthcare
349 professionals;
- 350 ○ Plans for new safety trials.
- 351 ● Important specific advice for safety reasons from a regulatory authority that
352 involves a constraint on development (e.g., requirement to conduct long-
353 term animal studies before initiating a long-term clinical trial; need for
354 thorough QT/QTc study prior to Phase III clinical trials). In addition a
355 cumulative listing of advice from regulatory authorities should be provided
356 as a table in an appendix.

357

358 In addition to the above, for drugs with a marketing approval, examples of
359 significant actions due to safety reasons include:

- 360 ● Failure to obtain a marketing approval renewal;
- 361 ● Marketing approval withdrawal or suspension for safety reasons;
- 362 ● Risk management activities including:
- 363 ○ Significant restrictions on distribution or introduction of risk minimisation
364 measures;
- 365 ○ Significant changes in labelling documents that could affect the
366 development programme, e.g., restrictions to indication or population or
367 a new warning;
- 368 ○ Communications to health care professionals as a result of the above
369 actions; and
- 370 ○ New postmarketing study requirement(s) imposed by regional
371 authorities.

372 4. *Changes to Reference Safety Information*
373 This section should list any significant safety-related changes to the IB within
374 the reporting period. This includes information relating to contraindications,
375 warnings, precautions, serious adverse drug reactions, adverse reactions of
376 special interest, interactions, and any important findings from non-clinical
377 studies (e.g. carcinogenicity studies). Specific information relevant to these
378 changes should be provided in the appropriate sections of the DSUR.

379 5. *Status of clinical trials ongoing and completed during the reporting period*
380 This section should refer to an appendix that presents a listing of each clinical
381 trial in progress and each clinical trial completed during the reporting period.
382 Separate tables can be provided by indication, formulation, and study
383 population if appropriate. In addition, where required by local authorities,
384 similar information should be provided for other therapeutic use of an
385 investigational drug in the reporting period e.g., compassionate use or
386 expanded access.

387 The table(s) should include the following information for each trial:

- 388 • Protocol number or other trial identifier;
- 389 • Clinical trial phase (I, II, III, or IV);
- 390 • Status:
 - 391 ○ Ongoing (study has begun; study has begun but is currently on hold;
 - 392 study is completed, but final clinical study report is not yet available);
 - 393 ○ Completed (final clinical study report is available);
- 394 • Countries/regions where there is at least one investigational site for the
395 protocol;
- 396 • Abbreviated study title ;
- 397 • Study design (uncontrolled, controlled, open, single blind, double blind,
398 parallel, cross-over, etc., including treatment arms);
- 399 • Dose and regimen of study drug and any comparators;
- 400 • Subject population as appropriate (age; sex; indication(s); specific patient
401 groups, e.g., trial subjects with impaired renal function or trial subjects
402 resistant to treatment);
- 403 • Date of first visit for first patient;
- 404 • Planned enrolment for study as a whole;

- 405 • Estimates of cumulative numbers of exposed subjects where available for
406 each treatment arm. The actual enrolment numbers for open or completed
407 trials, and/or an estimate based on the randomisation scheme for blinded
408 trials should also be provided.

409 An example of the column headings for this listing is provided in table 1.

410 6. *Estimated exposure*

411 The sponsor should clearly explain in the DSUR the method used to estimate
412 subject/patient exposure.

413 6.1 Cumulative subject exposure in development programme

414 Data on subject exposure to the investigational drug and placebo/active
415 comparators should be included in the DSUR. The DSUR should provide
416 summary tables including estimates of the overall numbers of subjects
417 exposed as of the DSUR data lock point, using either number of trial subjects
418 or patient-time, as appropriate.

419
420 When the data are available, the DSUR should provide cumulative exposure
421 data giving the number of trial subjects by age group, gender, and ethnic
422 origin⁹ for the development programme. Tabulation of demographic
423 characteristics for a single trial can be useful if the trial is of particular
424 importance, e.g., a pivotal phase III trial.

425
426 See table 2 for examples of these tables.

427
428 These exposure tables provide context for the cumulative summary tabulations
429 of serious adverse events (SAEs). Therefore, if the summary tabulations are
430 presented by indication, the exposure data should also be presented by
431 indication where available.

⁹ Ethnic factors are defined as those factors relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population as described in ICH E5(R1): Ethnic Factors in the Acceptability of Foreign Clinical Data.

432 6.2 Patient exposure from marketing experience
433 If the investigational product is marketed, the commercial sponsor should
434 provide the estimated patient exposure in the marketed setting based on the
435 information provided in the PSUR for that product or other suitable data
436 source.

437 7 *Presentation of Safety Data from Clinical Trials*
438 The DSUR should contain both cumulative and interval (periodic) safety
439 information relating to the investigational drug. This section of the report
440 should present important clinical safety information through interval line listings
441 of the serious adverse reactions that arose during the period covered by the
442 DSUR, and cumulative tabulations of serious adverse events that have been
443 reported to the sponsor since the DIBD. If MedDRA is used for coding the
444 adverse event/reaction terms, the Preferred Term level should be presented in
445 the line listings and summary tabulations.

446 In general, the tabulation(s) of serious adverse events should include only
447 those terms that were used in defining the case as serious. Non-serious and
448 incidental findings should not be included.

449
450 If important and appropriate, the report should also include adverse reactions
451 of special interest within the line listings and adverse events of special interest
452 in summary tabulations. The basis for selection of such events/reactions
453 should be explained.

454
455 Certain adverse events can be excluded from the summary tabulations and
456 line listings, but such exclusions should be explained in the report. For
457 example, adverse events that have been defined in the protocol as “exempt”
458 from special collection and entry into the safety database, and those that are
459 integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial
460 of a drug for congestive heart failure where all-cause mortality is the primary
461 efficacy endpoint or disease progression in cancer trials).

462 7.1 General considerations
463 This section of the DSUR should include the version of the coding dictionary
464 used, and the document and version used as Reference Safety Information for
465 determining expectedness for the tabulations, where required by regional
466 authorities.

467 7.2 Interval Line Listings of Serious Adverse Reactions (SARs)
468 This section of the DSUR should include general information about the content
469 of the line listings, the criteria for inclusion, and reference to appropriate
470 appendices.

471 The line listings should provide key information on all blinded and unblinded
472 SARs reported during the reporting period, organised by System Organ Class
473 (SOC). They can integrate data from all the trials being conducted with an
474 investigational drug. Alternatively, when useful and feasible, SARs can be
475 listed by protocol, indication, or other variables.

476 Where possible the line listing(s) should include each subject only once
477 regardless of how many SAR terms are reported for the case. If there is more
478 than one reaction, they should all be mentioned but the case should be listed
479 under the most serious adverse reaction (sign, symptom or diagnosis), as
480 judged by the sponsor. It is possible that the same subject could experience
481 different SARs on different occasions (e.g., weeks apart during a clinical trial).
482 Such experiences can be treated as separate reports. Under such
483 circumstances, the same subject can be included in a line listing more than
484 once, and the line listings should be cross-referenced when possible.

485 The format and content of the line listings described in ICH E2C can be used
486 with appropriate modifications (e.g., addition of the clinical trial identification
487 number). An example of the headings for a line listing is provided in Table 3.

488 7.3 Cumulative Summary tabulations
489 This section of the DSUR should include general information about the content
490 of the tabulations, the criteria for inclusion, and reference to appropriate
491 appendices.

492 Summary tabulations should present cumulative safety data from the DIBD to
493 the data lock point of the current DSUR. The summary tabulations in a DSUR
494 should include the number of serious adverse events,¹⁰ organised by SOC, for
495 the investigational drug, as well as for the comparator arm(s) (active
496 comparators, placebo, and treatment unknown due to blinding) used in the
497 programme. Data can be integrated across the programme. Alternatively,
498 when useful and feasible, tabulations of SAEs can be presented by protocol,
499 indication, or other variables.

500 An example is provided in Table 4.

501 7.4 Deaths in the Reporting Period

502 A list of subjects who died during participation in the investigation should be
503 provided as an appendix to the DSUR if required by regional authorities. The
504 list should include the following information at a minimum: case number,
505 assigned treatment (could still be blinded), and cause of death.

506 7.5 Subjects who dropped out in association with any adverse event in the 507 reporting period

508 Tabulations and listings of information on drop-outs should be provided as an
509 appendix to the DSUR, if required by regional authorities. Any safety issues
510 identified from a review of these withdrawals should be briefly described.

511 8 *Significant findings from clinical trials during the reporting period*

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

514 8.1 Completed trials and any interim analyses

515 The DSUR should provide a brief summary of the clinically important safety
516 findings included in the final study reports from all clinical trials completed and
517 any interim analyses conducted during the reporting period. This information

¹⁰ For DSURs to be submitted to an EU Member State, a regional appendix should be provided. It should contain a summary tabulation of all SARs, specifying the number of SARs by: a) SOC, b) reaction term and c) treatment arm, if applicable. Unexpected adverse reaction terms should be identified.

518 can be in narrative format, or in the study synopsis format provided as
519 Appendix 5 of the Report of CIOMS Working Group VII.

520 8.2 Ongoing clinical trials

521 The DSUR should provide a concise summary of any preliminary safety
522 findings from ongoing trials, including safety issues that are the same or similar
523 to those previously identified, as well as evidence of new clinically significant
524 safety signals.

525 8.3 Other Therapeutic use of Investigational Drug

526 The DSUR should include safety information from expanded access
527 programmes, compassionate use programmes and treatment INDs, because
528 they each follow a specific protocol.

529 8.4 New Safety Data Related to Combination Therapies

530 If the sponsor has prepared a separate DSUR for a multidrug regimen or fixed
531 combination product containing the single investigational drug that is the
532 subject of this DSUR, relevant findings from that DSUR should be summarised
533 in this section.

534
535 Conversely, if this DSUR is for a multidrug regimen or fixed combination
536 product, important safety information arising from trials on the individual
537 components should be briefly summarised here.

538
539 Alternatively, the information specific to the combination can be incorporated
540 into a separate section(s) of the DSUR for one or all of the individual
541 components of the combination.

542

543 9 *Relevant findings from non-interventional studies*

544 This section of the DSUR should summarise relevant safety information that
545 became available in the reporting period from non-interventional studies, e.g.,
546 observational studies, registries, active surveillance programmes or
547 epidemiological studies.

548 10 *Relevant findings from other sources*
549 The DSUR should also discuss relevant safety findings from any other
550 available sources (e.g., results from pooled or meta-analyses of randomised
551 clinical trials, lack of efficacy from trials in high morbidity/mortality disease
552 states and trials with vaccines).

553 11 *Safety findings from marketing experience*
554 If the investigational drug has been approved for marketing in any country, this
555 section should include a concise summary of key safety findings that have
556 arisen from marketing experience during the reporting period, particularly if the
557 findings resulted in changes to the labelling or amendments to the product's
558 risk management plan.

559 12 *Other Information*
560

561 12.1 Non-Clinical data
562 Major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g.
563 carcinogenicity, reproduction, or immunotoxicity studies) initiated or completed
564 during the reporting period should be summarised, and any impact on the
565 clinical safety of the investigational drug should be discussed.

566 12.2 Long-term follow-up
567 This section of the DSUR should provide information from long-term follow-up
568 of subjects from clinical trials of investigational drugs, particularly advanced
569 therapy products (e.g., gene therapy, cell therapy products and tissue
570 engineered products). This section could be the only information presented in
571 the DSUR when the clinical trials are completed and long-term follow-up is the
572 only ongoing activity generating data for the DSUR.

573 12.3 Literature
574 The commercial sponsor is expected to review the scientific literature
575 periodically for new safety information. This section should summarise new
576 and significant safety findings from non-clinical studies and clinical trials that
577 have been published during the reporting period. When available, this section

578 should also include relevant new information on drugs of the same class.
579 Significant new safety information published as an abstract for a scientific
580 meeting should be summarised and a copy provided if possible.

581 12.4 Other DSURs

582 When available, a commercial sponsor should summarise significant findings
583 from the DSUR provided by another sponsor conducting clinical trials with the
584 investigational drug during the reporting period.

585 12.5 Significant manufacturing changes

586 When required by regional authorities, this section should include a summary
587 of significant changes to the manufacturing process and/or formulation of an
588 investigational drug during the reporting period and discuss potential safety
589 issues arising from these changes, if applicable.

590 12.6 Lack of efficacy

591 For investigational drugs intended to treat serious or life-threatening illnesses,
592 lack of efficacy could constitute a significant risk to clinical trial subjects. In this
593 setting, data received during the reporting period that indicates lack of efficacy
594 relative to alternative therapies should be summarised.

595 12.7 Phase I protocol modifications

596 This section should describe significant Phase I protocol modifications not
597 previously reported, as required by regional authorities.

598

599 13 *Late-Breaking Information*

600 Information on potentially important safety findings that present while the
601 DSUR is in preparation after the data lock point should be included in this
602 section. Examples include clinically significant new case reports, important
603 follow-up data, and clinically relevant toxicological findings. Any action that the
604 sponsor, a Data and Safety Monitoring Board, or regulatory authority has
605 taken for safety reasons should also be included.

606 14 *Overall Safety Assessment*

607 The overall safety assessment should be a concise, integrated assessment of
608 all new relevant clinical, non-clinical, and epidemiologic information obtained
609 during the reporting period relative to previous knowledge of the
610 investigational drug. It should not summarise or repeat information presented
611 in previous sections of the DSUR, but should provide an interpretation of the
612 information, and its implications for the clinical trial population. If appropriate,
613 separate assessments can be provided by therapeutic area and/or indication.

614 14.1 Evaluation of the risks

615 When relevant, the following points should be considered:

- 616 • meaningful changes in previously identified reactions (e.g., increased
617 frequency or severity, outcome, specific at-risk populations);
- 618 • newly identified safety issues (detailed description of adverse reaction;
619 associated laboratory values; risk factors; relationship to dose, duration,
620 time course of the treatment; reversibility; factors that could be useful in
621 predicting or preventing reactions);
- 622 • particular emphasis should be placed on symptoms, signs, and laboratory
623 evidence of newly and previously identified, clinically significant:
 - 624 ○ hepatotoxicity;
 - 625 ○ cardiovascular effects, including QT interval prolongation and results
626 from thorough QT/QTc studies;
 - 627 ○ bone marrow toxicity;
 - 628 ○ renal toxicity;
 - 629 ○ central nervous system toxicity;
 - 630 ○ immunogenicity and hypersensitivity;
 - 631 ○ reactive metabolites;
- 632 • deaths that are an outcome of an adverse reaction;
- 633 • withdrawals due to safety reasons;
- 634 • any specific safety issues related to special populations, such as the
635 elderly, children, patients with hepatic or renal impairment, or any other at
636 risk groups (e.g., slow or fast metabolisers);

- 637 • positive and negative experiences during pregnancy or lactation;
- 638 • overdose and its treatment;
- 639 • drug misuse and abuse;
- 640 • experience with long-term treatment;
- 641 • risks associated with protocol procedures, including administration of the
- 642 investigational drug and diagnostic procedures;
- 643 • evidence of clinically significant medication errors;
- 644 • potential impact of significant new safety issues identified with another
- 645 drug in the same class; and
- 646 • drug–drug and other interactions.

647 The overall safety assessment should also discuss other relevant findings
648 such as: non-clinical research, manufacturing issues, lack of efficacy and lack
649 of patient compliance, when available.

650 14.2 Benefit-risk considerations

651 This section is not meant to be a full benefit-risk assessment but should be a
652 succinct statement on the balance between the theoretical benefits and the
653 identified risks, focusing particularly on whether there have been any changes
654 in this balance since the previous DSUR. If there has been a change, the
655 sponsor should provide an assessment of the impact on the clinical
656 development programme.

657 14.3 Conclusions

658 The section should present a brief conclusion, addressing any changes to the
659 previous knowledge of safety and risks resulting from information gained since
660 the last DSUR. Finally, the conclusion should describe how risks have been
661 managed in the trials and any additional actions that should be taken to
662 address emerging safety issues.

663 15 *Summary of important risks*

664 This section should provide a concise cumulative list of important identified
665 and potential risks (e.g., those that might lead to warnings, precautions, or
666 contraindications in labelling). The information in this section could provide the

667 basis for the Safety Specification of a risk management plan (ICH E2E). The
668 list should be continuously evaluated and updated from DSUR to DSUR and
669 include risks that require further evaluation, as well as safety concerns that
670 have been fully addressed or resolved.

671

672 *Appendices to the DSUR*

673 The following are appendices that might accompany the DSUR:

- 674 1 Investigator's Brochure (if required);
- 675 2 Cumulative Table of Important Regulatory Advice;
- 676 3 Status of Ongoing and Completed Clinical Trials;
- 677 4 Cumulative Summary Tabulations of Demographic Data;
- 678 5 Line Listings of Serious Adverse Reactions (SARs);
- 679 6 Cumulative Summary Tabulation of Serious Adverse Events (SAEs);
- 680 7 Scientific Abstracts (if relevant).

681 *Regional Appendices (as required by regional regulatory authority):*

- 682 1 Drop-outs in Association with Adverse Events;
- 683 2 Deaths;
- 684 3 Summary Tabulations of SARs.

685

686

687 **3 APPENDICES TO THE GUIDELINE**

688

689 Appendix A. Glossary

690

691 Appendix B Tables 1-4

692

693 APPENDIX A

694 Glossary

695 Throughout this guideline the Working Group has used terms previously defined by ICH and other groups e.g., CIOMS. Those terms
 696 that were previously defined in ICH documents are not repeated in this glossary. However, the glossary includes terms defined by
 697 CIOMS and other groups.

698
 699

Item	Glossary Term	Source of Definition	Definition/Commentary
1.	Adverse event of special interest	Based on CIOMS VII	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise 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.
2.	Clinical Trial Authorisation	Based on EU Clinical Trials Directive 2001/20/EC	The authorisation in writing by the relevant regulatory authority of a clinical trial(s) described in a valid application. <u>Commentary:</u> In this guideline the term "authorisation" is used to refer to permission to conduct a clinical trial and the term "approval" is used to refer to permission to place a medicine on the market.
3.	Other therapeutic use of an investigational drug <u>Synonym:</u> Expanded Access Compassionate Use 'Treatment IND'		Therapeutic use of an investigational drug under a protocol. This can include Expanded Access Programmes, Compassionate Use, and Treatment IND. <u>Expanded Access Programme:</u> IND-based programme in the US that allows a sponsor to supply an investigational drug to patients with an indication for which benefit has been demonstrated. <u>Compassionate Use Programme:</u> A programme in the EU to supply an investigational product to patients with an indication for which benefit has been demonstrated.

Item	Glossary Term	Source of Definition	Definition/Commentary
			<p><u>Treatment IND</u>: Allows the supply of an investigational drug to treat patients with serious or immediately life-threatening disease for whom no satisfactory alternative is available.</p> <p><u>Commentary</u>: This term does not include "particular patient", "named patient" prescribing which do not require a protocol.</p>
4.	Data lock point	CIOMS VII	The date (month and day) designated as the cut-off for data to be included in a DSUR. <u>Commentary</u> : it is based on the Development International Birth Date (DIBD) and should usually be in twelve-monthly increments.
5.	Development International Birth Date	CIOMS VII Glossary	Date of first approval (or authorisation) for conducting an interventional clinical trial in any country.
6.	Identified risk	Volume 9A Rules Governing Medicinal Products in the EU	<p>An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.</p> <p>Examples of identified risks include:</p> <ul style="list-style-type: none"> -an adverse reaction adequately demonstrated in non-clinical 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 or unexposed group) 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.
7.	Important identified risk; Important potential risk.	Volume 9A Rules Governing Medicinal Products in the EU	An identified risk or potential risk that could impact on the risk-benefit balance of the product or have implications for public health.

Item	Glossary Term	Source of Definition	Definition/Commentary
8.	Investigational drug		The term investigational drug is used in this guideline to indicate only the experimental product under study or development.
9.	Non-commercial sponsor		For the purposes of this guideline, examples of non-commercial sponsors include the following: (a) university, (b) healthcare centre, (c) a public scientific organisation, (d) a non-profit institution, (e) a patient organisation, and (f) an individual researcher who is responsible for the design, initiation, conduct, recording and publishing of the clinical trial.
10.	Non-interventional clinical study	Based on EU Directive 2001/20/EC on Clinical Trials	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. 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.
11.	Potential risk	Volume 9A Rules Governing Medicinal Products in the EU	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. Examples of potential risks include: <ul style="list-style-type: none"> • Non-clinical 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; • 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.
12.	Registry	ICH E2E	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 standardised questionnaires in a prospective fashion.

700 APPENDIX B

701 **TABLE 1 - EXAMPLES OF TABLE HEADINGS FOR CLINICAL TRIAL STATUS LISTINGS**

702

703 **STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS**

704 **OVERVIEW OF ONGOING [study drug] STUDIES**

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP*	Planned enrollment	Subject exposure**

705

706 * FVFP = first visit first patient

707 ** based upon total number of patients recruited as of [date] and applied randomisation schemes

708

709 **OVERVIEW OF [study drug] STUDIES COMPLETED DURING THE DSUR PERIOD**

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

710 APPENDIX B

711 TABLE 2 - EXAMPLES OF DEMOGRAPHIC DATA TABLES

712 CUMULATIVE SUMMARY TABULATIONS OF DEMOGRAPHIC DATA

713 Estimated cumulative subject exposure to [study drug] clinical studies by age and gender*

Age (yr)	Number of subjects		
	Male	Female	Total
<16			
16 - 25			
26 - 35			
36 - 45			
46 - 55			
56 - 65			
66 - 75			
>75			
Total			

714 * data from completed studies as of [date]

715
716 **Estimated cumulative subject exposure to [study drug] in all clinical studies by ethnic origin***

Ethnic origin	Number of subjects
Caucasian	
Black	
Oriental	
Other	
Total	

717 * data from completed studies as of [date]

718

719 **APPENDIX B**

720 **TABLE 3 - EXAMPLES OF HEADINGS FOR INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS**

721

722

723 **INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARs)**

724

Study ID EudraCT number	Case ID/ Subject number*	Country Gender Age	Serious ADR(s)	Outcome	Date of Onset** Time to Onset**	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
	-----	-----	-----	-----	-----	-----	-----	-----	-----

725

726 * Study/centre/patient

727 ** 'Primary' SADR only

728

729 **APPENDIX B**

730 **TABLE 4 - EXAMPLES OF CUMULATIVE TABULATIONS OF SERIOUS ADVERSE EVENTS**

731

732 **CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS (SAEs)**

733

<u>System Organ Class</u>		Total up to 31-Dec-07			734
Preferred Term	[study drug]	Blinded	Active comparator	Placebo	735
					736
<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	