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3 **Guideline on good pharmacovigilance practices (GVP)**
4 **Module VII – Periodic safety update report (Rev 1)**

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5 Note on public consultation:

6 The public consultation was restricted to the yellow highlighted revised texts (i.e. replaced by new
7 texts with deletions and additions) or deleted texts (i.e. not replaced). However, if revisions or
8 deletions impact or contradict other existing text, comments on such non-highlighted texts were
9 processed and taken into account for the finalisation process. Please note that ICH-E2C(R2) guideline
10 had already been subject to public consultation in the EU, and participants in the consultation process
11 were therefore asked not to comment on the underlying agreements reached at ICH level.

12 **This track-change version identifies the majority of changes introduced to the public consultation**
13 **version of this document as the Agency's response to the comments received from the public**
14 **consultation. This track-change version is published for transparency purposes and must not be taken**
15 **or quoted as the final version.**

16 *** For this reason, the timetable above, and in particular the date of coming into effect, apply only the**
17 **clean version published as final.**

See websites for contact details



18 For the final version of this module and any future updates, please see the GVP webpage of the
19 Agency's website.

20 *Note: Revision 1 contains the following:

21 - updates in VII.B and VII.C.5. following finalisation of the ICH-E2C(R2) guideline on "Periodic Benefit-
22 Risk Evaluation Report (PBRER)", which reached Step 4 of the ICH process in November 2012, in order
23 to harmonise the principles and agreements reached by the ICH Expert Working Group;

24 - further guidance regarding technical aspects on the implementation of Regulation (EU) No 1235/2010
25 and Directive 2010/84/EU based on the experience gained since July 2012;

26 - practical instructions for the application, description and maintenance of the EU reference date list in
27 VII.C.3.2., VII.C.3.3. and VII.C.3.4. and amendments to the marketing authorisation in VII.C.3.7.;

28 - further instructions regarding the PSUR assessment process, product information and transitional
29 arrangements within the EU regulatory network in VII.C..

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157 VII.A. Introduction

158 Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an
159 evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation
160 holders at defined time points during the post-authorisation phase.

161 The legal requirements for submission of PSURs are established in Regulation (EC) No 726/2004,
162 Directive 2001/83/EC and in the Commission Implementing Regulation (EU) No 520/2012 on the
163 performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive
164 2001/83/EC (hereinafter referred to as IR). All applicable legal requirements in this Module are
165 referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the
166 modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal
167 verb “should”.

168 The format of PSURs shall follow the structure described in the IR Article 35. This Module provides
169 guidance on the preparation, submission and assessment of PSURs.

170 The scope, objectives, format and content of the PSUR are described in VII.B.. The required format
171 and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report
172 (PBRER) described in the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)). The PBRER format
173 replaces the PSUR format previously described in the ICH-E2C(R1). In line with the EU legislation, the
174 report is described as PSUR in the GVP Modules.

175 Further details and guidance for the submission of PSURs in the EU, including the list of Union
176 references dates and frequency of submission are provided in VII.C., which also covers the single EU
177 assessment of PSURs in VII.C.4.. Details related to the quality system are provided in VII.C.6. and the
178 publication of PSUR-related documents in VII.C.7. as transparency provisions.

179 Each marketing authorisation holder shall be responsible for submitting PSURs for its own products
180 [DIR Art 107b] [REG Art 28 (2)] and should submit PSURs to the Agency (see VII.C.9. for transitional
181 arrangements) according to the following timelines:

- 182 • within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12
183 months (including intervals of exactly 12 months); and
- 184 • within 90 calendar days of the data lock (day 0) point (day 0) for PSURs covering intervals in
185 excess of 12 months;
- 186 • the timeline for the submission of ad hoc PSURs requested by competent authorities will normally
187 be specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar
188 days of the data lock point.

189 It should be noted that detailed listings of individual cases shall not be included systematically [IR Art
190 34(4)]. The PSUR should focus on summary information, scientific safety assessment and integrated
191 benefit-risk evaluation.

192 Recital 23 of Directive 2010/84/EU states explains that the obligations imposed in respect of PSURs
193 should be proportionate to the risks posed by medicinal products. PSUR reporting should therefore be
194 linked to the risk management systems of a medicinal product (see Module V). The “modular
195 approach” of the PSUR described in VII.B.5. aims to minimise duplication and improve efficiency during
196 the preparation and review of PSURs along with other regulatory documents such as the development
197 safety update report (DSUR)¹ or the safety specification in the Risk Management Plan (RMP), by

¹ See Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use; available on <http://ec.europa.eu/health/documents/eudralex/vol-10/>

198 enabling the common content of particular sections where appropriate to be utilised interchangeably
199 across different PSURs, DSURs and RMPs.

200 The ~~2010 amendment~~ Directive 2001/83/EC of the ~~legislation~~ also waives the obligation to submit
201 PSURs routinely for generic medicinal products (authorised under DIR Art 10(1)), well-established use
202 medicinal products (authorised under DIR Art 10a), homeopathic medicinal products (authorised under
203 DIR Art 14) and traditional herbal medicinal products (authorised under DIR Art 16a), [DIR Art
204 107b(3)]. For such products, PSURs shall be submitted where there is a condition in the marketing
205 authorisation or when requested by a competent authority in a Member State on the basis of concerns
206 relating to pharmacovigilance data or due to the lack of PSURs for an active substance after its
207 authorisation [DIR Art 107b(3)(a) and (3)(b)].

208 Competent authorities in the Member States shall assess PSURs to determine whether there are new
209 risks or whether risks have changed or whether there are changes to the risk-benefit balance of
210 medicinal products [DIR Art 107d].

211 In order to increase the shared use of resources between competent authorities in Member States, a
212 single assessment of PSURs should be performed in the EU for different medicinal products containing
213 the same active substance or the same combination of active substances authorised in more than one
214 Member State for which a Union reference date and frequency of submission of PSURs has been
215 established. The EU single assessment can include joint assessment for medicinal products authorised
216 through either national or centralised procedures for marketing authorisation. The Agency shall make
217 available a list of Union reference dates and frequency of submission [REG Art 26(g)] which will be
218 legally binding.

219 As part of the assessment, it should be considered whether further investigations need to be carried
220 out and whether any action concerning the marketing authorisations of products containing the same
221 active substance or the same combination of active substances, and their product information is
222 necessary.

223 The Agency shall make the PSURs available to the competent authorities in Member States, members
224 of the Pharmacovigilance Risk Assessment Committee (PRAC), of the Committee for Medicinal Products
225 for Human use (CHMP) and of the Coordination Group for Mutual Recognition and Decentralised
226 Procedures - Human (CMDh) and the European Commission by means of a PSUR repository [DIR Art
227 107b(2)].

228 **VII.B. Structures and processes**

229 ***VII.B.1. Objectives of the periodic update safety report (PSUR)***

230 The main objective of a PSUR is to present a comprehensive, **concise** and critical analysis of the risk-
231 benefit balance of the medicinal product taking into account new or emerging information in the
232 context of cumulative information on risks and benefits. The PSUR is therefore a tool for post-
233 authorisation evaluation at defined time points in the lifecycle of a product.

234 For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks
235 and benefits of a medicine in everyday medical practice and long term use in the post-authorisation
236 phase. This may extend to evaluation of populations and endpoints that could not be investigated in
237 the pre-authorisation clinical trials. A different **risk-benefit balance** may emerge as pharmacovigilance
238 reveals further information about safety. The marketing authorisation holder should therefore re-
239 evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured
240 evaluation should be undertaken in the context of ongoing pharmacovigilance (see **Module XII**) and

241 risk management (see Module V) to facilitate optimisation of the risk-benefit balance through effective
242 risk minimisation.

243 Urgent safety information should be reported through the appropriate mechanism. A PSUR is not
244 intended should not be used to provide, in the first instance, for initial notification of significant new
245 safety or efficacy information or, to as a general rule, provide the means by which new safety issues
246 are detected, or new efficacy data are submitted (see Module IX and XII). It is acknowledged that the
247 review of the data in the PSUR may lead to new safety issues being identified.

248 **VII.B.2. Principles for the evaluation of the risk-benefit balance within** 249 **PSURs and scope of the information to be included**

250 Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to
251 promote and protect public health and to enhance patient safety through effective risk minimisation.

252 After a marketing authorisation is granted, it is necessary to continue evaluating the benefits and risks
253 of medicinal products in actual use and/or long term use, to confirm that the **risk-benefit balance**
254 remains favourable.

255 The analysis of the risk-benefit balance should incorporate an evaluation of the safety, efficacy and
256 effectiveness information that becomes available², with reasonable and appropriate effort, during the
257 reporting interval for the medicinal product in the context of what was known previously.

258 The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation
259 of safety in real medical practice including use in unauthorised indications and use which is not in line
260 with the product information. If use of the medicinal product is identified where there are critical gaps
261 in knowledge for specific safety issues or populations, such use should be reported in the PSUR (e.g.
262 use in paediatric population or in pregnant women). Sources of information on use outside
263 authorisation may include drug utilisation data, information from spontaneous reports and publications
264 in the literature.

265 The scope of the benefit information should include both clinical trial and real world data in authorised
266 indications.

267 The integrated benefit-risk evaluation should be performed for based on all authorised indications and
268 but should incorporate the evaluation of risks in all use of the medicinal product (including use in
269 unauthorised indications).

270 The evaluation should involve:

- 271 1. Critically examining the information which has emerged during the reporting interval to determine
272 whether it has generated new signals, led to the identification of new potential or identified risks or
273 contributed to knowledge of previously identified risks.
- 274 2. Critically summarising relevant new safety, efficacy and effectiveness information that could have
275 an impact on the risk-benefit balance of the medicinal product.
- 276 3. Conducting an integrated benefit-risk analysis for all authorised indications based on the
277 cumulative information available since the development international birth date (DIBD), the date of
278 first authorisation for the conduct of an interventional clinical trial in any country. For the cases
279 where the DIBD is unknown or the marketing authorisation holder does not have access to data

² The ICH-E2C(R2) guideline should not serve to limit the scope of the information to be provided in the benefit-risk evaluation of a medicinal product. Please refer to the applicable laws and regulations in the countries and regions. For EU specific requirements, see VII.C.5.

280 from the clinical development period, the earliest possible applicable date should be used as
281 starting point for the inclusion and evaluation of the cumulative information.

282 4. Summarising any risk minimisation actions that may have been taken or implemented during the
283 reporting interval, as well as risk minimisation actions that are planned to be implemented.

284 5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional
285 pharmacovigilance activities.

286 ***VII.B.3. Principles for the preparation of PSURs***

287 Unless otherwise specified by competent authorities, the marketing authorisation holder shall prepare
288 a single PSUR for all its medicinal products containing the same active substance with information
289 covering all the authorised indications, route of administration, dosage forms and dosing regimens,
290 irrespective of whether authorised under different names and through separate procedures. Where
291 relevant, data relating to a particular indication, dosage form, route of administration or dosing
292 regimen, shall be presented in a separate section of the PSUR and any safety concerns shall be
293 addressed accordingly [IR Art 34(6)]. There might be exceptional scenarios where the preparation of
294 separate PSURs might be appropriate, for instance, in the event of different formulations for entirely
295 different indications. In this case, agreement should be obtained from the relevant competent
296 authorities preferably at the time of authorisation.

297 Case narratives shall be provided in the relevant risk evaluation section of the PSUR where integral to
298 the scientific analysis of a signal or safety concern [IR Art 34(4)]. In this context, the term “case
299 narratives” refers to clinical evaluations of individual cases rather than the CIOMS narratives. It should
300 not be necessary to provide the actual CIOMS narrative text included in the individual case safety
301 report (ICSR) but rather a clinical evaluation of important or illustrative cases in the context of the
302 evaluation of the safety concern/signal.

303 When data received at the marketing authorisation holder from a partner might contribute
304 meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing
305 authorisation holder’s product information, these data should be included and discussed in the PSUR.

306 The format and table of contents of all PSURs shall be as described in the IR Art 35 and each report
307 should include interval as well as cumulative data. As the PSUR should be a single stand-alone
308 document for the reporting interval, based on cumulative data, summary bridging reports and
309 addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

310 [The GVP Modules on Product- or Population-Specific Considerations³ should be consulted as applicable](#)
311 [when preparing a PSUR.](#)

312 ***VII.B.4. Reference information***

313 Risk minimisation activities evaluated in the PSUR include updates to the product information.

314 The reference product information for the PSUR should include “core safety” and “authorised
315 indications” components. In order to facilitate the assessment of benefit and risk-benefit balance by
316 indication in the evaluation sections of the PSUR, the reference product information document should
317 list all authorised indications in ICH countries⁴ or regions. When the PSUR is also submitted to other
318 countries in which there are additional locally authorised indications, these indications may be either
319 added to the reference product information or handled as a regional appendix as considered most
320 appropriate by the marketing authorization holder. The basis for the benefit evaluation should be the

³ <http://www.ema.europa.eu>

⁴ <http://www.ich.org/>

321 baseline important efficacy and effectiveness information summarised in the PSUR section 17.1
322 (“Important baseline efficacy and effectiveness information”).

323 Information related to a specific indication, formulation or route of administration should be clearly
324 identified in the reference product information.

325 The following possible options can be considered by the marketing authorisation holders when
326 selecting the most appropriate reference product information for a PSUR:

327 • **Company core data sheet (CCDS)**

328 – It is common practice for marketing authorisation holders to prepare their own company core
329 data sheet which covers data relating to safety, indications, dosing, pharmacology, and other
330 information concerning the product. The core safety information contained within the CCDS is
331 referred to as the company core safety information (CCSI). A practical option for the purpose
332 of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of
333 the reporting interval, as reference product information for both the risk sections of the PSUR
334 as well as the main authorised indications for which benefit is evaluated.

335 – When the CCDS does not contain information on authorised indications, the marketing
336 authorisation holder should clearly specify which document is used as reference information for
337 the authorised indications in the PSUR.

338 • **Other options for the reference product information**

339 – When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one
340 country or region, or for established/generics products on the market for many years), the
341 marketing authorisation holder should clearly specify the reference information being used.
342 This may comprise national or regional product information such as the EU summary of product
343 characteristics (SmPC).

344 – Where the reference information for the authorised indications is a separate document to the
345 reference safety information (the core safety information contained within the reference
346 product information), the version in effect at the end of the reporting interval should be
347 included as an appendix to the PSUR (see VII.B.5.20.).

348 The marketing authorisation holder should continuously evaluate whether any revision of the reference
349 product information/reference safety information is needed whenever new safety information is
350 obtained during the reporting interval and ensure that significant changes made over the interval are
351 described in PSUR section 4 (“Changes to the reference safety information”) and where relevant,
352 discussed in PSUR section 16 (“Signal and risk evaluation”). These changes may include:

353 • changes to contraindications, warnings/precautions sections;

354 • addition to adverse reactions and interactions;

355 • addition of important new information on use in overdose; and

356 • removal of an indication or other restrictions for safety or lack of efficacy reasons.

357 The marketing authorisation holder should provide a clean copy of all versions of the reference product
358 information in effect at the end of the reporting interval (e.g. different formulations included in the
359 same PSUR) as an appendix to the PSUR (see VII.B.5.20.). The reference product information should
360 be dated and version controlled.

361 Where new information on safety that could warrant changes to the authorised product information
362 (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety

363 information during the period from the data lock point to the submission of the PSUR, this information
364 should be included in the PSUR section 14 ("Late-breaking information"), **if feasible**.

365 **If stipulated by applicable regional requirements, the marketing authorisation holder should provide, in**
366 **the regional appendix, information on any final, ongoing and proposed changes to the national or local**
367 **authorised product information (see VII.C.5.)**

368 ~~The marketing authorisation holder should clearly highlight differences that may have an impact on~~
369 ~~labelling changes (e.g. adverse drug reactions, contraindications, warnings, interactions, overdose)~~
370 ~~between the version of the reference safety information in effect at the end of the reporting interval,~~
371 ~~taking into account any changes made during the late-breaking period, and their proposals for the local~~
372 ~~authorised product information based on the evaluation of the information contained in the PSUR.~~
373 ~~These differences should be included in PSUR regional appendix (see VII.B.5.20. and VII.C.5.2).~~

374 **VII.B.5. Format and contents of the PSUR**

375 The PSUR shall be based on all available data and shall focus on new information which has emerged
376 since the data lock point of the last PSUR [IR Art 34(1)]. Cumulative information should be taken into
377 account when performing the overall safety evaluation and integrated benefit-risk assessment.

378 Because clinical development of a medicinal product frequently continues following marketing
379 authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised
380 indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of
381 a medicinal product may be derived from evaluation of other data associated with off-label use, such
382 knowledge should be reflected in the risk evaluation where relevant and appropriate.

383 The PSUR shall provide summaries of data relevant to the benefits and risks of the medicinal product,
384 including results of all studies with a consideration of their potential impact on the marketing
385 authorisation [DIR Art 107b(1)(a)].

386 Examples of sources of efficacy, effectiveness and safety information that may be used in the
387 preparation of PSURs include the following:

- 388 • non-clinical studies;
- 389 • **spontaneous reports (e.g. on the marketing authorisation holder's safety database);**
- 390 • active surveillance systems (e.g. sentinel sites);
- 391 • investigations of product quality;
- 392 • product usage data and drug utilisation information;
- 393 • clinical trials, including research in unauthorised indications or populations;
- 394 • observational studies, including registries;
- 395 • patient support programs;
- 396 • systematic reviews and meta-analysis;
- 397 • marketing authorisation holders sponsored websites⁵;
- 398 • published scientific literature or **reports from** abstracts, including information presented at scientific
399 meetings;

⁵ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

- 400 • unpublished manuscripts;
- 401 • licensing partners, other sponsors or academic institutions and research networks;
- 402 • competent authorities (worldwide).

403 The above list is not intended to be all inclusive, and additional data sources may be used by the
404 marketing authorisation holder to present safety, efficacy and effectiveness information in the PSUR
405 and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging
406 important benefits and risks. When desired by the marketing authorisation holder, a list of the sources
407 of information used to prepare the PSUR can be provided as an appendix to the PSUR.

408 A PSUR shall be prepared following the full modular structure set out in Annex II of the IR [IR Art 35].

409 For the purposes of this Module, sources of information include data regarding the active substance(s)
410 included in the medicinal product, or the medicinal product that the marketing authorisation holder
411 may reasonably be expected to have access to and that are relevant to the evaluation of the safety,
412 and/or risk-benefit balance. It is therefore recognised that while the same format (as defined in the IR)
413 shall be followed for all products, the extent of the information provided may vary where justified
414 according to what is accessible to the marketing authorisation holder. For example, for a marketing
415 authorisation holder sponsored clinical trial, there should be access to patient level data while for a
416 clinical trial not sponsored by the marketing authorisation holder, only the published report may be
417 accessible.

418 The level of detail provided in certain sections of the PSUR should depend on known or emerging
419 important information on the medicinal product's benefits and risks. This approach is applicable to
420 those sections of the PSUR in which there is evaluation of information about safety, efficacy,
421 effectiveness, safety signals and risk-benefit balance.

422 When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on PBRER should
423 also be applied. Guidance on the titles, order and content of the PSUR sections is provided in VII.B.5.1.
424 to VII.B.5.21.. When no relevant information is available for any of the sections, this should be stated.

- 425 • Part I: Title page including signature⁶
- 426 • Part II: Executive Summary
- 427 • Part III: Table of Contents
 - 428 1. Introduction
 - 429 2. Worldwide marketing authorisation status
 - 430 3. Actions taken in the reporting interval for safety reasons
 - 431 4. Changes to reference safety information
 - 432 5. Estimated exposure and use patterns
 - 433 5.1. Cumulative subject exposure in clinical trials
 - 434 5.2. Cumulative and interval patient exposure from marketing experience
 - 435 6. Data in summary tabulations
 - 436 6.1. Reference information

⁶ For PSURs submission in the EU, it is at the discretion of the QPPV to determine the most appropriate person to sign the document according to the marketing authorisation holder structure and responsibilities. A statement confirming the designation by the QPPV should be included. No delegation letters should be submitted.

437	6.2. Cumulative summary tabulations of serious adverse events from clinical trials
438	6.3. Cumulative and interval summary tabulations from post-marketing data sources
439	7. Summaries of significant findings from clinical trials during the reporting interval
440	7.1. Completed clinical trials
441	7.2. Ongoing clinical trials
442	7.3. Long-term follow-up
443	7.4. Other therapeutic use of medicinal product
444	7.5. New safety data related to fixed combination therapies
445	8. Findings from non-interventional studies
446	9. Information from other clinical trials and sources
447	9.1. Other clinical trials
448	9.2. Medication errors
449	10. Non-clinical Data
450	11. Literature
451	12. Other periodic reports
452	13. Lack of efficacy in controlled clinical trials
453	14. Late-breaking information
454	15. Overview of signals: new, ongoing or closed
455	16. Signal and risk evaluation
456	16.1. Summaries of safety concerns
457	16.2. Signal evaluation
458	16.3. Evaluation of risks and new information
459	16.4. Characterisation of risks
460	16.5. Effectiveness of risk minimisation (if applicable)
461	17. Benefit evaluation
462	17.1. Important baseline efficacy and effectiveness information
463	17.2. Newly identified information on efficacy and effectiveness
464	17.3. Characterisation of benefits
465	18. Integrated benefit-risk analysis for authorised indications
466	18.1. Benefit-risk context – Medical need and important alternatives
467	18.2. Benefit-risk analysis evaluation
468	19. Conclusions and actions
469	20. Appendices to the PSUR

470 **PSUR title page**

471 The title page should include the name of the medicinal product(s)⁷ and substance, international birth
472 date (IBD) (the date of the first marketing authorisation for any product containing the active
473 substance granted to any company in any country in the world), reporting interval, date of the report,
474 marketing authorisation holder details and statement of confidentiality of the information included in
475 the PSUR.

476 The title page shall also contain the signature.

477 **PSUR executive summary**

478 An executive summary should be placed immediately after the title page and before the table of
479 contents. The purpose of the executive summary is to provide a concise summary of the content and
480 the most important information in the PSUR and should contain the following information:

- 481 • introduction and reporting interval;
- 482 • medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical
483 formulation(s), dose(s) and route(s) of administration;
- 484 • estimated cumulative clinical trials exposure;
- 485 • estimated interval and cumulative exposure from marketing experience;
- 486 • number of countries in which the medicinal product is authorised;
- 487 • summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk
488 analysis evaluation” of the PSUR);
- 489 • actions taken and proposed for safety reasons, (e.g. significant changes to the reference product
490 information, or other risk minimisation activities);
- 491 • conclusions.

492 **PSUR table of contents**

493 The executive summary should be followed by the table of contents.

494 **VII.B.5.1. PSUR section “Introduction”**

495 The marketing authorisation holder should briefly introduce the product(s) so that the PSUR “stands
496 alone” but it is also placed in perspective relative to previous PSURs and circumstances. The
497 introduction should contain the following information:

- 498 • IBD, and reporting interval;
- 499 • medicinal product(s), therapeutic class(es), mechanism(s) of action, authorised indication(s),
500 pharmaceutical form(s), dose(s) and route(s) of administration;
- 501 • a brief description of the population(s) being treated and studied;

⁷ For PSURs covering multiple products, for practical reasons, this information may be provided in the PSUR Cover Page (See Annex II)

502 **VII.B.5.2. PSUR section “Worldwide marketing authorisation status”**

503 This section of the PSUR should contain a brief narrative overview including: date of the first
504 authorisation worldwide, indications(s), authorised dose(s), and where authorised.

505 **VII.B.5.3. PSUR section “Actions taken in the reporting interval for safety**
506 **reasons”**

507 This section of the PSUR should include a description of significant actions related to safety that have
508 been taken worldwide during the reporting interval, related to either investigational uses or marketing
509 experience by the marketing authorisation holder, sponsors of clinical trial(s), data monitoring
510 committees, ethics committees or competent authorities that had either:

- 511 • a significant influence on the risk-benefit balance of the authorised medicinal product; and/or
512 • an impact on the conduct of a specific clinical trial(s) or on the overall clinical development
513 programme.

514 If known, the reason for each action should be provided and any additional relevant information should
515 be included as appropriate. Relevant updates to previous actions should also be summarised in this
516 section.

517 Examples of significant actions taken for safety reasons include:

518 Actions related to investigational uses:

- 519 • refusal to authorise a clinical trial for ethical or safety reasons;
520 • partial⁸ or complete clinical trial suspension or early termination of an ongoing clinical trial because
521 of safety findings or lack of efficacy;
522 • recall of investigational drug or comparator;
523 • failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a
524 marketing authorisation application;
525 • risk management activities, including:
526 – protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in
527 study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial
528 duration);
529 – restrictions in study population or indications;
530 – changes to the informed consent document relating to safety concerns;
531 – formulation changes;
532 – addition by regulators of a special safety-related reporting requirement;
533 – issuance of a communication to investigators or healthcare professionals; and
534 – plans for new studies to address safety concerns.

535 Actions related to marketing experience:

- 536 • failure to obtain **or apply for** a marketing authorisation renewal;

⁸“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). ICH-E2C(R2) guideline (see [Annex IV](#)).

- 537 • withdrawal or suspension of a marketing authorisation;
- 538 • actions taken due to product defects and quality issues;
- 539 • suspension of supply by the marketing authorisation holder;
- 540 • risk management activities including:
 - 541 – significant restrictions on distribution or introduction of other risk minimisation measures;
 - 542 – significant safety-related changes in labelling documents including restrictions on use or
 - 543 population treated;
 - 544 – communications to health care professionals; and
 - 545 – new post-marketing study requirement(s) imposed by competent authorities.

546 **VII.B.5.4. PSUR section “Changes to reference safety information”**

547 This PSUR section should list any significant changes made to the reference safety information within
 548 the reporting interval. Such changes might include information relating to contraindications, warnings,
 549 precautions, serious adverse drug reactions, interactions, important findings from ongoing or
 550 completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific
 551 information relevant to these changes should be provided in the appropriate sections of the PSUR.

552 **VII.B.5.5. PSUR section “Estimated exposure and use patterns”**

553 PSURs shall provide an accurate estimate of the population exposed to the medicinal product, including
 554 all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be
 555 accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where
 556 appropriate, how actual use differs from the indicated use based on all data available to the marketing
 557 authorisation holder, including the results of observational or drug utilisation studies [IR Art 34 (2)].

558 This PSUR section should provide estimates of the size and nature of the population exposed to the
 559 medicinal product including a brief description of the method(s) used to estimate the subject/patient
 560 exposure and the limitations of that method.

561 Consistent methods for calculating subject/patient exposure should be used across PSURs for the same
 562 medicinal product. If a change in the method is appropriate, both methods and calculations should be
 563 provided in the PSUR introducing the change and any important difference between the results using
 564 the two methods should be highlighted.

565 **VII.B.5.5.1. PSUR sub-section “Cumulative subject exposure in clinical trials”**

566 This section of the PSUR should contain the following information on the patients studied in clinical
 567 trials sponsored by the marketing authorisation holder, if applicable presented in tabular formats:

- 568 • cumulative numbers of subjects from ongoing and completed clinical trials exposed to the
 569 investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is
 570 recognised that for “old products”, detailed data might not be available;
- 571 • more detailed cumulative subject exposure in clinical trials should be presented if available (e.g.
 572 sub-grouped by age, sex, and racial/ethnic group for the entire development programme);+
- 573 • important differences among trials in dose, routes of administration, or patient populations can be
 574 noted in the tables, if applicable, or separate tables can be considered;

- 575 • if clinical trials have been or are being performed in special populations (e.g. pregnant women;
576 patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic
577 polymorphisms), exposure data should be provided as appropriate;
- 578 • when there are substantial differences in time of exposure between subjects randomised to the
579 investigational medicinal product or comparator(s), or disparities in length of exposure between
580 clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -
581 years);
- 582 • investigational drug exposure in healthy volunteers might be less relevant to the overall safety
583 profile, depending on the type of adverse reaction, particularly when subjects are exposed to a
584 single dose. Such data can be presented separately with an explanation as appropriate;
- 585 • if the serious adverse events from clinical trials are presented by indication in the summary
586 tabulations, the patient exposure should also be presented by indication, where available;
- 587 • for individual trials of particular importance, demographic characteristics should be provided
588 separately.

589 Examples of tabular format for the estimated exposure in clinical trials are presented in VII. Appendix
590 1, Tables VII.2, VII.3 and VII.4.

591 **VII.B.5.5.2. PSUR sub-section “Cumulative and interval patient exposure from marketing**
592 **experience”**

593 Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and
594 interval exposure (since the data lock point of the previous PSUR). Although it is recognised that it is
595 often difficult to obtain and validate exposure data, the number of patients exposed should be provided
596 whenever possible, along with the method(s) used to determine the estimate. Justification should be
597 provided if it is not possible to estimate the number of patients exposed. In this case, alternative
598 estimates of exposure, if available, should be presented along with the method(s) used to derive them.
599 Examples of alternative measures of exposure include patient-days of exposure and number of
600 prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or
601 dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient
602 exposure estimates.

603 The data should be presented according to the following categories:

604 1. Post-authorisation (non-clinical trial) exposure:

605 An overall estimation of patient exposure should be provided. In addition, the data should be
606 routinely presented by sex, age, indication, dose, formulation and region, where applicable.
607 Depending upon the product, other variables may be relevant, such as number of vaccination
608 courses, route(s) of administration, and duration of treatment.

609 When there are patterns of reports indicating a safety signal, exposure data within relevant
610 subgroups should be presented, if possible.

611 2. Post-authorisation use in special populations:

612 Where post-authorisation use has occurred in special populations, available information regarding
613 cumulative patient numbers exposed and the method of calculation should be provided. Sources of
614 such data ~~may would~~ include ~~for instance~~ non-interventional studies designed to obtain this
615 information, including registries. [Other sources of information may include data collection outside a
616 study environment including information collected through spontaneous reporting systems \(e.g.
617 information on reports of pregnancy exposure without an associated adverse event may be](#)

618 | [summarised in this section](#)). –Populations to be considered for discussion include, but might not be
619 | limited to:

- 620 | • paediatric population;
- 621 | • elderly population;
- 622 | • pregnant or lactating women;
- 623 | • patients with hepatic and/or renal impairment;
- 624 | • patients with other relevant co-morbidity;
- 625 | • patients with disease severity different from that studied in clinical trials;
- 626 | • sub-populations carrying relevant genetic polymorphism(s);
- 627 | • populations with specific racial and/or ethnic origins.

628 | 3. **Other post-authorisation use:**

629 | If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product,
630 | which may be regional, considered relevant for the interpretation of safety data, provide a brief
631 | description thereof. [Examples of such patterns of use information may include evidence of](#)
632 | [overdose, abuse, misuse and use beyond the recommendation\(s\) in the reference product](#)
633 | [information](#) (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine
634 | [headaches](#)). [Where relevant to the evaluation of safety and/or benefit-risk, information reported](#)
635 | [on patterns of use without reference to adverse reactions should be summarised in this section as](#)
636 | [applicable. Such information may be received via spontaneous reporting systems, reports, medical](#)
637 | [information queries, customer's complaints, screening of digital media or via other information](#)
638 | [sources available to the marketing authorisation holder.](#) ~~If quantitative information on use is~~
639 | ~~available, it should be provided. Examples of such patterns of use may include overdose, abuse,~~
640 | ~~misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti-~~
641 | ~~epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches).~~

642 | If known, the marketing authorisation holder may briefly comment on whether [other use beyond](#)
643 | [the recommendation\(s\) in the reference product information may be linked to is supported by](#)
644 | clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. ~~If~~
645 | ~~quantitative use information is available, it should be provided.~~ For purposes of identifying patterns
646 | of use outside the terms of the reference product information, the marketing authorisation holder
647 | should use the appropriate sections of the reference product information that was in effect at the
648 | end of the reporting interval of the PSUR (e.g. authorised indication, [route of administration,](#)
649 | [contraindications](#)).

650 | [Signals or risks identified from any data or information source should be presented and evaluated](#)
651 | [in the relevant sections of the PSUR.](#)

652 | Examples of tabular format for the estimated exposure from marketing experience are presented in
653 | VII. Appendix 1, Tables VII.5 and VII.6.

654 | VII.B.5.6. PSUR section “Data in summary tabulations”

655 | The objective of this PSUR section is to present safety data through summary tabulations of serious
656 | adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing
657 | experience (including reports from healthcare professionals, consumers, scientific literature, competent
658 | authorities (worldwide)) and serious reactions from non-interventional studies and other non-

659 interventional solicited source. At the discretion of the marketing authorisation holder graphical
660 displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

661 When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the
662 adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be
663 presented in the summary tabulations.

664 The seriousness of the adverse events/reactions in the summary tabulations should correspond to the
665 seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-
666 E2A⁹ (see Annex IV). When serious and non-serious events/reactions are included in the same ICSR,
667 the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness
668 should not be changed specifically for the preparation of the PSURs.

669 **VII.B.5.6.1. PSUR sub-section “Reference information”**

670 This sub-section of the PSUR should specify the version(s) of the coding dictionary used for
671 presentation of adverse events/reactions.

672 **VII.B.5.6.2. PSUR sub-section “Cumulative summary tabulations of serious adverse events 673 from clinical trials”**

674 This PSUR sub-section should provide background for the appendix that provides a cumulative
675 summary tabulation of serious adverse events reported in the marketing authorisation holder’s clinical
676 trials, from the DIBD to the data lock point of the current PSUR. The marketing authorisation holder
677 should explain any omission of data (e.g. clinical trial data might not be available for products
678 marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the
679 internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active
680 comparators, placebo) used in the clinical development programme. Data can be integrated across the
681 programme. Alternatively, when useful and feasible, data can be presented by trial, indication, route of
682 administration or other variables.

683 This sub-section should not serve to provide analyses or conclusions based on the serious adverse
684 events.

685 The following points should be considered:

- 686 • Causality assessment is generally useful for the evaluation of individual rare adverse drug
687 reactions. Individual case causality assessment has less value in the analysis of aggregate data,
688 where group comparisons of rates are possible. Therefore, the summary tabulations should include
689 all serious adverse events and not just serious adverse reactions for the investigational drug,
690 comparators and placebo. It may be useful to give rates by dose.
- 691 • In general, the tabulation(s) of serious adverse events from clinical trials should include only those
692 terms that were used in defining the case as serious and non-serious events should be included in
693 the study reports.
- 694 • The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse
695 events might originate from completed trials and individual cases that have been unblinded for
696 safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and
697 marketing authorisation holders should not unblind data for the specific purpose of preparing the
698 PSUR.

⁹ ICH Topic E2A. Clinical safety data management: Definitions and standards for expedited reporting.

- 699 • Certain adverse events can be excluded from the clinical trials summary tabulations, but such
700 exclusions should be explained in the report. For example, adverse events that have been defined
701 in the protocol as “exempt” from special collection and entry into the safety database because they
702 are anticipated in the patient population, and those that represent study endpoints, can be
703 excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause
704 mortality is the primary efficacy endpoint, disease progression in cancer trials).

705 An example of summary tabulation of serious adverse events from clinical trials can be found in VII.
706 Appendix 1 Table VII.7.

707 **VII.B.5.6.3. PSUR sub-section “Cumulative and interval summary tabulations from post- 708 marketing data sources”**

709 This sub-section of the PSUR should provide background for the appendix that provides cumulative and
710 interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current
711 PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare
712 professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited
713 non-interventional ICSRs including those from non-interventional studies¹⁰. Serious and non-serious
714 reactions from spontaneous sources, as well as serious adverse reactions from non-interventional
715 studies and other non-interventional solicited sources should be presented in a single table, with
716 interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC
717 (listed in the internationally agreed order). For special issues or concerns, additional tabulations of
718 adverse reactions can be presented by indication, route of administration, or other variables.

719 As described in ICH-E2D¹¹ (see Annex IV) guideline, for marketed medicinal products, spontaneously
720 reported adverse events usually imply at least a suspicion of causality by the reporter and should be
721 considered to be suspected adverse reactions for regulatory reporting purposes.

722 Analysis or conclusions based on the summary tabulations should not be provided in this PSUR sub-
723 section.

724 An example of summary tabulations of adverse drug reactions from post-marketing data sources can
725 be found in VII. Appendix 1 Table VII.8.

726 **VII.B.5.7. PSUR section “Summaries of significant findings from clinical 727 trials during the reporting interval”**

728 This PSUR section should provide a summary of the clinically important emerging efficacy and safety
729 findings obtained from the marketing authorisation holder’s sponsored clinical trials during the
730 reporting interval, from the sources specified in the sub-sections listed below. When possible and
731 relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and
732 region should be presented.

733 Signals arising from clinical trial sources should be tabulated in PSUR section 15 (“Overview on signals:
734 new, ongoing or closed”). Evaluation of the signals, whether or not categorised as refuted signals or
735 either potential or identified risk, that were closed during the reporting interval should be presented in
736 PSUR section 16.2 (“Signal evaluation”). New information in relation to any previously known potential
737 or identified risks and not considered to constitute a newly identified signal should be evaluated and
738 characterised in PSUR sections 16.3 (“Evaluation of risks and new information”) and 16.4
739 (“Characterisation of risks”) respectively.

¹⁰ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

¹¹ [ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting](#). See footnote 8.

740 Findings from clinical trials not sponsored by the marketing authorisation holder should be described in
741 the relevant sections of the PSUR.

742 When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for
743 treatments of non-life-threatening diseases in authorised indications should also be summarised in this
744 section. Information on lack of efficacy from clinical trials with products intended to treat or prevent
745 serious or life-threatening illness should be summarised in section 13 (“Lack of efficacy in controlled
746 clinical trials”) (VII.B.5.13).

747 [Information from other clinical trials/study sources should be included in the PSUR sub-section 9.1](#)
748 [\(“other clinical trials”\) \(VII.B.5.9.1\)](#)

749 In addition, the marketing authorisation holder should include an appendix listing the sponsored **post-**
750 **authorisation** interventional trials with the primary aim of identifying, characterising, or quantifying a
751 safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing
752 during the reporting interval. **The listing should include the following information for each trial:**

- 753 • study ID (e.g. protocol number or other identifier);
- 754 • study title (abbreviated study title, if applicable);
- 755 • study type (e.g. randomised clinical trial, cohort study, case-control study);
- 756 • population studied, including country and other relevant population descriptors (e.g. paediatric
757 population or trial subjects with impaired renal function);
- 758 • study start (as defined by the marketing authorisation holder) and projected completion dates;
- 759 • status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

760 **VII.B.5.7.1. PSUR sub-section “Completed clinical trials”**

761 This sub-section of the PSUR should provide a brief summary of clinically important emerging efficacy
762 and safety findings obtained from clinical trials completed during the reporting interval. This
763 information can be presented in narrative format or as a synopsis¹². It could include information that
764 supports or refutes previously identified safety concerns as well as evidence of new safety signals.

765 **VII.B.5.7.2. PSUR sub-section “Ongoing clinical trials”**

766 If the marketing authorisation holder is aware of clinically important information that has arisen from
767 ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of
768 subjects with adverse events), this sub-section should briefly summarise the concern(s). It could
769 include information that supports or refutes previously identified safety concerns, as well as evidence
770 of new safety signals.

771 **VII.B.5.7.3. PSUR sub-section “Long term follow-up”**

772 Where applicable, this sub-section should provide information from long-term follow-up of subjects
773 from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy,
774 cell therapy products and tissue engineered products).

¹² Examples of synopses can be found in ICH-E3: Structure and Content of Clinical Study Reports and CIOMS VII (Council for International Organizations of Medical Sciences (CIOMS). Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials - Report of CIOMS Working Group VII). Geneva: CIOMS; 2006. <http://www.cioms.ch/>.

775 **VII.B.5.7.4. PSUR sub-section “Other therapeutic use of medicinal product”**

776 This sub-section of the PSUR should include clinically important safety information from other
777 programmes conducted by the marketing authorisation holder that follow a specific protocol, with
778 solicited reporting as per ICH-E2D¹³ (e.g. expanded access programmes, compassionate use
779 programmes, particular patient use, and other organised data collection).

780 **VII.B.5.7.5. PSUR sub-section “New safety data related to fixed combination therapies”**

781 Unless otherwise specified by national or regional regulatory requirements, the following options can
782 be used to present data from combination therapies:

- 783 • If the active substance that is the subject of the PSURs is also authorised or under development as
784 a component of a fixed combination product or a multi-drug regimen, this sub-section should
785 summarise important safety findings from use of the combination therapy.
- 786 • If the product itself is a fixed combination product, this PSUR sub-section should summarise
787 important safety information arising from the individual components whether authorised or under
788 development.

789 The information specific to the combination can be incorporated into a separate section(s) of the PSUR
790 for one or all of the individual components of the combination.

791 **VII.B.5.8. PSUR section “Findings from non-interventional studies”**

792 This section should also summarise relevant safety information or information with potential impact in
793 the benefit-risk assessment from marketing authorisation holder-sponsored non-interventional studies
794 that became available during the reporting interval (e.g. observational studies, epidemiological studies,
795 registries, and active surveillance programmes). This should include relevant information from drug
796 utilisation studies when relevant to multiple regions (see VII.B.5.7. for the information that should be
797 included in the listing).

798 The marketing authorisation holder should include an appendix listing marketing authorisation holder-
799 sponsored non-interventional studies conducted with the primary aim of identifying, characterising or
800 quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the
801 effectiveness of risk management measures which were completed or ongoing during the reporting
802 interval. (see VII.B.5.7. for the information that should be included in the listing).

803 Final study reports completed during the reporting interval for the studies mentioned in the paragraph
804 above should also be included in the regional appendix of the PSUR (see VII.B.5.20. and VII.C.5.4.).

805 [Summary information based on aggregate evaluation of data generated from patient support programs](#)
806 [may be included in this section when not presented elsewhere in the PSUR. As for other information](#)
807 [sources, the marketing authorisation holder should present signals or risks identified from such](#)
808 [information in the relevant sections of the PSUR.](#)

809 **VII.B.5.9. PSUR section “Information ~~for~~om other clinical trials and**
810 **sources”**

811 ~~Other sources of information may include data collection outside of a study~~
812 ~~environment. Information obtained from reports of events or patterns of~~
813 ~~use which do not result in suspected adverse reactions may be included in~~
814 ~~sub-sections VII.B.5.9.1. and VII.B.5.9.2. For example, this would include~~

¹³ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

815 available information on reports of asymptomatic overdose, abuse, use
816 beyond that recommended in the reference product information, or use in
817 special populations (see Module VI). Such information may be received via
818 spontaneous reports, medical information queries, customer's complaints,
819 screening of digital media or via other information sources available to the
820 marketing authorisation holder.

821 Signals or risks identified from any information source and/or category of reports should be presented
822 and evaluated in the relevant sections of the PSUR.

823 **VII.B.5.9 1. PSUR sub-section "Other clinical trials"**

824 This PSUR sub-section should summarise information relevant to the benefit-risk assessment of the
825 medicinal product from other clinical trial/study sources, including patient support programs, which are
826 accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool
827 analysis or meta-analysis of randomised clinical trials, safety information provided by co-development
828 partners or from investigator-initiated trials).

829 **VII.B.5.9 2. PSUR sub-section "Medication errors"**

830 This sub-section should summarise relevant information on patterns of medication errors and potential
831 medication errors, even when not associated with adverse outcomes. A potential medication error is
832 the recognition of circumstances that could lead to a medication error, and may or may not involve a
833 patient. Such information may be relevant to the interpretation of safety data or the overall benefit-
834 risk evaluation of the medicinal product. A medication error may arise at any stage in the medication
835 use process and may involve patients, consumers, or healthcare professionals.

836 **VII.B.5.10. PSUR section "Non-clinical data"**

837 This PSUR section should summarise major safety findings from non-clinical in vivo and in vitro studies
838 (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the
839 reporting interval. Results from studies designated to address specific safety concerns should be
840 included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in
841 the relevant evaluation sections of the PSUR.

842 **VII.B.5.11. PSUR section "Literature"**

843 This PSUR section should include a summary of new and significant safety findings, either published in
844 the peer-reviewed scientific literature or made available as unpublished manuscripts that the
845 marketing authorisation holder became aware of during the reporting interval, when relevant to the
846 medicinal product.

847 Literature searches for PSURs should be wider than those for individual adverse reaction cases as they
848 should also include studies reporting safety outcomes in groups of subjects and other products
849 containing the same active substance.

850 The special types of safety information that should be included, but which may not be found by a
851 search constructed specifically to identify individual cases, include:

- 852 • pregnancy outcomes (including termination) with no adverse outcomes;
- 853 • use in paediatric populations;
- 854 • compassionate supply, named patient use;

- 855 • lack of efficacy;
 - 856 • asymptomatic overdose, abuse or misuse;
 - 857 • medication error where no adverse events occurred;
 - 858 • important non-clinical safety results.
- 859 If relevant and applicable, information on other active substances of the same class should be
860 considered.
- 861 The publication reference should be provided in the style of the Vancouver Convention^{14,15}.

862 **VII.B.5.12. PSUR section “Other periodic reports”**

863 This PSUR section will only apply in certain circumstances concerning fixed combination products or
864 products with multiple indications and/or formulations where multiple PSURs are prepared in
865 agreement with the competent authority. In general, the marketing authorisation holder should
866 prepare a single PSUR for a single active substance (unless otherwise specified by the competent
867 authority); however if multiple PSURs are prepared for a single medicinal product, this section should
868 also summarise significant findings from other PSURs if they are not presented elsewhere within the
869 report.

870 When available, based on the contractual agreements, the marketing authorisation holder should
871 summarise significant findings from periodic reports provided during the reporting interval by other
872 parties (e.g. sponsors, other marketing authorisation holders or other contractual partners).

873 **VII.B.5.13. PSUR section “Lack of efficacy in controlled clinical trials”**

874 This section should summarise data from clinical trials indicating lack of efficacy, or lack of efficacy
875 relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening
876 illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute
877 coronary syndromes) that could reflect a significant risk to the treated population.

878 **VII.B.5.14. PSUR section “Late-breaking information”**

879 The marketing authorisation holder should summarise in this PSUR section the potentially important
880 safety, efficacy and effectiveness findings that arise after the data lock point but during the period of
881 preparation of the PSUR. Examples include clinically significant new publications, important follow-up
882 data, clinically relevant toxicological findings and any action that the marketing authorisation holder, a
883 data monitoring committee, or a competent authority (worldwide) has taken for safety reasons. New
884 individual case reports should not be routinely included unless they are considered to constitute an
885 important index case (i.e. the first instance of an important event) or an important safety signal or
886 where they may add information to the evaluation of safety concerns already presented in the PSUR
887 (e.g. a well documented case of aplastic anaemia in a medicinal product known to be associated with
888 adverse effects on the bone marrow in the absence of possible alternative causes).

¹⁴ Uniform requirements for manuscripts submitted to biomedical journals. International Committee of Medical Journal Editors. N Engl J Med. 1997 Jan 23; 336(4):309-15. Available online: <http://www.nejm.org/doi/full/10.1056/NEJM199701233360422>

¹⁵ Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Updated April 2010] Publication Ethics: Sponsorship, Authorship, and Accountability, International Committee of Medical Journal Editors. http://www.icmje.org/urm_full.pdf

889 Any significant change proposed to the reference product information –(e.g. new adverse reaction,
890 warning or contraindication) which has occurred during this period, should also be included in this
891 section of the PSUR (see VII.B.4.), where feasible.

892 The data presented in this section should also be taken into account in the evaluation of risks and new
893 information (see VII.B.5.16.3.).

894 VII.B.5.15. PSUR section “Overview of signals: new, ongoing, or closed”

895 The general location for presentation of information on signals and risks within the PSUR is shown in
896 figure VII.1 (see VII.B.5.21.). The purpose of this section is to provide a high level overview of
897 signals¹⁶ that were closed (i.e. evaluation was completed) during the reporting interval as well as
898 ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes
899 of the PSUR, a signal should be included once it has undergone the initial screening or clarification
900 step, and a determination made to conduct further evaluation by the marketing authorisation
901 holder¹⁷. It should be noted that a safety signal is not synonymous with a statistic of disproportionate
902 reporting for a specific medicine/event combination as a validation step is required. Signals may be
903 qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a
904 disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the
905 form of an information request or inquiry on a safety issue from a competent authority (worldwide)
906 (see Module IX).

907 Decisions regarding the subsequent classification of these signals and the conclusions of the
908 evaluation, involve medical judgement and scientific interpretation of available data, which is
909 presented in section 16 (“Signal and risk evaluation”) of the PSUR.

910 A new signal refers to a signal that has been identified during the reporting interval. Where new
911 clinically significant information on a previously closed signal becomes available during the reporting
912 interval of the PSUR, this would also be considered a new signal on the basis that a new aspect of a
913 previously refuted signal or recognised risk warrants further action to verify. New signals may be
914 classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting
915 interval of the PSUR.

916 Examples of new signals would therefore include new information on a previously:

- 917 • Close and refuted signal, which would result in the signal being re-opened.
- 918 • Identified risk where the new information suggests a clinically significant difference in the severity
919 or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new
920 information indicative of a more severe outcome such as hepatic failure is received, or neutropenia
921 is an identified risk and a well documented case report of agranulocytosis with no presence of
922 possible alternative causes is received).
- 923 • Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an
924 indicated subpopulation).
- 925 • Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication
926 or restriction in indication(s) or population or other risk minimisation activities.

¹⁶ “Signal” means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].

¹⁷ In the EU-regulatory network and for the purpose of the PSUR, the term “signal” in this section corresponds with the term “validated signal” described in GVP Module IX.

927 | Within this section, or as an appendix the marketing authorisation holder should provide a tabulation
928 of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the
929 following information:

- 930 • a brief description of the signal;
- 931 • date when the marketing authorisation holder became aware of the signal;
- 932 • status of the signal at the end of the reporting interval (close or ongoing);
- 933 • date when the signal was closed, if applicable;
- 934 • source of the signal;
- 935 • a brief summary of the key data;
- 936 • plans for further evaluation; and
- 937 • actions taken or planned.

938 | An example of tabulation of signals can be found in VII. Appendix 2.

939 The detailed signal assessments for closed signals are not to be included in this section but instead
940 should be presented in sub-section 16.2 (“Signal evaluation”) of the PSUR.

941 Evaluation of new information in relation to any previously known identified and potential risks and not
942 considered to constitute a new signal should be provided in PSUR sub-section 16.3 (“Evaluation of risks
943 and new information”).

944 When a competent authority (worldwide) has requested that a specific topic (not considered a signal)
945 be monitored and reported in a PSUR, the marketing authorisation holder should summarise the result
946 of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be
947 included in the signal tabulation and discussed in sub-section 16.2 (“Signal evaluation”).

948 **VII.B.5.16. PSUR section “Signal and risk evaluation”**

949 The purpose of this section of the PSUR is to provide:

- 950 | • A succinct summary of what is known about important identified and potential risks and important
951 missing information at the beginning of the reporting interval covered by the report
952 (VII.B.5.16.1.).
- 953 • An evaluation of all signals closed during the reporting interval (VII.B.5.16.2.).
- 954 • An evaluation of new information with respect to previously recognised identified and potential
955 risks (VII.B.5.16.3).
- 956 • An updated characterisation of important potential and identified risks, where applicable
957 (VII.B.5.16.4.).
- 958 • A summary of the effectiveness of risk minimisation activities in any country or region which may
959 have utility in other countries or regions (VII.B.5.16.5.).

960 A flowchart illustrating the mapping of signals and risks to specific sections/sub-sections of the PSUR
961 can be found in VII.B.5.21..

962 These evaluation sub-sections should not summarise or duplicate information presented in previous
963 sections of the PSUR but should rather provide interpretation and critical appraisal of the information,
964 with a view towards characterising the profile of those risks assessed as important. In addition, as a

965 general rule, it is not necessary to include individual case narratives in the evaluation sections of the
966 PSUR but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or
967 illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to
968 a class known to be associated with this adverse reaction) should be provided (see VII.B.3.).

969 **VII.B.5.16.1. PSUR sub-section "Summary of safety concerns"**

970 The purpose of this sub-section is to provide a summary of important safety concerns at the beginning
971 of the reporting interval, against which new information and evaluations can be made. For products
972 with an existing safety specification, this section can be either the same as, or derived from the safety
973 specification summary¹⁸ that is current at the start of the reporting interval of the PSUR. It should
974 provide the following safety information:

- 975 • important identified risks;
- 976 • important potential risks; and
- 977 • ~~important~~ missing information.

978 The following factors should be considered when determining the importance of each risk:

- 979 • medical seriousness of the risk, including the impact on individual patients;
- 980 • its frequency, predictability, preventability, and reversibility;
- 981 • potential impact on public health (frequency; size of treated population); and
- 982 • potential for avoidance of the use of a medicinal product with a preventive benefit due to a
983 disproportionate public perception of risk (e.g. vaccines).

984 For products without an existing safety specification, this section should provide information on the
985 important identified and potential risks and ~~important~~ missing information associated with use of the
986 product, based on pre- and post-authorisation experience. Important identified and potential risks may
987 include, for example:

- 988 • important adverse reactions;
- 989 • interactions with other medicinal products;
- 990 • interactions with foods and other substances;
- 991 • medication errors;
- 992 • effects of occupational exposure; and
- 993 • pharmacological class effects.

994 The summary on ~~important~~ missing information should take into account whether there are critical
995 gaps in knowledge for specific safety issues or populations that use the medicinal product.

996 **VII.B.5.16.2. PSUR sub-section "Signal evaluation"**

997 This sub-section of the PSUR should summarise the results of evaluations of all safety signals (whether
998 or not classified as important) that were closed during the reporting interval. A safety signal can be
999 closed either because it is refuted or because it is determined to be a potential or identified risk,
1000 following evaluation. The two main categories to be included in this sub-section are:

¹⁸ ICH-E2E – Pharmacovigilance planning (see Annex IV).

1001 1. Those signals that, following evaluation, have been **refuted** as “false” signals based on **medical**
1002 **judgement and** scientific evaluation of the currently available information.

1003 2. Those signals that, following evaluation, have been categorised as either a potential or identified
1004 risk, including lack of efficacy.

1005 For both categories of closed signals, a **concise** description of each signal evaluation should be included
1006 in order to clearly describe the basis upon which the signal was either **refuted** or considered to be a
1007 **potential or identified** risk by the marketing authorisation holder.

1008 It is recommended that the level of detail provided in the description of the signal evaluation should
1009 reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or
1010 mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside
1011 the recommendations of the product information) and the extent of the available evidence. Where
1012 multiple evaluations will be included under both categories of closed signals, they can be presented in
1013 the following order:

- 1014 • Closed and refuted signals.
- 1015 • Closed signals that are categorised as important potential risks.
- 1016 • Closed signals that are categorised as important identified risks.
- 1017 • Closed signals that are potential risks not categorised as important.
- 1018 • Closed signals that are identified risks not categorised as important.

1019 Where applicable the evaluations of closed signals can be presented by indication or population.

1020 **The description(s) of the signal evaluations can be included in this sub-section of the PSUR or in an**
1021 **appendix.** Each evaluation should include the following information as appropriate:

- 1022 • source or trigger of the signal;
- 1023 • background relevant to the evaluation;
- 1024 • method(s) of evaluation, including data sources, search criteria (where applicable, the specific
1025 MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were
1026 reviewed), and analytical approaches;
- 1027 • results - a summary and critical analysis of the data considered in the signal evaluation; where
1028 integral to the assessment, this may include a description of a case series or an individual case
1029 (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
- 1030 • discussion;
- 1031 • conclusion.

1032 Marketing authorisation holder’s evaluations and conclusions for refuted signals should be supported
1033 by data and clearly presented.

1034 **VII.B.5.16.3. PSUR sub-section “Evaluation of risks and new information”**

1035 This sub-section should provide a critical appraisal of new information relevant to previously
1036 recognised risks **that is not already included in sub-section 16.2 (“Signal evaluation”).**

1037 New information that constitutes a signal with respect to a previously recognised risk or previously
1038 refuted signal should be **presented in the signals tabulation (see VII.B.5.15.) and** evaluated in sub-
1039 **section 16.2 (“Signal evaluation”), if the signal is also closed during the reporting interval of the PSUR.**

1040 Updated information on a previously recognised risk that does not constitute a signal should be
1041 included in this sub-section. Examples includes information that confirms a potential risk as an
1042 identified risk,

1043 -or information which allows any other further characterisation of a previously recognised risk.

1044 New information can be organised as follows:

- 1045 1. New information on important potential risks.
- 1046 2. New information on important identified risks.
- 1047 3. New information on other potential risks not categorised as important.
- 1048 4. New information on other identified risks not categorised as important.
- 1049 5. Update on ~~important~~ missing information.

1050 The focus of the evaluation(s) is on new information which has emerged during the reporting interval
1051 of the PSUR. This should be concise and interpret the impact, if any, on the understanding and
1052 characterisation of the risk. Where applicable, the evaluation will form the basis for an updated
1053 characterisation of important potential and identified risks in sub-section 16.4 (“Characterisation of
1054 risks”) of the report. It is recommended that the level of detail of the evaluation included in this sub-
1055 section should be proportional to the available evidence on the risk and its medical significance and
1056 public health relevance.

1057 The evaluation(s) of the new information and missing information update(s) can be included in this
1058 sub-section of the PSUR, or in an appendix. Each evaluation should include the following information as
1059 appropriate:

- 1060 • source of the new information;
- 1061 • background relevant to the evaluation;
- 1062 • method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- 1063 • results – a summary and critical analysis of the data considered in the risk evaluation;
- 1064 • discussion;
- 1065 • conclusion, including whether or not the evaluation supports an update of the characterisation of
1066 any of the important potential and identified risks in sub-section 16.4 (“Characterisation of risks”)

1067 Any new information on populations exposed or data generated to address previously missing
1068 information should be critically assessed in this sub-section. Unresolved concerns and uncertainties
1069 should be acknowledged.

1070 **VII.B.5.16.4. PSUR sub-section “Characterisation of risks”**

1071 This sub-section should characterise important identified and potential risks based on cumulative data
1072 (i.e. not restricted to the reporting interval), and describe ~~important~~ missing information.

1073 Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- 1074 • frequency;
- 1075 • numbers of cases (numerator) and precision of estimate, taking into account the source of the
1076 data;

- 1077 • extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of
- 1078 estimate;
- 1079 • estimate of relative risk and precision of estimate;
- 1080 • estimate of absolute risk and precision of estimate;
- 1081 • impact on the individual patient (effects on symptoms, quality or quantity of life);
- 1082 • public health impact;
- 1083 • patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal
- 1084 impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- 1085 • dose, route of administration;
- 1086 • duration of treatment, risk period;
- 1087 • preventability (i.e. predictability, ability to monitor for a “sentinel” adverse reaction or laboratory
- 1088 marker);
- 1089 • reversibility;
- 1090 • potential mechanism; and
- 1091 • strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

1092 When missing information could constitute an important risk, it should be included as a safety concern.

1093 The limitations of the safety database (in terms of number of patients studied, cumulative exposure or

1094 long term use, etc.) should be discussed.

1095 For PSURs for products with several indications, formulations, or routes of administration, where there

1096 may be significant differences in the identified and potential risks, it may be appropriate to present

1097 risks by indication, formulation, or route of administration. Headings that could be considered include:

- 1098 • risks relating to the active substance;
- 1099 • risks related to a specific formulation or route of administration (including occupational exposure);
- 1100 • risks relating to a specific population; [and](#)
- 1101 • risks associated with non-prescription use (for compounds that are available as both prescription
- 1102 and non-prescription products). ~~and~~

1103 **VII.B.5.16.5. PSUR sub-section: “Effectiveness of risk minimisation (if applicable)”**

1104 Risk minimisation activities are public health interventions intended to prevent the occurrence of an

1105 adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity

1106 should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an

1107 adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g.

1108 product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional

1109 Communication/educational materials).

1110 The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities

1111 relevant to the risk-benefit assessment [IR Art 34(3)].

1112 Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for

1113 important identified risks that has become available during the reporting interval should be

1114 summarised in this sub-section of the PSUR.

1115 Insights into the effectiveness of risk minimisation activities in any country or region that may have
1116 utility in other countries or -regions are of particular interest. Information may be summarised by
1117 region, if applicable and relevant.

1118 When required for reporting in a PSUR, results of evaluations that became available during the
1119 reporting interval, which refer to an individual region should be provided in the PSUR regional appendix
1120 (see VII.B.5.20. and VII.C.5.5.).

1121 **VII.B.5.17. PSUR section “Benefit evaluation”**

1122 PSUR sub-sections 17.1 (“Important baseline efficacy and effectiveness information”) and 17.2 (“Newly
1123 identified information on efficacy and effectiveness”) provide the baseline and newly identified benefit
1124 information that support the characterisation of benefit described in sub-section 17.3
1125 (“Characterisation of benefits”) that in turn supports the benefit-risk evaluation in section 18
1126 (“Integrated benefit-risk analysis for authorised indications”).

1127 **VII.B.5.17.1. PSUR sub-section “Important baseline efficacy and effectiveness information”**

1128 This sub-section of the PSUR summarises information on both efficacy and effectiveness of the
1129 medicinal product at the beginning of the reporting interval and provides the basis for the benefit
1130 evaluation. This information should relate to authorised indication(s) of the medicinal product listed in
1131 the reference product information (See VII.B.4.)-.

1132 For medicinal products with multiple indications, populations, and/or routes of administration, the
1133 benefit should be characterised separately by these factors when relevant.

1134 The level of detail provided in this sub-section should be sufficient to support the characterisation of
1135 benefit in the PSUR sub-section 17.3 (“Characterisation of benefits”) and the benefit-risk assessment
1136 in section 18 (“Integrated benefit-risk analysis for authorised indications”).

1137 **VII.B.5.17.2. PSUR sub-section “Newly identified information on efficacy and effectiveness”**

1138 For some products, additional information on efficacy or effectiveness in authorised indications may
1139 have become available during the reporting interval. Such information should be presented in this sub-
1140 section of the PSUR. For authorised indications, new information on efficacy and effectiveness under
1141 conditions of actual use should also be described in this sub-section, if available. New -information on
1142 efficacy and effectiveness in uses other than the authorised indications should not be included unless
1143 relevant for the benefit-risk evaluation in the authorised indications.

1144 Information on indications newly authorised during the reporting interval should also be included in
1145 this sub-section. The level of detail provided in this section should be sufficient to support the
1146 characterisation of benefit in sub-section 17.3 (“Characterisation of benefits”) and the benefit-risk
1147 assessment in section 18 (“Integrated benefit-risk analysis for authorised indications”).

1148 In this sub-section, particular attention should be given to vaccines, anti-infective agents or other
1149 medicinal products where changes in the therapeutic environment may impact on
1150 efficacy/effectiveness over time.

1151 **VII.B.5.17.3. PSUR sub-section “Characterisation of benefits”**

1152 This sub-section provides an integration of the baseline benefit information and the new benefit
1153 information that has become available during the reporting interval, for authorised indications.

1154 The level of detail provided in this sub-section should be sufficient to support the analysis of benefit-
1155 risk in section 18 (“Integrated benefit-risk analysis for authorised indications”).

1156 When there are no new relevant benefit data, this sub-section should provide a characterisation of the
1157 information in sub-section 17.1 (“Important baseline efficacy and effectiveness information”).

1158 When there is new positive benefit information and no significant change in the risk profile in this
1159 reporting interval, the integration of baseline and new information in this sub-section should be
1160 succinct.

1161 This sub-section should provide a concise but critical evaluation of the strengths and limitations of the
1162 evidence on efficacy and effectiveness, considering the following when available:

- 1163 • a brief description of the strength of evidence of benefit, considering comparator(s), effect size,
1164 statistical rigor, methodological strengths and deficiencies, and consistency of findings across
1165 trials/studies;
- 1166 • new information that challenges the validity of a surrogate endpoint, if used;
- 1167 • clinical relevance of the effect size;
- 1168 • generalisability of treatment response across the indicated patient population (e.g. information that
1169 demonstrates lack of treatment effect in a sub-population);
- 1170 • adequacy of characterization of dose-response;
- 1171 • duration of effect;
- 1172 • comparative efficacy; and
- 1173 • a determination of the extent to which efficacy findings from clinical trials are generalisable to
1174 patient populations treated in medical practice.

1175 **VII.B.5.18. PSUR section “Integrated benefit-risk analysis for authorised** 1176 **indications”**

1177 The marketing authorisation holder should provide in this PSUR section an overall appraisal of the
1178 benefit and risk of the medicinal product as used in clinical practice. Whereas sub-sections 16.4
1179 (“Characterisation of risks”) and 17.3 (“Characterisation of benefits”) present the risks and benefits,
1180 this section should provide a critical analysis and integration of the key information in the previous
1181 sections and should not simply duplicate the benefit and risk characterisation presented in the sub-
1182 sections mentioned above.

1183 ***VII.B.5.18.1. PSUR sub-section “Benefit-risk context - medical need and important*** 1184 ***alternatives”***

1185 This sub-section of the PSUR should provide a brief description of the medical need for the medicinal
1186 product in the authorised indications and summarised alternatives (medical, surgical or other;
1187 including no treatment).

1188 ***VII.B.5.18.2. PSUR sub-section “Benefit-risk analysis evaluation”***

1189 A risk-benefit balance is specific to an indication and population. Therefore, for products authorised for
1190 more than one indication, risk-benefit balances should be evaluated and presented by each indication
1191 individually. If there are important differences in the risk-benefit balance among populations within an
1192 indication, the benefit-risk evaluation should be presented by population, if possible.

1193 The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison
1194 of benefits and risks and should take into account the following points-:

1195 • Whereas previous sections/sub-sections should include all important benefit and risk information,
1196 not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore,
1197 the key benefits and risks considered in the evaluation should be specified. The key information
1198 presented in the previous benefit and risk section/sub-sections should be carried forward for
1199 integration in the benefit-risk evaluation.

1200 • Consider the context of use of the medicinal product: the condition to be treated, prevented, or
1201 diagnosed; its severity and seriousness; and the population to be treated (relatively healthy;
1202 chronic illness, rare conditions).

1203 • With respect to the key benefit(s), consider its nature, clinical importance, duration, and
1204 generalisability, as well as evidence of efficacy in non-responders to other therapies and alternative
1205 treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g.
1206 for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic
1207 progression of joint damage).

1208 • With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness,
1209 frequency, predictability, preventability, reversibility, impact on patients), and whether it arose
1210 from clinical trials in unauthorised indications or populations, off-label use, or misuse.

1211 • The strengths, weaknesses, and uncertainties of the evidence should be considered when
1212 formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact
1213 the evaluation. Limitations of the assessment should be discussed.

1214 Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk
1215 evaluation:

1216 • The assumptions, considerations, and judgement or weighting that support the conclusions of the
1217 benefit-risk evaluation should be clear.

1218 • If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of
1219 the methods should be included.

1220 • Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk
1221 evaluation.

1222 When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-
1223 risk analysis should be presented based on cumulative data-. Conversely, where little new information
1224 has become available during the reporting interval, the primary focus of the benefit-risk evaluation
1225 might consist of an evaluation of updated interval safety data.

1226 VII.B.5.19. PSUR section “Conclusions and actions”

1227 A PSUR should conclude with the implications of any new information that arose during the reporting
1228 interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for
1229 relevant subgroups, if appropriate.

1230 Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing
1231 authorisation holder should assess the need for changes to the reference product information and
1232 propose changes as appropriate.

1233 In addition and as applicable, the conclusions should include preliminary proposal(s) to optimise or
1234 further evaluate the risk-benefit balance for further discussion with the relevant competent
1235 authority(ies). This may include proposals for additional risk minimisation activities.

1236 For products with a pharmacovigilance or risk management plan, the proposals should also be
1237 considered for incorporation into the pharmacovigilance plan and/or risk minimisation plan, as
1238 appropriate (see Module V).

1239 Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing
1240 authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions,
1241 including implications for the approved summary of product characteristics (SmPC) for the product(s)
1242 for which the PSUR is submitted [IR Art 34(5)].

1243 Proposed changes to the reference product information should be described in this section of the PSUR.

1244 The regional appendix should include proposals for product information (SmPC and package leaflet)
1245 together with information on ongoing changes when applicable.

1246 VII.B.5.20. Appendices to the PSUR

1247 A PSUR should contain the following appendices as appropriate, numbered as follows:

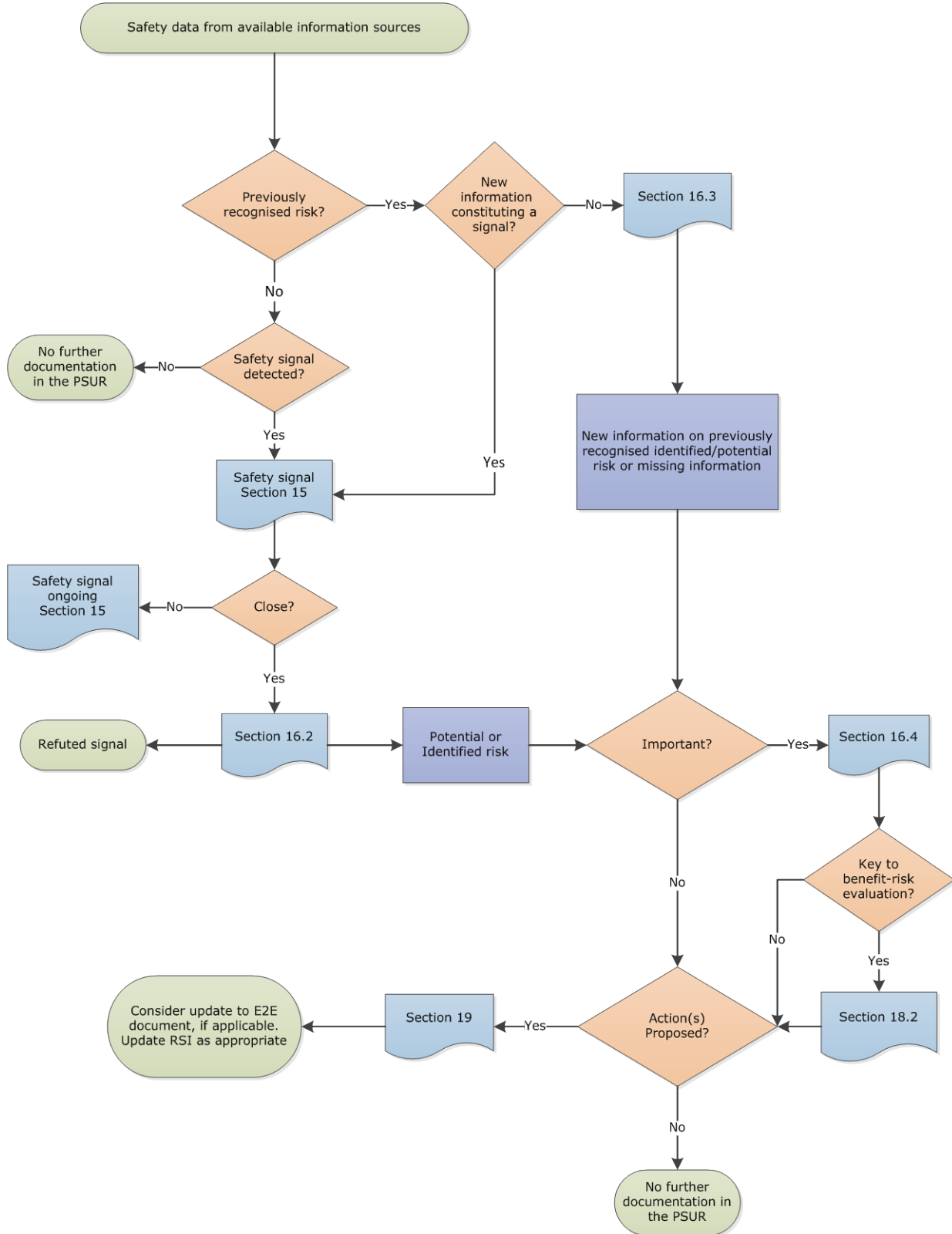
- 1248 1. Reference information (see VII.B.4.).
- 1249 2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and
1250 interval summary tabulations of serious and non-serious adverse reactions from post-marketing
1251 data sources.
- 1252 3. Tabular summary of safety signals (if not included in the body of the report)¹⁹.
- 1253 4. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional
1254 studies- with the primary aim of identifying, characterising, or quantifying a safety hazard or
1255 confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk
1256 management measures, in case of non-interventional studies.
- 1257 5. List of the sources of information used to prepare the PSUR (when desired by the marketing
1258 authorisation holder).
- 1259 6. Regional appendix:
1260 The requirements for the regional appendix in the EU are provided in section VII.C.5..
1261

¹⁹ It is preferred to include the tabulation of signals in the body of the PSUR, if feasible.

1262 **VII.B.5.21. Mapping signals and risks to PSUR sections/sub-sections**

1263 The following flowchart (Figure VII.1) reflects the general location for the presentation of information
 1264 on signals and risks within the PSUR.

1265 **Figure VII.1. PSUR Sections/subsections – signals and risks.**



1266

1267 **VII.B.6. Quality systems for PSURs at the level of marketing authorisation**
1268 **holders**

1269 Marketing authorisation holders should have in place structures and processes for the preparation,
1270 quality control, review and submission of PSURs including follow-up during and after their assessment.
1271 These structures and processes should be described by means of written policies and procedures in the
1272 marketing authorisation holder's quality system (see Module I).

1273 There are a number of areas in the pharmacovigilance process that can directly impact the quality of
1274 PSURs, some examples are case management of spontaneous and study reports, literature screening,
1275 signal management, additional pharmacovigilance and post-marketing research activities, procedures
1276 for integration of information on benefits and risks from all available data sources and maintenance of
1277 product information. The quality system should describe the links between the processes, the
1278 communication channels and the responsibilities with the aim of gathering all the relevant information
1279 for the production of PSURs. There should be documented procedures including quality control checks
1280 in place to check the accuracy and completeness of the data presented in the PSURs. In ensuring
1281 completeness of data, a documented template or plan for drawing data from various data sources
1282 could be developed. The importance of an integrated approach to benefit-risk evaluation should
1283 underpin processes and cross departmental input to PSUR preparation.

1284 The PSUR should also contain the assessment of specific safety issues requested **to be addressed in the**
1285 **PSUR** by competent authorities **(worldwide) in accordance with agreed timelines and procedures**. The
1286 marketing authorisation holder should have mechanisms in place to ensure that the requests made by
1287 competent authorities **(worldwide)** during the time of their PSUR assessment are properly addressed.

1288 The provision of the data included in the summary tabulations (see VII.B.5.6.) should undergo source
1289 data verification against the marketing authorisation holder's safety database to ensure accuracy of the
1290 number of events/reactions provided. The process for querying the safety database, the parameters
1291 used for the retrieval of the data and the quality control performed should be properly documented.

1292 An appropriate quality system should be in place in order to avoid failure to comply with PSUR
1293 requirements such as:

- 1294 • non-submission: complete non-submission of PSURs, submission outside the correct submission
1295 schedule or outside the correct time frames (without previous agreement with the competent
1296 authorities);
- 1297 • unjustified omission of information required by VII.B.5.;
- 1298 • poor quality reports: poor documentation or insufficient information or evaluation provided to
1299 perform a thorough assessment of the new safety information, signals, risk evaluation, benefit
1300 evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of
1301 standardised medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no
1302 reported risk factors in cumulative reviews;
- 1303 • submission of a PSUR where previous requests from competent authorities **(worldwide)** have not
1304 been addressed;
- 1305 • **failure to provide an explicit evaluation of the risk-benefit balance of the medicinal product;**
- 1306 • **failure to provide adequate proposals for the local authorised product information.**

1307 Any significant deviation from the procedures relating to the preparation or submission of PSURs
1308 should be documented and the appropriate corrective and preventive action should be taken. This
1309 documentation should be available at all times.

1310 When marketing authorisation holders are involved in contractual arrangements (e.g. licensor-
1311 licensee), respective responsibilities for preparation and submission of the PSUR to the competent
1312 authorities ~~(worldwide)~~ should be clearly specified in the written agreement.

1313 When the preparation of the PSUR is delegated to third parties, the marketing authorisation holder
1314 should ensure that they are subject to a quality system compliant with the current legislation. Explicit
1315 procedures and detailed agreements should exist between the marketing authorisation holder and third
1316 parties. The agreements may specifically detail the options to audit the PSUR preparation process.

1317 ***VII.B.7. Training of staff members related to the PSUR process***

1318 For all organisations, it is the responsibility of the person responsible for the pharmacovigilance system
1319 to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in
1320 the preparation, review, quality control, submission and assessment of PSURs are adequately qualified,
1321 experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and this GVP Module
1322 VII). When appropriate, specific training for the different processes, tasks and responsibilities relating
1323 to the PSUR should be in place.

1324 Training to update knowledge and skills should also take place as necessary.

1325 Training should cover legislation, guidelines, scientific evaluation and written procedures related to the
1326 PSUR process. Training records should demonstrate that the relevant training was delivered prior to
1327 performing PSUR-related activities.

1328 **VII.C. Operation of the EU network**

1329 ***VII.C.1. PSUR process in the EU - General process***

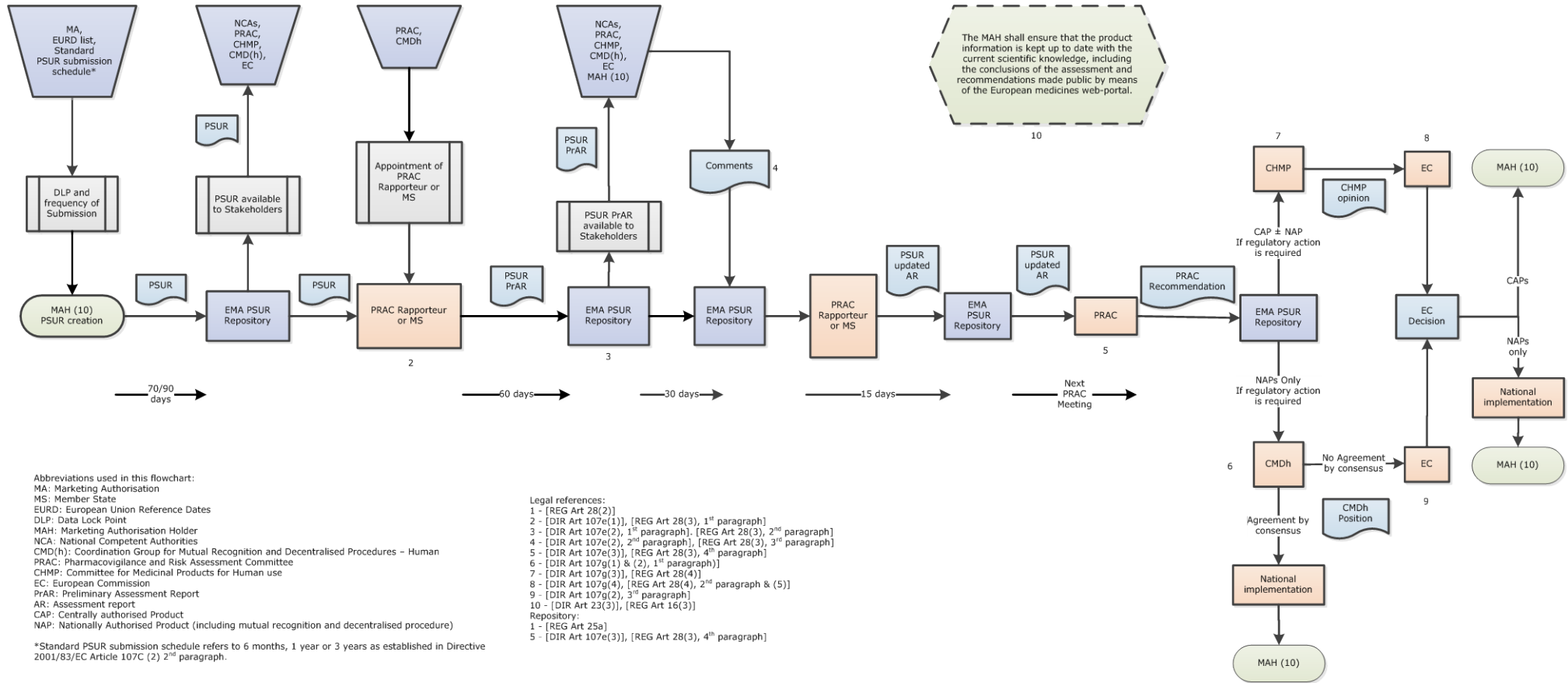
1330 The following flowchart (Figure VII.2.) reflects the general process cycle for the PSUR procedure at the
1331 EU level when recommendations by the PRAC are issued. This represents a high level cycle to outline
1332 the entire process, from the preparation of the report to the implementation of the European
1333 Commission decision/national actions when applicable. Different single steps in this flowchart are
1334 formed by intermediate steps further explained and developed in different sections in this Module.

1335

Figure VII.2. PSUR procedure - general process

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1343 **VII.C.2. Standard submission schedule of PSURs**

1344 Marketing authorisation holders for products authorised before 02 July 2012 (centrally authorised
1345 products) and 21 July 2012 (nationally authorised products) and for which the frequency and dates of
1346 submission of PSURs are not laid down as a condition to the marketing authorisation or determined
1347 otherwise in the list of Union reference dates, shall submit PSURs according to the following submission
1348 schedule (~~hereafter “standard” submission schedule~~)[REG 28(2), DIR Art 107c(2)]:

- 1349 • at 6 months intervals once the product is authorised, even if it is not marketed;
- 1350 • once a product is marketed, 6 monthly PSUR submission should be continued following initial
1351 placing on the market in the EU for 2 years, then once a year for the following 2 years and
1352 thereafter at 3-yearly intervals.

1353 **VII.C.3. List of European Union reference dates and frequency of**
1354 **submission of PSURs²⁰**

1355 **VII.C.3.1. Objectives of the EU reference dates list**

1356 The Agency shall make public a list of Union reference dates (hereinafter referred to as list of EU
1357 reference dates) and frequency of submission of PSURs by means of the European medicines web-
1358 portal [DIR Art 107c(7), REG Art 26(1)(g)].

1359 The objectives of the list of EU reference dates and frequency of submission of PSURs are:

- 1360 • Harmonisation of data lock point and frequency of submission of PSURs for the same active
1361 substance and combination of active substances:

1362 For medicinal products containing the same active substance or combination of active substances
1363 subject to different marketing authorisations, an EU reference date should be set up and the
1364 frequency and date of submission of PSURs harmonised in order to allow the preparation of a
1365 single assessment established in DIR Art 107e(1). Such information **should** be included in the list
1366 published by the Agency.

- 1367 • Optimisation of the management of PSURs and PSURs assessments within the EU:

1368 The list overrules the submission schedule described in DIR Art 107c(2)(b).

1369 For active substances or combinations of active substances included in the list, marketing
1370 authorisation holders shall vary, if applicable, the condition laid down in their marketing
1371 authorisations in order to allow the submission of PSURs in accordance to the frequency and
1372 submission date as indicated in the list [DIR 107c(4) to (7)].

1373 The periodicity is defined on the basis of a risk-based approach in order to prioritise the periodic
1374 re-evaluation of the risk-benefit balance of active substances in a way that best protects public
1375 health²⁰ [Directive 2010/84/EU Preamble Recital 23].

- 1376 • Single EU assessment and reassessment of the risk-benefit balance of an active substance based
1377 on all available safety data:

1378 The list enables the harmonisation of PSUR submissions for medicinal products containing the
1379 same active substance or the same combination of active substances.

²⁰ The initial EU reference dates list was adopted by the CHMP/CMDh following consultation of the PRAC in September 2012 and was published on 01 October 2012.

1380 A single EU PSUR assessment provides a mechanism for evaluating the totality of available data on
1381 the benefits and risks of an active substance or combination of active substances. The effective
1382 application of work sharing principles is important in avoiding duplication of efforts and in
1383 prioritising the use of limited resources in the best interests of European citizens.

1384 VII.C.3.2. Description of the EU reference dates list

1385 The Union reference date of medicinal products containing the same active substance or the same
1386 combination of active substances shall be [DIR Art 107c(5)]:

- 1387 • the date of the first marketing authorisation in the EU of a medicinal product containing that active
1388 substance or that combination of active substances; or
- 1389 • if the date of first marketing authorisation cannot be ascertained, the earliest of the known dates
1390 of the marketing authorisations for a medicinal product containing that active substance or that
1391 combination of active substances.

1392 The list of EU reference dates and frequency of submission of PSURs consists of a comprehensive list of
1393 substances and combinations of active substances in alphabetical order, for which PSURs, where
1394 required, shall be submitted in accordance with the EU reference date and the frequency as
1395 determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination
1396 Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation
1397 with the Pharmacovigilance ~~and~~ Risk Assessment Committee (PRAC) [DIR Art 107c(4) and (6)]. The
1398 list should be updated in line with the “list of all medicinal products for human use authorised in the
1399 Union” as referred to in REG Art 57(1)(b).

1400 The EU reference dates list should contain the following information:

- 1401 • the EU reference dates;
- 1402 • the frequencies of submission of PSURs;
- 1403 • the data lock points of the next submissions of PSURs;
- 1404 • the date of publication (on the European Medicines web-portal) of the frequency for PSURs
1405 submission and data lock point for each active substance and combination of active substances.
1406 Any change to the dates of submission and frequency on PSURs specified in the marketing
1407 authorisation shall take effect 6 months after the date of such publication [DIR Art 107c(7)].

1408 Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU
1409 single assessment procedure (see VII.C.3.3.) such as:

- 1410 • whether or not it should cover all the indications of the substance or combination of active
1411 substances;
- 1412 • whether or not it should cover all the formulations/routes of administration of the products
1413 containing a substance or combination of active substances;
- 1414 • whether generic, well-established use, traditional herbal and homeopathic medicinal products shall
1415 submit a PSUR due to a request from a competent authority or due to concerns relating to
1416 pharmacovigilance data or due to the lack of PSURs relating to an active substance after the
1417 marketing authorisation has been granted [DIR Art 107c(2) second subparagraph] (see
1418 VII.C.3.3.2.).

1419

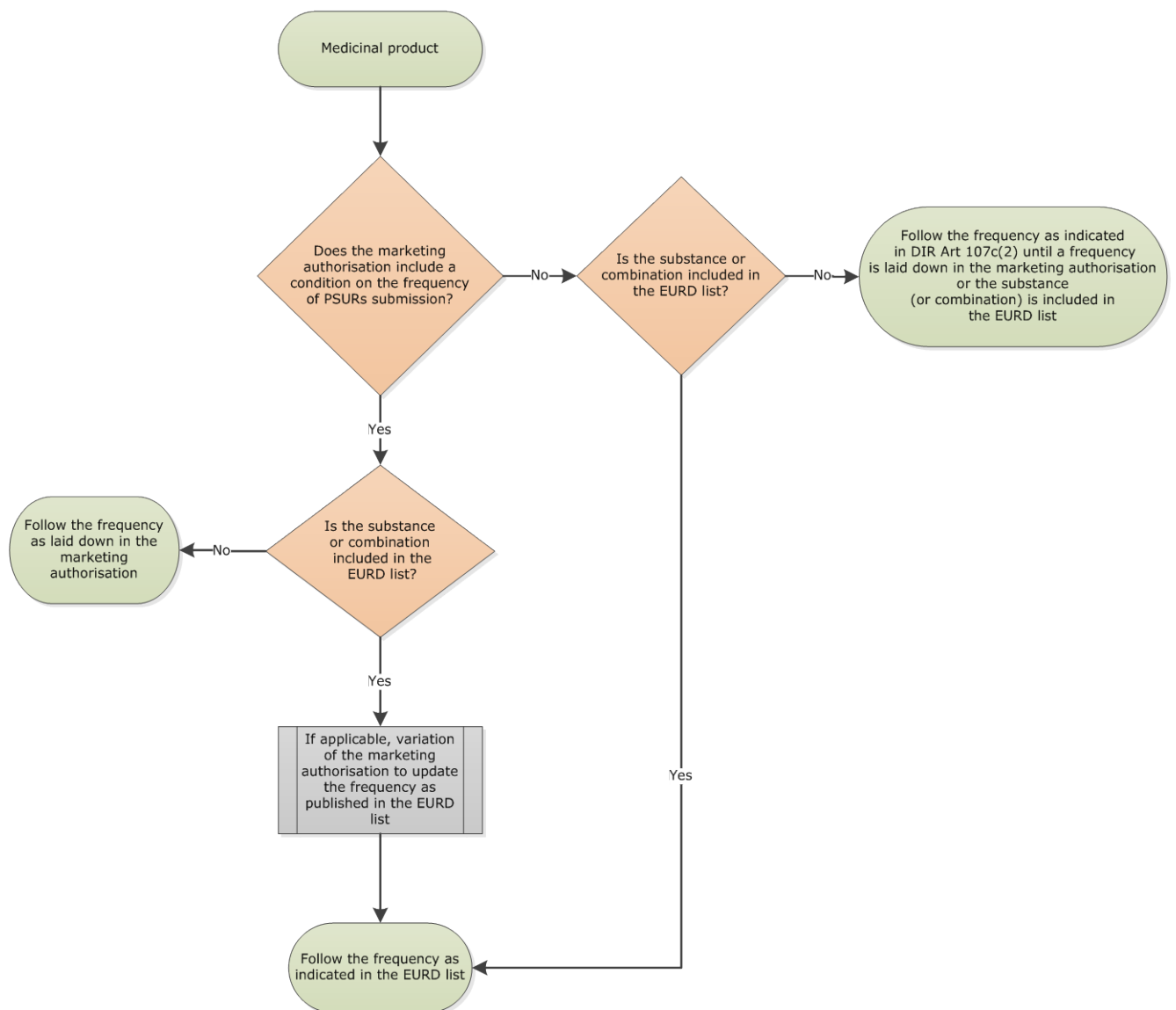
1420 **VII.C.3.3. Application of the list of EU reference dates to submission of**
1421 **PSURs**

1422 **VII.C.3.3.1. Submission of PSURs for medicinal products: general requirement**

1423 Figure VII.3. presents the various potential scenarios for the submission of a PSUR as a general
1424 requirement.

1425 **Figure VII.3. Conditions for PSURs submission as general requirement**

1426



1427

1428 The data lock points included in the list of EU reference dates enable the synchronisation of PSURs
1429 submission for products subject to different marketing authorisations and permit the EU single
1430 assessment. These data lock points are fixed on a certain date of the month, and should be used to
1431 determine the submission date (which has legal status) of the PSUR. Marketing authorisation holders
1432 can request to amend those dates in accordance with section VII.C.3.5.2.

1433 Unless otherwise specified in the list of EU reference dates and frequency of submission, or agreed with
1434 competent authorities in Member States or the Agency, as appropriate, a single PSUR shall be
1435 prepared for all medicinal products containing the same active substance and authorised for one
1436 marketing authorisation holder. The PSUR shall cover all indications, routes of administration, dosage
1437 forms and dosing regimens, irrespective of whether authorised under different names and through
1438 separate procedures. Where relevant, data relating to a particular indication, dosage form, route of
1439 administration or dosing regimen shall be presented in a separate section of the PSUR and any safety
1440 concerns shall be addressed accordingly [IR Art 34(6)].

1441 For medicinal products containing an active substance or a combination of active substances not
1442 included in the EU reference dates list, PSURs shall be submitted according to the PSUR frequency
1443 defined in the marketing authorisation or if not specified, in accordance with the submission schedule
1444 specified in DIR Art 107c(2) and REG Art 28(2).

1445 **VII.C.3.3.2. Submission of PSURs for generic, well-established use, traditional herbal and** 1446 **homeopathic medicinal products**

1447 By way of derogation, generics (authorised under DIR Art 10(1)), well-established use (authorised
1448 under DIR Art 10a), homeopathic (authorised under DIR Art 14) and traditional herbal (authorised
1449 under DIR Art 16a) medicinal products are exempted from submitting PSURs except in the following
1450 circumstances [DIR Art 107b(3)]:

- 1451
- the marketing authorisation provides for the submission of PSURs as a condition;
 - PSURs is (are) requested by a competent authority in a Member State on the basis of concerns
1452 relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after
1453 the marketing authorisation has been granted (e.g. when the “reference” medicinal product is no
1454 longer marketed). The assessment reports of the requested PSURs shall be communicated to the
1455 PRAC, which shall consider whether there is a need for a single assessment report for all marketing
1456 authorisations for medicinal products containing the same active substance and inform the CMDh
1457 or CHMP accordingly, in order to apply the procedures laid down in DIR Art 107c(4) and 107e.
1458

1459 In order to facilitate and optimise the PSUR EU single assessment process, to avoid duplications of
1460 requests for PSURs and to provide transparency and predictability for the marketing authorisation
1461 holders, the legislative provision laid down in DIR 107b(3)(b) is applied by specifying in the list of EU
1462 reference dates, the substances for which PSURs for generic, well-established use, traditional herbal
1463 and homeopathic medicinal products are required. This specification is based on the request made by a
1464 competent authority in a Member State during the creation or maintenance of the list of EU reference
1465 dates and on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs
1466 relating to an active substance.

1467 The harmonised frequency for the submission of the reports and the EU reference dates are
1468 determined by the CHMP and/or CMDh after consultation of the PRAC.

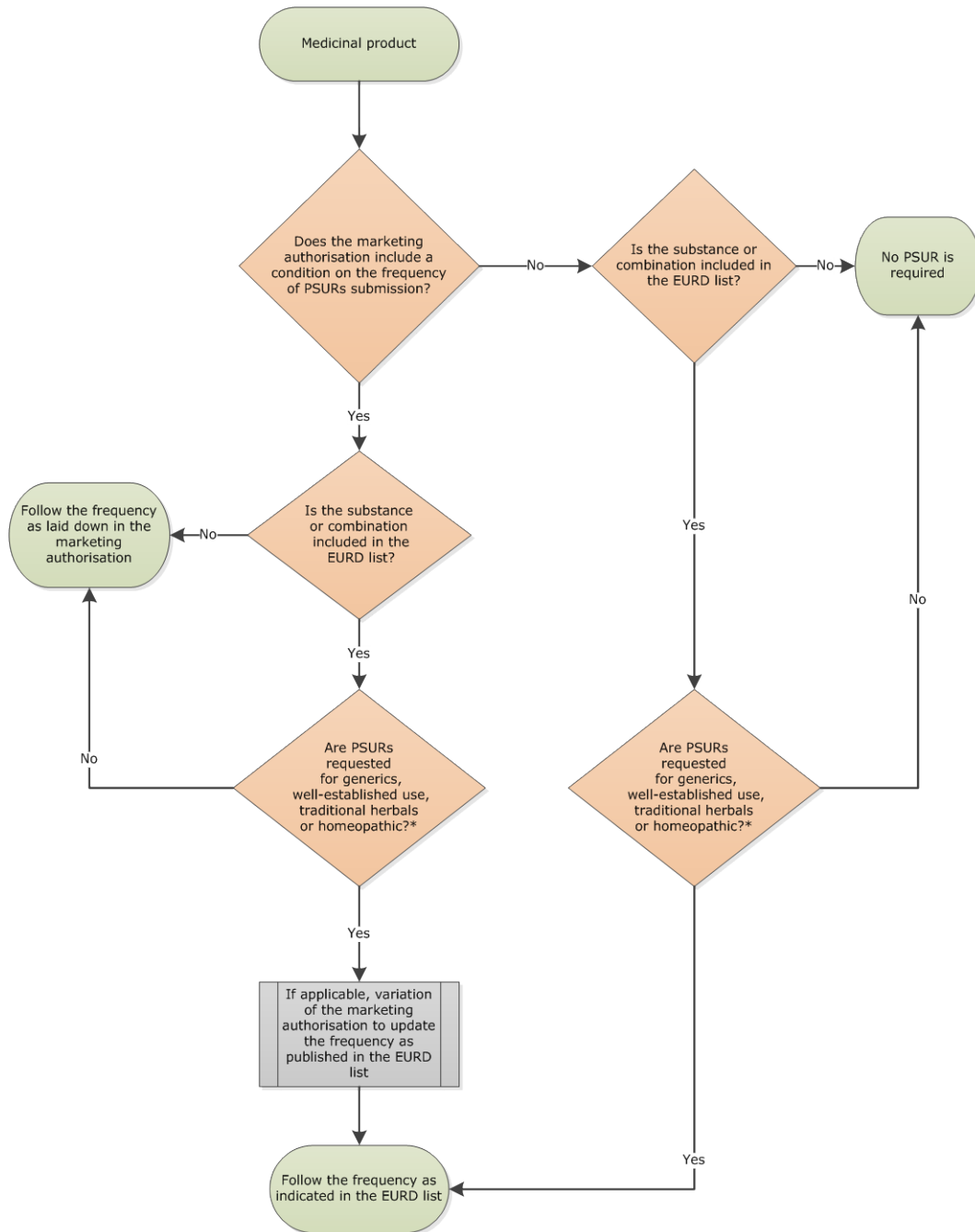
1469 The application of the list of EU reference dates for the submission of PSURs for generic, well-
1470 established use, traditional herbal and homeopathic medicinal products does not undermine the right
1471 of a competent authority in a Member State to request the submission of PSURs at any time under the
1472 provision laid down in [DIR Art 107c(2) second subparagraph].

1473 For products where PSURs are no longer required to be submitted routinely, it is expected that
 1474 marketing authorisation holders will continue to evaluate the safety of their products on a regular basis
 1475 and report any new safety information that impacts on the risk-benefit balance or the product
 1476 information (See Module VI and Module IX).

1477 Figure VII.4. presents the various potential scenarios as regard the submission of a PSUR for generic,
 1478 well-established use, traditional herbal and homeopathic medicinal products:

1479 **Figure VII.4. Conditions for PSURs submission for generic, well-established use, traditional herbal**
 1480 **and homeopathic medicinal products**

1481



* Whether marketing authorisation holders for generics, well-established use, traditional herbal and homeopathic medicinal products are requested to submit PSURs following a request of a competent authority in a Member State due to concerns relating to pharmacovigilance data or lack of PSUR submission.

1482

1483 **VII.C.3.3.3. Submission of PSURs for fixed dose combination products**

1484 Unless otherwise specified in the list of EU reference dates and frequency of submission, if the
1485 substance that is the subject of the PSUR is also authorised as a component of a fixed combination
1486 medicinal product, the marketing authorisation holder shall either submit a separate PSUR for the
1487 combination of active substances authorised for the same marketing authorisation holder with cross-
1488 references to the single-substance PSUR(s), or provide the combination data within one of the single-
1489 substance PSURs [IR Art 34(7)].

1490 **VII.C.3.3.4. Submission of PSURs on demand of a competent authority in a Member State**

1491 Marketing authorisation holders shall submit PSURs immediately upon request from a competent
1492 authority in a Member State [DIR Art 107c(2)]. To facilitate the EU assessment and avoid duplication
1493 of requests, the competent authorities in the Member States should normally make use of the list of EU
1494 reference dates to request the submission of PSURs, however in especial circumstances competent
1495 authorities in Member States can directly request the submission of a PSUR. When the timeline for
1496 submission has not been specified in the request, marketing authorisation holders should submit the
1497 PSUR within 90 calendar days of the data lock point.

1498 **VII.C.3.4. Criteria used for defining the frequency of submission of PSURs**

1499 When deviating from the PSUR submission schedule defined in DIR Art 107c(2)(b), the frequencies of
1500 submission of PSURs and the corresponding data lock points should be defined on a risk-based
1501 approach by the CHMP where at least one of the marketing authorisations concerned has been granted
1502 in accordance with the centralised procedure or by the CMDh otherwise, after consultation with the
1503 PRAC.

1504 The following prioritisation criteria should be taken into account when defining the frequency of
1505 submission for a given active substance or combination of active substances:

- 1506 • information on risks or benefits that may have an impact on the public health;
- 1507 • new product for which there is limited safety information available to date (includes pre- and post-
1508 authorisation experiences);
- 1509 • significant changes to the product (e.g. new indication has been authorised, new pharmaceutical
1510 form or route of administration broadening the exposed patient population);
- 1511 • vulnerable patient populations/poorly studied patient populations, ~~important~~-missing information
1512 (e.g. children, pregnant women) while these populations are likely to be exposed in the post-
1513 authorisation setting;
- 1514 • signal of/potential for misuse, medication error, risk of overdose or dependency;
- 1515 • the size of the safety database and exposure to the medicinal product;
- 1516 • medicinal products subjected to additional monitoring.

1517 Any change in the criteria listed above for a given active substance or combination of active substances
1518 may lead to an amendment of the list of EU reference dates (e.g. increase of the frequency for PSUR
1519 submission).

1520 **VII.C.3.5. Maintenance of the list of EU reference dates**

1521 **VII.C.3.5.1. General principles**

1522 The maintenance of the list of EU reference dates should facilitate regulatory responsiveness to public
1523 health concerns identified within the EU and therefore the list will be subject to changes to reflect the
1524 decisions taken (e.g. by the Agency's committees following signal detection).

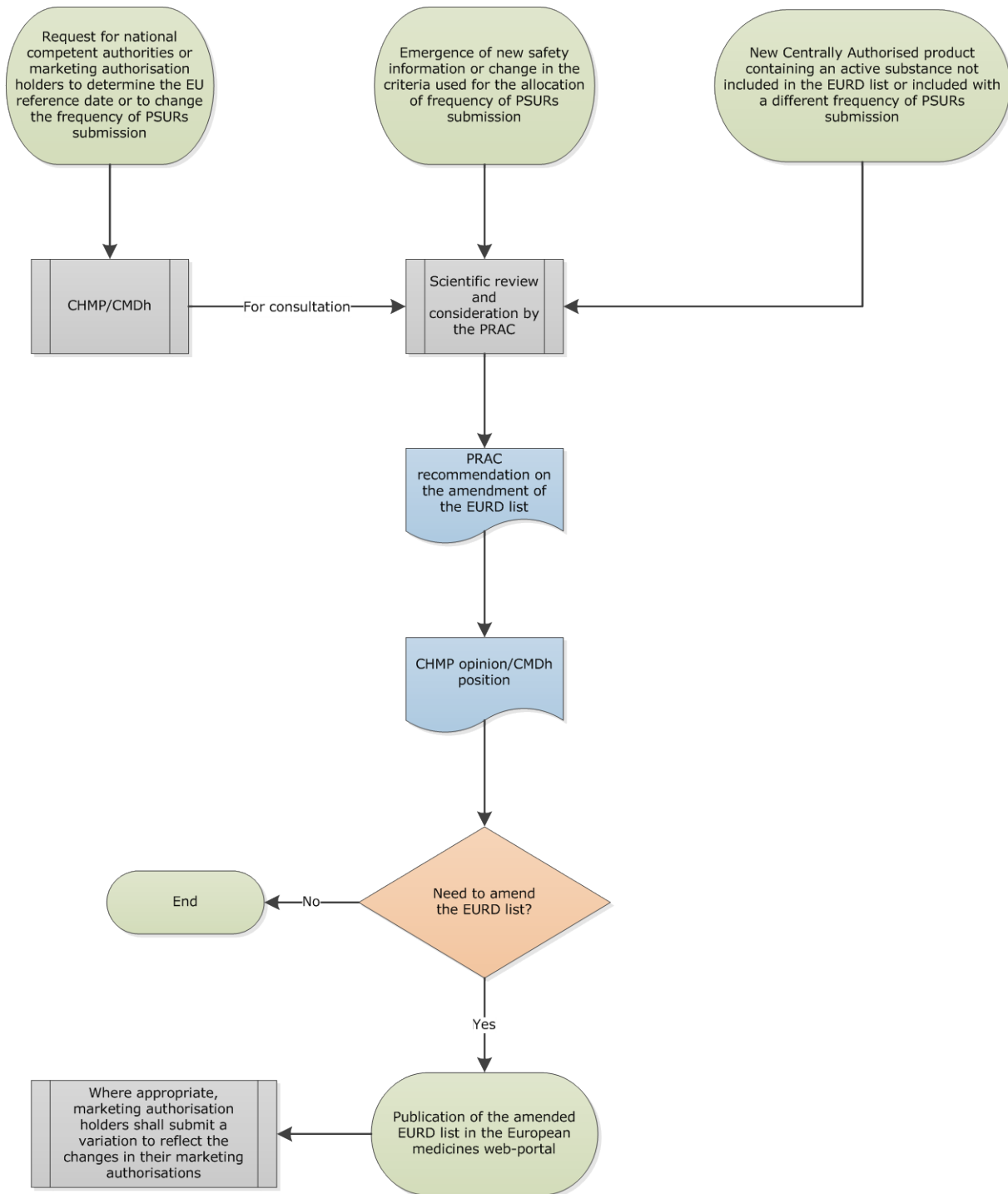
1525 The information included in the list such as the active substances and combinations of active
1526 substances, the frequencies of submission of PSURs and data lock points may need to be updated
1527 when considered necessary by the CHMP or CMDh after consultation with the PRAC. Changes to the list
1528 may be applied on one of the following grounds:

- 1529 • emergence of new information that might have an impact on the risk-benefit balance of the active
1530 substances or combinations of active substances, and potentially on public health;
- 1531 • any change in the criteria used for the allocation of frequency for PSUR submission and defined
1532 under VII.C.3.4.;
- 1533 • a request from the marketing authorisation holders as defined under DIR Art 107c(6);
- 1534 • active substance newly authorised.

1535 Figure VII.5. provides a general overview of the maintenance of the list of EU reference dates and
1536 frequency of submission of PSURs.

1537
1538

Figure VII.5. Maintenance of the list of EU reference dates and frequency of submission of PSURs



1539
1540

1541 **VII.C.3.5.2. Requests from marketing authorisation holders to amend the list of EU**
1542 **reference dates**

1543 Marketing authorisation holders shall be allowed to submit a request to the CHMP or the CMDh, as
1544 appropriate, to determine the Union reference dates or to change the frequency of submission of
1545 PSURs on one of the following grounds [DIR Art 107c(6)]:

- 1546 • for reasons relating to public health;
- 1547 • in order to avoid a duplication of the assessment;
- 1548 • in order to achieve international harmonisation.

1549 The request and its grounds should be considered by the PRAC and the CHMP if it concerns at least one
1550 marketing authorisation granted in accordance with the centralised procedure or the CMDh otherwise,
1551 which will either approve or deny the request.

1552 The list will then be amended accordingly when appropriate and published on the European medicines
1553 web-portal (see section VII.C.3.6.).

1554 For details about how to submit requests for amendments to the list, refer to the EU reference dates
1555 cover note and the related template published on the European medicines web-portal²¹

1556 **VII.C.3.6. Publication of the list**

1557 Upon its establishment and adoption by the CHMP and CMDh following PRAC consultation, the list of EU
1558 reference dates and frequency of submission of PSURs is published on the European medicines web-
1559 portal.

1560 In case of amendments, the updated list should be published following its adoption by the CHMP or the
1561 CMDh. It is expected to be updated monthly.

1562 **VII.C.3.7. Amendment of the marketing authorisation according to the list**
1563 **of EU reference dates**

1564 Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six
1565 months after the date of the publication on the European medicines web-portal. Where appropriate,
1566 marketing authorisation holders shall submit the relevant variation in order to reflect the changes in
1567 their marketing authorisation [DIR 107c(6)], unless the marketing authorisation contains a direct cross
1568 reference to the list of EU reference dates. ~~Where appropriate, marketing authorisation holders shall~~
1569 ~~submit the relevant variation in order to reflect the new information in their marketing authorisations~~
1570 ~~[DIR 107c(6)].~~

1571 **VII.C.4. Processes for PSUR Assessment in the EU network**

1572 The competent authorities in the Member States shall assess PSURs to determine whether there are
1573 new risks or whether risks have changed or whether there are changes to the risk-benefit balance of
1574 the medicinal product [DIR Art 107d].

1575 For purely nationally authorised medicinal products authorised in one Member State, the assessment of
1576 PSURs is conducted by the competent authority in the Member State where the product is authorised
1577 (see VII.C.4.1.).

²¹ <http://www.emea.europa.eu>

1578 For medicinal products authorised in more than one Member State, ~~(i.e. centrally authorised products,~~
1579 ~~products authorised through the mutual recognition and decentralised procedures)~~ and for medicinal
1580 ~~products subject to different national marketing authorisations~~ containing the same active substance or
1581 the same combination of active substances whether or not held by the same marketing authorisation
1582 holders and for which the frequency and dates of submission of PSURs have been harmonised in the
1583 list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation
1584 from the PRAC in accordance with the procedure described in VII.C.4.2.1. and VII.C.4.2.2..

1585 Further to assessment of the PSUR and opinion from the CHMP or position from the CMDh, as
1586 applicable, following the recommendation from the PRAC, the competent authorities in Member States,
1587 or the European Commission for centrally authorised products, shall take the necessary measures to
1588 vary, suspend or revoke the marketing authorisation(s), in accordance with outcome of the
1589 assessment [DIR Art 107g(2)] [REG Art 28(4) and (5)] (see VII.C.4.2.3. and VII.C.4.2.4.).

1590 The outcome of the PSUR assessment results in a legally binding decision or position in case of any
1591 action to vary, suspend, revoke the marketing authorisations of the medicinal products containing the
1592 concerned active substance or combination of active substances, on the basis of the position of the
1593 CMDh or the opinion of the CHMP following the recommendations from the PRAC. Furthermore,
1594 marketing authorisation holders are reminded of their obligation to keep their marketing authorisation
1595 up to date in accordance with REG Art 16(3) and DIR Art 23(3). The recommendations are therefore
1596 implemented in a harmonised and timely manner for all products within the scope of the procedure
1597 across the EU.

1598 Amendments to the SmPC, package leaflet and labelling as a result of the PSUR assessment should be
1599 implemented without subsequent variation submission for centrally authorised products and through
1600 the appropriate variation for nationally authorised products, including those authorised through the
1601 mutual recognition and decentralised procedures.

1602 When the proposals for the product information include new adverse reactions in section 4.8
1603 (“Undesirable effects”) of the SmPC, or modifications in the description, frequency and severity of the
1604 existing reactions, marketing authorisation holders should provide in the relevant sections of the –PSUR
1605 detailed appropriate information to allow the adequate description and classification of the frequency of
1606 the adverse reactions. If other sections of the SmPC (e.g. SmPC section 4.4 “Special warnings and
1607 precautions for use”) are considered to be updated, clear proposals should be provided for the
1608 competent authorities in the Member States to consider during the PSUR assessment²². The proposals
1609 should be included in the PSUR regional appendix (VII.C.5.).

1610 Harmonisation of the entire product information in all the Member States where the product is
1611 authorised is not one of the objectives of the PSUR assessment procedure. Instead, the outcome of the
1612 assessment should incorporate the new safety warnings and key risk minimisation recommendations,
1613 arising from the assessment of the data in the PSUR, to be included in the relevant sections of the
1614 product information.

1615 VII.C.4.1. PSURs for purely nationally authorised medicinal products

1616 It is the responsibility of the competent authority in the Member State where the product is authorised
1617 to evaluate the PSURs for these medicinal products and the assessment is conducted in accordance
1618 with the national legislation.

1619 Listings of individual cases may be requested in the context of the PSUR assessment procedure for
1620 adverse reactions of special interest and should be provided by the marketing authorisation holder

²² See “Guideline on Summary of Product Characteristics” as published on the Website of the European Commission in the Notice to Applicants, Volume 2C: <http://ec.europa.eu/health/files/eudralex>

1621 within an established timeframe to be included in the request. This may be accompanied by a request
1622 for an analysis of [individual cases safety reports, \(-classified as non-serious including information on](#)
1623 [numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases\), where](#)
1624 [necessary for the scientific evaluation. Information on the context or rationale for the request should](#)
1625 [generally be provided.](#)

1626 -

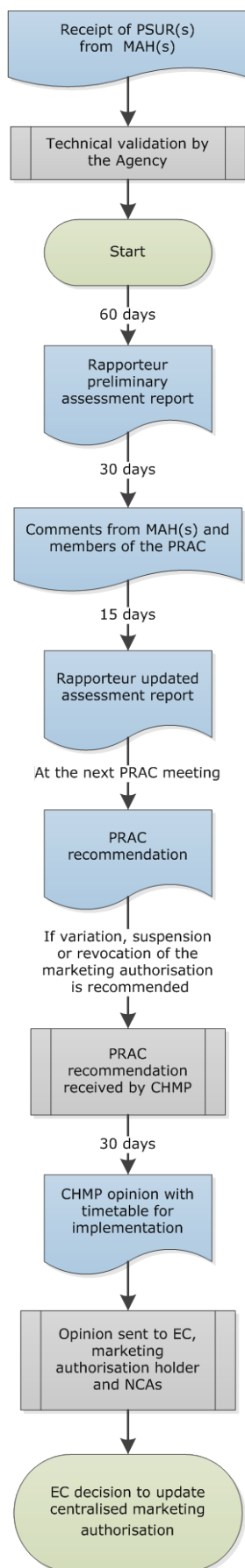
1627 Following the assessment of PSURs, the competent authority in the Member State should consider
1628 whether any action concerning the marketing authorisation for the medicinal product concerned is
1629 necessary. They should vary, suspend or revoke the marketing authorisation **when applicable**
1630 according to the appropriate procedure at national level.

1631 The assessment report and conclusions of the competent authority in the Member State should be
1632 provided to the marketing authorisation holder.

1633 **VII.C.4.2. Medicinal products authorised in more than one Member State**

1634 ***VII.C.4.2.1. Assessment of PSURs for a single centrally authorised medicinal product***

1635 This section describes the assessment of PSURs where only one centrally authorised medicinal product
1636 is involved according to the procedure set up in Article 28 of Regulation (EC) No 726/2004 (see figure
1637 [VII.6.](#)).



1640 The assessment of PSURs for a single centrally authorised medicinal product is coordinated by the
1641 Agency and shall be conducted by a Rapporteur appointed by the PRAC [REG Art 28(3)] (hereinafter
1642 referred to as "PRAC Rapporteur").

1643 Upon receipt, the Agency should perform a technical validation of the report to ensure that the PSUR
1644 application is in a suitable format.

1645 Listings of individual cases from EudraVigilance database may be retrieved to support the PSUR
1646 assessment.

1647 Further to the above verifications, the ~~Agency acknowledges receipt of the report and starts the~~
1648 procedure starts in accordance with the official starting dates published on the Agency's website. The
1649 ~~submission deadlines and~~ detailed procedural timetables are published as a generic calendar on the
1650 Agency's website.

1651 The published timetables identify the submission, start and finish dates of the procedures as well as
1652 other interim dates/milestones that occur during the procedure.

1653 During the assessment, additional listings of individual cases may be requested by the PRAC
1654 Rapporteur through the Agency, for adverse reactions of special interest and should be provided by the
1655 marketing authorisation holder(s) within an established timeframe to be included in the request. This
1656 may be accompanied by a request for an analysis of individual cases safety reports, (including
1657 information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious
1658 cases), where necessary for the scientific evaluation. Information on the context or rationale for the
1659 request should generally be provided. ~~eases classified as non-serious.~~

1660 During the drafting of the assessment report, the PRAC Rapporteur shall closely collaborate with the
1661 CHMP Rapporteur [REG Art 28(3)].

1662 The PRAC Rapporteur shall prepare an assessment report and send it to the Agency and to the
1663 members of the PRAC [REG Art 28(3)] within 60 days of the start of the procedure.

1664 The Agency shall send the PRAC Rapporteur's preliminary assessment report to the marketing
1665 authorisation holder [REG Art 28(3)].

1666 By Day 90, the marketing authorisation holder and members of the PRAC may send comments on the
1667 PRAC Rapporteur's preliminary assessment report to the Agency and the PRAC Rapporteur. Those
1668 comments should also include responses to outstanding issues or questions raised by the PRAC
1669 Rapporteur in the preliminary assessment report and which can be addressed within the timeframe of
1670 the comments phase.

1671 Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG
1672 Art 28(3)] within 15 days (i.e. by Day 105). The updated assessment report is made available to the
1673 members of the PRAC and should be forwarded to the marketing authorisation holder by the Agency.

1674 An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation
1675 holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new
1676 contraindication, a restriction of the indication or a reduction of the recommended dose.

1677 The PRAC shall adopt the updated assessment report with or without further changes at its next
1678 meeting [REG Art 28(3)], together with a recommendation on the maintenance of the marketing
1679 authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC
1680 recommendation may also highlight the need to conduct a post-authorisation safety study, request an
1681 update of the RMP, ~~review of safety issues and/or~~ close monitoring of events of interest.

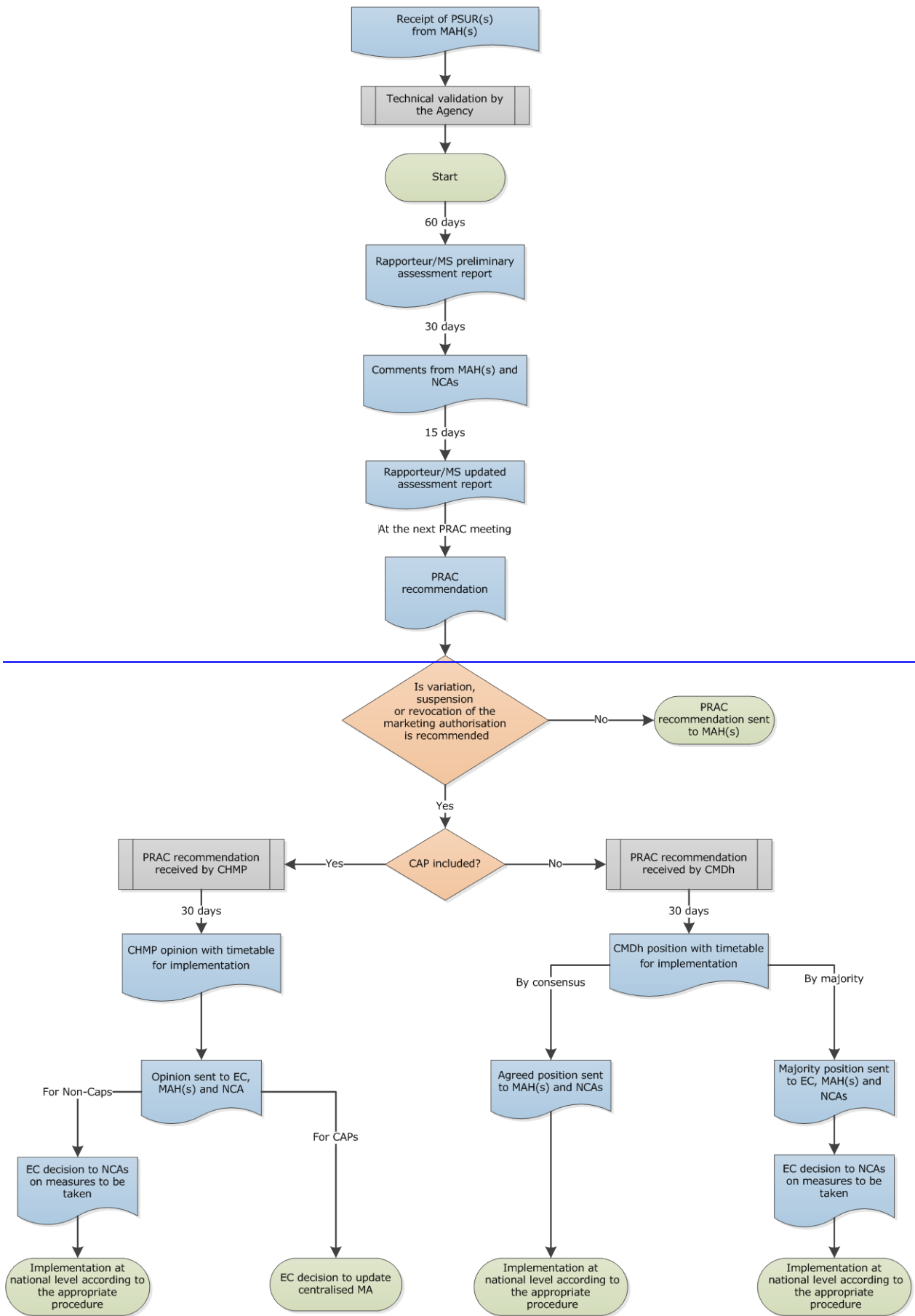
1682 Divergent positions of PRAC members and the grounds on which they are based shall be reflected in
1683 the recommendation issued by the PRAC [REG Art 28(3)].

1684 The Agency shall include the PRAC recommendation and adopted assessment report in the repository,
1685 and forward both to the marketing authorisation holder [REG Art 28(3)].

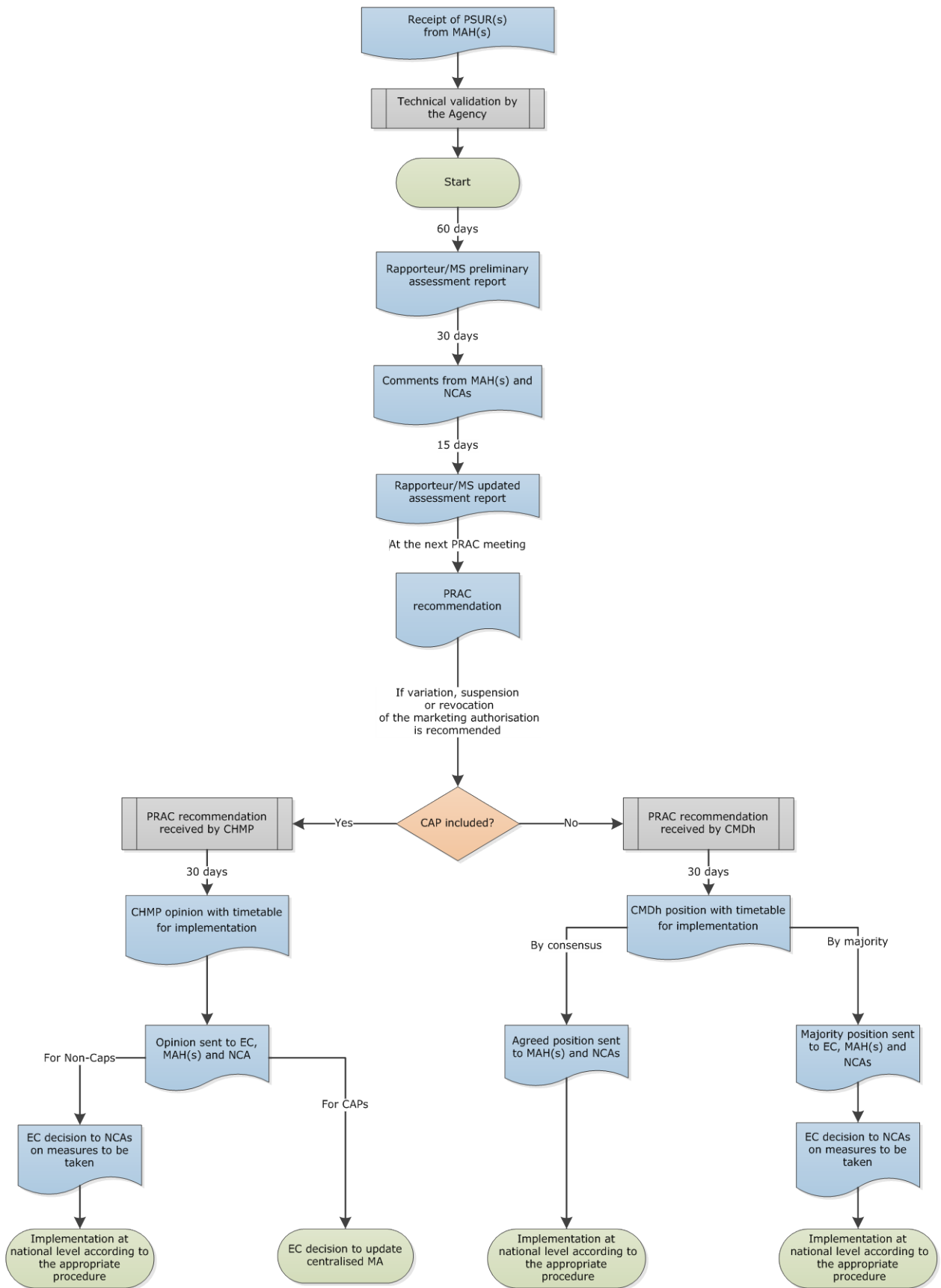
1686 Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the
1687 assessment report and PRAC recommendation are sent to the CHMP for adoption of an opinion for the
1688 centrally authorised product concerned as described in VII.C.4.2.3..

1689 ***VII.C.4.2.2. Assessment of PSURs for medicinal products subject to different marketing***
1690 ***authorisations containing the same active substance (EU single assessment)***

1691 This section describes the assessment of PSURs for medicinal products subject to different marketing
1692 | authorisations, [authorised in more than one Member State](#), containing the same active substance or
1693 | the same combination of active substances whether or not held by the same marketing authorisation
1694 | holder and for which the frequency and dates of submission of PSURs have been harmonised in the list
1695 | of EU reference dates. This could include a mixture of centrally authorised products, products
1696 | authorised through the mutual recognition, ~~and~~ decentralised [and national](#) procedures, ~~and purely~~
1697 | [nationally authorised products](#) [DIR Art 107e to 107g] (so-called PSUR “EU single assessment”
1698 | procedure).



1700



1701

1702

1703 The assessment of PSURs for medicinal products, also called “EU single assessment”, shall be
 1704 conducted by [DIR Art 107e(1)]:

1705 • a “Member State” appointed by the CMDh where none of the marketing authorisations concerned
1706 has been granted in accordance with the centralised procedure;

1707 • a “Rapporteur” appointed by the PRAC, where at least one of the marketing authorisations
1708 concerned has been granted in accordance with the centralised procedure (hereinafter referred to
1709 as “PRAC Rapporteur”).

1710 The PSUR EU single assessment procedure is coordinated by the Agency. Upon receipt, the Agency
1711 should perform a technical validation of the reports to ensure that the PSURs applications are in a
1712 suitable format.

1713 Upon establishment of the list of all medicinal products for human use authorised in the EU referred to
1714 in REG Art 57, the Agency should ensure that all marketing authorisation holder(s) of the given
1715 substance have submitted PSUR(s), as required. In the event where a PSUR has not been submitted,
1716 the Agency should contact the concerned marketing authorisation holder(s). However, this will not
1717 preclude the start of the single assessment procedure for other PSUR(s) of the same active substance.

1718 Listings of individual cases from EudraVigilance database may be retrieved to support the PSURs
1719 assessment.

1720 Further to the above verifications, the ~~Agency acknowledges receipt of the report(s) and starts the~~
1721 procedure [starts](#) in accordance with the official starting dates published on the Agency’s website. The
1722 ~~submission deadlines and full procedural~~ detailed [procedural](#) timetables are published as a generic
1723 calendar on the Agency’s website.

1724 The published timetables identify the submission, start and finish dates of the procedures as well as
1725 other interim dates/milestones that occur during the procedure.

1726 Further to the start of procedure, the PRAC Rapporteur or Member State conducts the single
1727 assessment of all PSURs submitted for the given active substance.

1728 During the assessment, additional listings of individual cases may be requested by the PRAC
1729 Rapporteur or Member State through the Agency for adverse drug reactions of special interest and
1730 should be provided by the marketing authorisation holder(s) within an established timeframe to be
1731 included in the request. This may be accompanied by a request for an analysis of [individual cases](#)
1732 [safety reports, \(including information on numbers of cases, details of fatal cases and as necessary,](#)
1733 [analysis of non-serious cases\), where necessary for the scientific evaluation. Information on the](#)
1734 [context or rationale for the request should generally be provided. ~~eases classified as non-serious~~](#)

1735
1736 The PRAC Rapporteur or Member State shall prepare an assessment report and send it to the Agency
1737 and to the Member States concerned [DIR Art 107e(2)] within 60 days of the start of the procedure.
1738 This preliminary assessment report should be circulated to the members of the PRAC.

1739 The Agency shall send the PRAC Rapporteur’s/Member State preliminary assessment report to the
1740 concerned marketing authorisation holder(s) [DIR Art 107e(2)]. [This assessment report should be](#)
1741 [circulated amongst all the marketing authorisation holders whose medicinal product\(s\) are part of the](#)
1742 [EU single assessment.](#)

1743 By Day 90, the marketing authorisation holder(s), Member States and members of the PRAC as
1744 applicable may send comments on the PRAC Rapporteur’s/Member State’s preliminary assessment
1745 report to the Agency and the PRAC Rapporteur/Member State, as applicable. **Those comments should**
1746 **also include responses to outstanding issues or questions raised by the PRAC Rapporteur/Member**
1747 **State in the preliminary assessment report and which can be addressed within the timeframe of the**
1748 **comments phase.**

1749

1750 Following receipt of comments, the PRAC Rapporteur/Member State shall prepare an updated
1751 assessment report [DIR Art 107e (3)] within 15 days (i.e. by Day 105). The updated assessment
1752 report is forwarded to the members of the PRAC [and should be circulated by the Agency amongst all](#)
1753 [the marketing authorisation holders whose medicinal product\(s\) are part of the EU single assessment.](#)

1754 An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation
1755 holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new
1756 contraindication, a restriction of the indication or a reduction of the recommended dose.

1757 The PRAC shall adopt the updated assessment report with or without further changes at its next
1758 meeting [DIR Art 107e(3)], together with a recommendation on maintenance of the marketing
1759 authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC
1760 recommendation may also highlight the need to conduct a post-authorisation safety study (see Module
1761 VIII), request an update of the RMP (see Module V), review of safety issue and/or close monitoring of
1762 events of interest.

1763 Divergent positions of PRAC members and the grounds on which they are based shall be reflected in
1764 the recommendation issued by the PRAC [DIR Art 107e(3)].

1765 The Agency shall include the PRAC recommendation and adopted assessment report in the repository,
1766 and forward both to the marketing authorisation holder(s) [DIR Art 107e(3)].

1767 Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the
1768 assessment report and PRAC recommendation are sent to:

- 1769 • the CHMP where at least one centrally authorised product is included in the single assessment, for
1770 adoption of an opinion as described in VII.C.4.2.3.;
- 1771 • the CMDh where no centrally authorised product is included in the single assessment, for
1772 agreement of a position as described in VII.C.4.2.4..

1773 **VII.C.4.2.3. Single assessment including at least one centrally authorised product leading to**
1774 **a CHMP opinion**

1775 The CHMP acknowledges receipt of the PRAC recommendation and assessment report, in case of any
1776 regulatory action, at their next meeting following the PRAC adoption. Within 30 days from receipt, the
1777 CHMP shall consider the PRAC assessment report and recommendation and adopt an opinion on the
1778 maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned [DIR
1779 107g(3)].

1780 An oral explanation to the CHMP can be held at the request of the CHMP or the marketing authorisation
1781 holder(s) only in case of differences with the PRAC recommendation where CHMP considers the
1782 possibility of adopting an opinion on the suspension or revocation of the marketing authorisation(s), a
1783 new contraindication, a restriction of the indication or a reduction of the recommended dose.

1784 The opinion will contain the following:

- 1785 • the final assessment report and recommendation adopted by the PRAC;
- 1786 • detailed explanation of the scientific grounds for differences with the PRAC recommendation, if
1787 applicable [DIR Art 107g(3)];
- 1788 • in the case of a CHMP opinion to vary the marketing authorisation(s):

- 1789 – the scientific conclusions and grounds recommending the variation to the terms of the
1790 marketing authorisation;
- 1791 – for centrally authorised products, revised product information and if applicable, conditions
1792 imposed to the marketing authorisation holder and where appropriate, the conditions or
1793 restrictions imposed to the Member States for the safe and effective use of the medicinal
1794 product, in accordance with the provision provided in DIR Art 127a;
- 1795 – for nationally authorised products, including those authorised through the mutual recognition
1796 and decentralised procedures, an annex indicating the new safety warnings and key risk
1797 minimisation recommendations to be included in the relevant sections of the product
1798 information as applicable.
- 1799 • in the case of a CHMP opinion to suspend the marketing authorisation(s), the scientific conclusions
1800 together with the grounds for suspension and conditions for lifting the suspension;
- 1801 • in the case of a CHMP opinion to revoke the marketing authorisation(s), the scientific conclusions
1802 together with the grounds for revocation;
- 1803 • divergent positions of CHMP members, where applicable.
- 1804 Further to adoption, the Agency should send the CHMP opinion together with its annexes and
1805 appendices to the European Commission, marketing authorisation holder(s) and competent authorities
1806 in Member States.
- 1807 The final assessment conclusions and recommendations are published in the European medicines web-
1808 portal (VII.C.7.).
- 1809 **a. Post CHMP opinion - Centrally authorised products**
- 1810 Where the CHMP opinion states that the terms of the marketing authorisation(s) needs to be varied,
1811 the marketing authorisation holder(s) of centrally authorised products should provide the translations
1812 of the product information [and the scientific conclusions and grounds recommending the variation to](#)
1813 [the terms of the marketing authorisation](#), in all EU official languages, in accordance with the translation
1814 timetable adopted by the CHMP.
- 1815 Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing
1816 authorisation is necessary, the European Commission shall adopt a decision addressed to marketing
1817 authorisation holders to vary, suspend or revoke the marketing authorisation(s) of centrally authorised
1818 product(s) [DIR Art 107g(4b)].
- 1819 Further to adoption, the European Commission should notify the decisions amending the terms of the
1820 marketing authorisation of centrally authorised products to the marketing authorisation holder(s).
- 1821 **b. Post CHMP opinion - Nationally authorised products, including those authorised through**
1822 **the mutual recognition and decentralised procedures**
- 1823 Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing
1824 authorisations is necessary, the European Commission shall adopt a decision addressed to the
1825 competent authorities in Member States concerning the measures to be taken [DIR Art 107g(a)] in
1826 respect of nationally authorised products, including those authorised through the mutual recognition
1827 and decentralised procedures.
- 1828 Further to the receipt of the decision from the European Commission, the competent authorities in
1829 Member States shall take the necessary measures to vary, suspend or revoke the marketing
1830 authorisation(s) within 30 days [DIR Art 107g(4)].

1831 **VII.C.4.2.4. Single assessment not including centrally authorised product leading to a CMDh**
1832 **position**

1833 The CMDh acknowledges receipt of the PRAC recommendation and assessment report, in case of any
1834 regulatory action, at their next meeting following the PRAC adoption.

1835 Within 30 days from receipt, the CMDh shall consider the PRAC assessment report and
1836 recommendation and reach a position on the maintenance, variation, suspension, revocation of the
1837 marketing authorisation(s) concerned [DIR Art 107g(1)].

1838 An oral explanation to the CMDh can be held at the request of the CMDh or the marketing
1839 authorisation holder(s), only in case of differences with the PRAC recommendation where the CMDh
1840 considers the possibility to reach a position on the suspension or revocation of the marketing
1841 authorisation(s), a new contraindication, a restriction of the indication or a reduction of the
1842 recommended dose.

1843 The position will contain the following:

- 1844 • the final assessment report and recommendation adopted by the PRAC;
- 1845 • detailed explanation of the scientific grounds for differences with the PRAC recommendation, if
1846 applicable [DIR Art 107g(2)];
- 1847 • in the case of a CMDh position to vary the marketing authorisation(s), the scientific conclusions
1848 and grounds recommending the variation to the terms of the marketing authorisation and -an
1849 annex indicating the new safety warnings and key risk minimisation recommendations to be
1850 included in the relevant sections of the product information, as applicable;
- 1851 • in the case of a CMDh position to suspend the marketing authorisation(s), the scientific conclusions
1852 together with the grounds for suspension and conditions for lifting the suspension;
- 1853 • in the case of a CMDh position to revoke the marketing authorisation(s), the scientific conclusions
1854 together with the grounds for revocation;
- 1855 • divergent position(s) for the CMDh members, where applicable.

1856 The final assessment conclusions and recommendations shall be published by the Agency in the
1857 European medicines web-portal [DIR Art 107I] (VII.C.7.).

1858 If the CMDh position is reached by consensus:

1859 The position agreed including the action to be taken is recorded by the chairperson in the minutes of
1860 the CMDh meeting where agreed.

1861 The chairman shall send the agreed CMDh position [DIR Art 107g(2)] and its appendices to the
1862 marketing authorisation holder(s) and competent authorities in Member States.

1863 Further to receipt of the CMDh position stating that regulatory action to the concerned marketing
1864 authorisation is necessary, the competent authorities in Member States shall adopt necessary
1865 measures to vary, suspend or revoke the marketing authorisation(s) concerned in accordance with the
1866 timetable for implementation determined in the agreed position [DIR Art 107g(2)].

1867 In case the position of the CMDh agreed that variation to the terms of marketing authorisation is
1868 required, the marketing authorisation holder(s) shall submit the relevant variation to that effect within
1869 the timetable for implementation [DIR Art 107g(2)] as appended to the agreed position.

1870 If the CMDh position is reached by majority vote:

1871 The majority position on the action to be taken is recorded by the chairman in the minutes of the
 1872 CMDh meeting where agreed.

1873 The majority position of the CMDh together with its annexes and its appendices, including translations
 1874 in all EU official languages where applicable, shall be forwarded to the European Commission [DIR Art
 1875 107g(2)]. The position of the CMDh should also be forwarded to the competent authorities in Member
 1876 States.

1877 Further to receipt of a CMDh position stating that regulatory action to the concerned marketing
 1878 authorisation is necessary, the European Commission shall adopt decision(s) [DIR Art 107g(2)]
 1879 addressed to the competent authorities in Member States in order for them to vary, suspend or revoke
 1880 the marketing authorisation(s) of nationally authorised product(s) which is addressed to marketing
 1881 authorisation holders.

1882 Further to receipt of the decision from the European Commission, the competent authorities in Member
 1883 States shall take the necessary measures to maintain, vary, suspend or revoke the marketing
 1884 authorisation(s) within 30 days [DIR Art 107g(2)].

1885 **VII.C.4.3. Relationship between PSUR and risk management plan**

1886 The general relationship between the risk management plan (RMP) and the PSUR is described in
 1887 **Module V**, while an overview of the common RMP/PSUR modules is provided in **VII.C.4.3.1**.

1888 During the preparation of a PSUR, the marketing authorisation holder should consider whether any
 1889 identified or potential risks discussed within the PSUR is important and requires an update of the RMP.
 1890 In these circumstances, updated **revised** RMP including the new important safety concern should be
 1891 submitted with the PSUR and assessed in parallel, following the timetable for the assessment of PSUR
 1892 as described above.

1893 If important safety concerns are identified **by the national competent authorities in the Member States**
 1894 during the assessment of a PSUR and no updated RMP or no RMP has been submitted,
 1895 recommendations should be made to submit an update or a new RMP within a defined timeline.

1896 **VII.C.4.3.1. PSUR and risk management plan – common modules**

1897 The proposed modular formats for the PSUR and the RMP aim to address duplication and facilitate
 1898 flexibility by enabling common PSUR/RMP sections to be utilised interchangeably across both reports.
 1899 Common sections with the above mentioned reports are identified in Table VII.1.:

1900 **Table VII.1.** Common sections between PSUR and RMP

PSUR section	RMP section
Section 3 – “Actions taken in the reporting interval for safety reasons”	Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”
Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”	Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation exposure”
Sub-section 16.1 – “Summary of safety concerns”	Part II, module SVIII – “Summary of the safety concerns” (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)
Sub-section 16.4 – “Characterisation of risks”	Part II, Module SVII – “Identified and potential

PSUR section	RMP section
	risks”
Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”	Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”

1901 **VII.C.5. EU-specific requirements for periodic safety update reports**

1902 The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR
 1903 detailed in VII.B.5. shall be based on all available data, including data from clinical trials in
 1904 unauthorised indications and populations according to the provisions of DIR Art 107b and IR Art 34(1).

1905 The EU-specific requirements should be included in the PSUR EU regional appendix.

1906 **VII.C.5.1. PSUR EU regional appendix, sub-section “Proposed product**
 1907 **information”**

1908 The assessment of the need for amendments to the product information is incorporated within the
 1909 PSUR assessment procedure in the EU. The regulatory opinion/position should include
 1910 recommendations for updates to product information where needed. Marketing authorisation holders
 1911 should provide the necessary supportive documentation and references within the PSUR [or in this](#)
 1912 [appendix](#) to facilitate this.

1913 Within the PSUR, the marketing authorisation holder is required to consider the impact of the data and
 1914 evaluations presented within the report, on the marketing authorisation. Based on the evaluation of
 1915 the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw
 1916 conclusions in the PSUR as to the need for changes and/or actions, including implications for the
 1917 approved SmPC(s) for the product(s) for which the PSUR is submitted [IR Art 34 (5)].

1918 In this sub-section, the marketing authorisation holder should provide the proposals for product
 1919 information (SmPC and package leaflet) based on the above mentioned evaluation. These should be
 1920 based on all EU authorised indications.

1921 A track change version of the proposed SmPCs and package leaflets based on the assessment and
 1922 conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed
 1923 product information should also be submitted to Module 1.3.1 of the Electronic Common Technical
 1924 Document (eCTD).

1925 All the SmPCs and packages leaflets covered by the PSUR [and in effect at the data lock point](#), should
 1926 be reviewed to ensure that they reflect the appropriate information according [ly](#) to the cumulative data
 1927 included and analysed in the PSUR.

1928 Amendments to the product information should not be postponed or delayed until the PSUR submission
 1929 and amendments not related to the information presented in the PSUR, should not be proposed within
 1930 the PSUR procedure. It is the obligation of the marketing authorisation holder to submit a variation in
 1931 accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a marketing
 1932 authorisation.

1933 [A brief description of ongoing procedures \(e.g. variations\) to update the product information should be](#)
 1934 [provided in this section.](#)

1935 ~~VII.C.5.2. PSUR EU regional appendix, sub-section “reference information comparison”~~

1936 In this sub-section, the marketing authorisation holder should highlight any important differences
1937 between the reference information in use and the proposals for product information in the EU.
1938 Examples of important differences may be those relating to adverse drug reactions, contraindications,
1939 warnings, interactions and overdose. For the purposes of this comparison, the reference information in
1940 effect at the end of the reporting interval may be used but the marketing authorisation holder should
1941 highlight any important changes proposed/introduced in the time period between the data lock point
1942 and submission of the PSUR.

1943 **VII.C.5.2. PSUR EU regional appendix, sub-section “Proposed additional** 1944 **pharmacovigilance and risk minimisation activities”**

1945 Considering the provision established in IR Art 34 (5), this sub-section should include proposals for
1946 additional pharmacovigilance and additional risk minimisation activities based on the conclusions and
1947 actions of the PSUR, including a statement of the intention to submit a RMP or an updated RMP when
1948 applicable.

1949 **VII.C.5.3. PSUR EU regional appendix, sub-section “Summary of ongoing** 1950 **safety concerns”**

1951 In order to support the information provided in the PSUR section 16.1 “Summary of safety concerns”
1952 (see VII.B.5.16.1.), Table 1.10 (according to the current RMP template) “Summary – Ongoing safety
1953 concerns” should be included in this PSUR sub-section. This table should be extracted from the version
1954 of RMP available at the beginning of the PSUR reporting interval (see Module V).

1955 **VII.C.5.4. PSUR EU regional appendix, sub-section “Reporting of results** 1956 **from post-authorisation safety studies”**

1957 Findings from both interventional and non-interventional (for further guidance see Module VIII) post-
1958 authorisation safety studies (PASS) should be reported in the PSUR. While the marketing authorisation
1959 holder should inform competent authorities in Member States and the Agency as applicable about any
1960 new information that may impact on the risk-benefit balance immediately, the PSUR should provide
1961 comprehensive information on the findings of all PASS, both interventional and non-interventional, in
1962 PSUR sections 7 and 8 respectively.

1963 Final study reports for studies conducted with the primary aim of identifying, characterising or
1964 quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the
1965 effectiveness of risk management measures which were completed during the reporting interval should
1966 also be included as an annex to the PSUR. For such studies discontinued during the reporting interval,
1967 the reasons for stopping the study should also be explained.

1968 If an important safety concern has been identified in the course of a study, regardless of whether it
1969 has been detected through pre-specified methods and whether the study is considered a PASS, the
1970 marketing authorisation holder and specifically the qualified person responsible for pharmacovigilance
1971 (QPPV) will have informed the relevant competent authorities in Member States immediately.

1972 PSURs should not be used as the initial communication method either for the submission of final study
1973 reports to the competent authorities in Member States or for the notification of any new information
1974 that might influence the evaluation of the risk-benefit balance.

1975 **VII.C.5.5. PSUR EU regional appendix, sub-section “Effectiveness of risk**
1976 **minimisation”**

1977 Risk minimisation activities are public health interventions intended to prevent the occurrence of an
1978 adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity
1979 should it occur. The success of risk minimisation activities in delivering these objectives needs to be
1980 evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is
1981 minimised and hence the overall risk-benefit balance is optimised. In accordance with section
1982 VII.B.5.16.5., evaluation of broad global experience should be reflected in the body of the report, when
1983 provides insights into the effectiveness of risk minimisation activities in any country or region that may
1984 have utility in other countries or regions are of particular interest.

1985 This sub-section should additionally provide an evaluation of the effectiveness of routine and/or
1986 additional risk minimisation activities specifically relevant to an EU context. This should take account of
1987 regulatory imposed obligations for implementation of risk minimisation measures in addition to the
1988 overall requirement for monitoring of safety and benefit-risk. Results of any studies to assess the
1989 impact or other formal assessment(s) of risk minimisation activities in the EU should be included when
1990 available. As part of this critical evaluation, the marketing authorisation holder should make
1991 observations on factors contributing to the success or weakness of risk minimisation activities. If a
1992 particular risk minimisation strategy proves ineffective, then alternative activities need to be put in
1993 place. In certain cases, it may be judged that risk minimisation cannot control the risks to the extent
1994 possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn
1995 either from the market or restricted to those patients in whom the benefits outweigh the risks. More
1996 extensive guidance on monitoring the effectiveness of risk minimisation activities is included in Module
1997 XVI. As a principle, the marketing authorisation holder should distinguish in their evaluation between
1998 implementation success and attainment of the intended outcome.

1999 **VII.C.6. Quality systems and record management systems for PSURs in the**
2000 **EU network**

2001 **VII.C.6.1. Quality systems and record management systems at the level of**
2002 **the marketing authorisation holder**

2003 Specific quality system procedures and processes shall be in place in order to ensure the update of
2004 product information by the marketing authorisation holder in the light of scientific knowledge, including
2005 the assessments and recommendations made public via the European medicines web-portal, and on
2006 the basis of a continuous monitoring by the marketing authorisation holder of information published on
2007 the European medicines web-portal [IR Art 11(1)(f)].

2008 It is the responsibility of the marketing authorisation holder to check regularly the list of EU reference
2009 dates and frequency of submission published in the European medicines web-portal to ensure
2010 compliance with the PSUR reporting requirements for their medicinal products (see VII.C.3.).

2011 Systems should be in place to schedule the production of PSURs according to:

- 2012 • the list of EU reference dates and frequency of PSURs submission; or
- 2013 • the conditions laid down in the marketing authorisation; or
- 2014 • the standard PSUR submission schedule established according to DIR Art 107c(2) for products
2015 authorised before 2 July 2012 (for centrally authorised products) and 21 July 2012 (for nationally
2016 authorised products) as applicable (without any conditions in their marketing authorisation or not

2017 included in the list of EU references dates and frequency of submission or not affected by the
2018 derogation established in [DIR Art 107b(3)]; or

- 2019 • ad hoc requests for PSURs by a competent authority in a Member State or the Agency.

2020 For those medicinal products where the submission of an RMP is not required, the marketing
2021 authorisation holder should maintain on file a specification of important identified risks, important
2022 potential risks and ~~important~~ missing information in order to support the preparation of the PSURs.

2023 The marketing authorisation holder should have procedures in place to follow the requirements
2024 established by the Agency for the submission of PSURs.

2025 The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system
2026 [DIR Art 104(e)] and therefore should ensure that the pharmacovigilance system in place enables the
2027 compliance with the requirements established for the production and submission of PSURs. In relation
2028 to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities
2029 of the QPPV in relation to PSURs should include:

- 2030 • ensuring the necessary quality, including the correctness and completeness, of the data submitted
2031 in the PSURs;
- 2032 • ensuring full response according to the timelines and within the procedure agreed (e.g. next PSUR)
2033 to any request from the competent authorities in Member States and the Agency related to PSURs;
- 2034 • awareness of the PSUR and assessment report conclusions, PRAC recommendations, CHMP
2035 opinions, CMDh positions and European Commission decisions in order to ensure that appropriate
2036 action takes place.

2037 The record retention times for product-related documents in Module I also apply to PSURs and source
2038 documents related to the creation of PSURs, including documents related to actions taken for safety
2039 reasons, clinical trials and post-authorisation studies, relevant benefit information and documents
2040 utilised for the calculation of patient exposure.

2041 **VII.C.6.2. Quality systems and record management systems at the level of** 2042 **the European Medicines Agency**

2043 The application of the Agency's quality system (see Module I) should support compliance by the
2044 Agency when fulfilling its tasks and responsibilities for the management of PSUR procedures and EU
2045 single assessments.

2046 The Agency should have in place a process to technically validate the completeness of PSUR
2047 submissions.

2048 Line listings and summary tabulations from the EudraVigilance database utilised to support the PSUR
2049 assessment **should** be created using reports by means of the EudraVigilance data analysis system.

2050 Effective communication and circulation of PSURs and related documents is crucial for the successful
2051 completeness of the procedure; therefore processes have to be in place for the circulation of
2052 documents between the Agency, marketing authorisation holders, the Commission and the competent
2053 authorities in Member States. Where applicable, the procedures **should** establish the necessity for
2054 quality checks with the aim to remove any information of a personal or commercially confidential
2055 nature.

2056 **Written procedures should reflect the different steps to follow for the maintenance of the** list of EU
2057 references dates and frequency of submission of PSURs published by the Agency in the European
2058 medicines web-portal (see VII.C.3.).

2059 Prior to the publication of summaries of PSUR assessment reports in the European medicines web-
2060 portal (see VII.C.7.) the appropriate personnel at the Agency should adhere to the procedures
2061 established for web publication of documents produced by the Agency or competent authorities in the
2062 Member States.

2063 All records related to PSURs created by the Agency's staff members, experts or consultants are the
2064 property of the Agency and all PSURs and related documents received are in the custody of the
2065 Agency. Both types of PSURs records (created or received by the Agency) are subject to the Agency's
2066 overall control via the PSUR repository set up according to the provisions laid down in REG Art 25a.

2067 The Agency's policy on records management (EMA/590678/2007)²³, provides the basis for a
2068 consistent, sustainable and efficient records management program and it has been developed in
2069 accordance with the commonly recognised international standard for records management, "ISO
2070 15489-1:2001 Information and documentation – Records management²⁴". According to the records
2071 classification stated by the Agency's policy, PSURs would be considered business, legal, evidential and
2072 research/historical value records.

2073 The record retention times for product-related documents in Module I also apply to PSUR- system
2074 related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs,
2075 assessment reports, the data retrieved from the EudraVigilance database or other data used to support
2076 the PSUR assessment).

2077 **VII.C.6.3. Quality systems and record management systems at the level of** 2078 **the competent authorities in Member States**

2079 Each competent authority in the Member States shall have in place a pharmacovigilance system [DIR
2080 Art 101] for the surveillance of medicinal products and for receipt and evaluation of all
2081 pharmacovigilance data including PSURs. For the purpose of operating its tasks relating to PSURs in
2082 addition to the pharmacovigilance system the national competent authorities in Member States should
2083 implement a quality system (see Module I).

2084 Competent authorities in the Member States should monitor marketing authorisation holders for
2085 compliance with regulatory obligations for PSURs. Additionally, competent authorities should exchange
2086 information in cases of non-compliance and take appropriate regulatory actions as required.

2087 No PSUR assessment at EU level is foreseen for purely nationally authorised products authorised in
2088 only one Member State; therefore the national competent authority in the Member State where the
2089 medicinal product is authorised should have procedures in place for the assessment of PSURs related
2090 to those medicinal products.

2091 The procedures established by the national competent authorities in Member States for the
2092 performance of the EU single assessment of PSURs, should be in line with the procedures established
2093 by the Agency for the coordination of PSUR assessment in the EU regulatory network (see VII.C.4.).
2094 These procedures should establish effective communication across the EU regulatory network and the
2095 actions to be taken regarding the variation, suspension or revocation of the marketing authorisation
2096 following the PRAC recommendations, CHMP opinion, CMDh position and European Commission
2097 decision as applicable.

2098 The procedures established by the Agency for the use of the PSUR repository to support the single
2099 assessment, should be followed by the national competent authorities in Member States.

²³ www.ema.europa.eu

²⁴ www.iso.org

2100 Where tasks related to PSUR procedures are delegated to third parties, the national competent
2101 authorities in Member States should ensure that they are subject to a quality system in compliance
2102 with the obligations provided by the European legislation.

2103 The record retention times for product-related documents in **Module I** also apply to PSUR- system
2104 related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs,
2105 assessment reports, the data retrieved from the EudraVigilance database or other data used to support
2106 the PSUR assessment).

2107 ***VII.C.7. Transparency***

2108 **VII.C.7.1. Publication of PSUR-related documents on the European** 2109 **medicines and national medicines web-portals**

2110 The following documents shall be made publicly available by means of the European medicines web-
2111 portal [DIR Art 107I, REG Art 26(g)]:

- 2112 • list of EU reference dates and frequency of submission of PSURs (see **VII C.3.**);
- 2113 • final assessment conclusions of the adopted assessment reports;
- 2114 • PRAC recommendations including relevant annexes;
- 2115 • CMDh position including relevant annexes and where applicable, detailed explanation on scientific
2116 grounds for any differences with the PRAC recommendations;
- 2117 • CHMP opinion including relevant annexes and where applicable, detailed explanation on scientific
2118 grounds for any differences with the PRAC recommendations;
- 2119 • European Commission decision.

2120 The version and date of publication are reflected in each document as they define the issue of the
2121 PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions at a
2122 certain point of time.

2123 Links between the European medicines web-portal and the National medicines web-portals should be
2124 made whenever possible and relevant.

2125 Any personal or confidential data made public by the Agency or the competent authorities in Member
2126 States as referred to in paragraphs 2 and 3 of Article 106a of Directive 2001/83/EC shall be deleted
2127 unless considered necessary in terms of protection of the public health [DIR Art 106a(4)].

2128 ***VII.C.8. Renewal of marketing authorisations***

2129 Marketing authorisations need to be renewed after 5 years on the basis of a re-evaluation of the risk-
2130 benefit balance in order to continue to be valid to place the product on the market. This renewal is
2131 irrespective of whether the marketing authorisation is suspended. Further details on the procedure and
2132 the documentation requirements can be found in the current versions of the “Guideline on Processing
2133 of Renewals in the Centralised Procedure” (EMA/CHMP/2990/00) for Centralised products and the
2134 “CMDh Best Practice Guide on the processing of renewals in the MRP/DCP” (CMDh/004/2005) for other
2135 products.

2136 No PSURs, addendum reports and summary bridging reports should be submitted within the renewal
2137 application. The clinical overview should include an addendum containing the relevant sections for the
2138 re-assessment of the risk-benefit balance of the medicinal product. These sections are identified in the

2139 above-mentioned guidelines for renewal. Marketing authorisation holders are advised to consider this
2140 GVP Module VII as guidance for the preparation of the addendum to the clinical overview.

2141 Following the submission of a renewal application, the PRAC may be consulted for medicinal products
2142 authorised through the centralised procedure as regards safety issues. For nationally authorised
2143 products, including those authorised through the mutual recognition or decentralised procedure, the
2144 PRAC may also be consulted upon request by a competent authority in a Member State on the basis of
2145 safety concerns.

2146 Conditional marketing authorisations should be renewed annually [REG Art 14(7)]. Further details on
2147 the procedure and the documentation to be submitted can be found in the “Guideline on the scientific
2148 application and the practical arrangements necessary to implement Commission Regulation (EC) No
2149 507/2006 on the conditional marketing authorisation for medicinal products for human use falling
2150 within the scope of regulation (EC) no 726/2004” (EMEA/509951/2006).

2151 ***VII.C.9. Transition and interim arrangements***

2152 **VII.C.9.1. Submission and availability of documents before the Agency’s** 2153 **repository is in place**

2154 The Agency shall, in collaboration with the competent authorities in Member States and the European
2155 Commission set up and maintain a repository for PSURs and the corresponding assessment reports so
2156 that they are fully and permanently accessible to European Commission, the competent authorities in
2157 Member States, the PRAC, the CHMP and the CMDh [REG Art 25a].

2158 The repository shall undergo an independent audit before the functionalities are announced by the
2159 Agency’s management board [REG Art 25a].

2160 As established in the transitional provisions introduced in Directive 2010/84/EU Art 2(7), until the
2161 Agency can ensure the functionalities agreed for the repository, marketing authorisation holders under
2162 the obligation to submit PSURs irrespective of whether the medicinal product is authorised in one or
2163 more Member States and irrespective of whether the active substance or combination of active
2164 substances is on the EU reference date list shall submit the PSURs to all competent authorities in
2165 Member States in which the medicinal products are authorised. For the substances or combination of
2166 active substances subject to ~~the a~~ EU single assessment, ~~or and~~ -for which an EU reference date has
2167 been established, the PSURs should be also sent to the Agency.

2168 The competent authorities in Member States requirements for the submission of PSURs during this
2169 transitional period are published in the Agency web-site²⁵.

2170 From 12 months after the functionalities of the repository have been established and have been
2171 announced by the Agency, the marketing authorisation holders shall submit the PSURs electronically to
2172 the Agency regardless of the authorisation procedure of the medicinal product [DIR Art 107b(1)]. The
2173 competent authorities in Member States shall ensure that this obligation applies as required [DIR Art
2174 2(7)].

2175 Once the structured electronic format “ePSUR”, based on content agreed in the ICH-E2C(R2), becomes
2176 available, marketing authorisation holders will have the possibility to submit PSURs and related
2177 documents automatically via an electronic gateway.

2178 Until the repository is in place, the ~~relevant following~~ documents should be circulated as follows:
2179 ~~through a dedicated mailbox or according to the instructions for submissions published by the Agency:~~

²⁵ www.ema.europa.eu

2180 • The preliminary assessment report created by the PRAC Rapporteur/Member State within 60 days
2181 of the start of the ~~procedure~~ procedure. The report should be circulated to the Agency and the
2182 members of the PRAC through a dedicated mailbox. The Agency should send the report to the
2183 concerned marketing authorisation holder(s);

2184 • members of the PRAC should circulate their comments through a dedicated mailbox by Day 90 on
2185 the PRAC Rapporteur/Member State preliminary assessment report;

2186 • comments submitted by the marketing authorisation holders(s) and members of the PRAC by Day
2187 90 on the PRAC Rapporteur/Member State preliminary assessment report, should be submitted to
2188 the Agency, PRAC Rapporteur and all members of the PRAC, according to the instructions for
2189 submission published by the Agency; ~~These comments should also be circulated to all members of~~
2190 ~~the PRAC by the marketing authorisation holder.~~

2191 • updated PRAC Rapporteur/Member State assessment report created within 15 days (i.e. by Day
2192 105) should be circulated forwarded to the Agency and members of the PRAC through a dedicated
2193 mailbox. The Agency should forward the updated PRAC Rapporteur/Member State assessment
2194 report to the marketing authorisation holders concerned.

2195 Further to adoption, the Agency should send the CHMP opinion together with its annexes and
2196 appendices to the European Commission, marketing authorisation holder(s) and competent authorities
2197 in Member States, through secure email until the repository is in place.

2198 **VII.C.9.2. Quality systems and record management systems at the level of** 2199 **the competent authorities in Member States**

2200 Special considerations should be taken for the management of the PSURs submitted to the concerned
2201 competent authorities in Member States until the Agency can ensure the functionalities agreed for the
2202 PSUR repository and 12 months after the establishment of the repository according to the transitional
2203 provisions.

2204 **VII.C.9.3. Publication of the EU list of union references dates and start of** 2205 **the EU- PSUR single assessment procedure**

2206 As stated in VII.C.3.6., the list of EU reference dates and frequency of submission should be published
2207 in the European medicines web-portal, nevertheless, the EU single assessment procedure for
2208 substances included only in nationally authorised products, detailed in VII.C.4.2.2., and VII.C.4.2.4.
2209 will be delayed until funds are available.

2210

2211

2212 **VII.APPENDICES**

2213 **VII.Appendix 1. Examples of tabulations for estimated exposure and**
 2214 **adverse events/reactions data**

2215 Marketing authorisation holders can modify these examples tabulations to suit specific situations, as
 2216 appropriate.

2217 **Table VII.2.** Estimated cumulative subject exposure from clinical trials

2218 Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical
 2219 trials and the enrolment/randomisation schemes for ongoing trials.

Treatment	Number of Subjects
Medicinal product	
Comparator	
Placebo	

2220

2221 **Table VII.3.** Cumulative subject exposure to investigational drug from completed clinical trials by age
 2222 and sex

Age range	Number of subjects		
	Male	Female	Total

2223 Data from completed trials as of [date]

2224 **Table VII.4.** Cumulative subject exposure to investigational drug from completed clinical trials by
 2225 racial/ethnic group

Racial/ethnic group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

2226 Data from completed trials as of [date]

2227 **Table VII.5.** Cumulative exposure from marketing experience

Indication	Sex		Age (years)				Dose			Formulation		Region				
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	EU	Japan	Colombia	US/Canada	Other
Overall																
Depression																
Migraine																

2228 Table VII.5 includes cumulative data obtained from day/month/year throughout day/month/year, where available

2229 **Table VII.6.** Interval exposure from marketing experience

Indication	Sex		Age (years)				Dose			Formulation			Region			
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	EU	Japan	Colombia	US/Canada	Other
Depression																
Migraine																

2230 Table VII. 6 includes interval data obtained from day/month/year throughout day/month/year

2231 **Table VII.7.** Cumulative tabulation of serious adverse events from clinical trials

System Organ Class	Preferred Term	Investigational	Blinded	Active comparator	Placebo
		medicinal product			
<u>Blood and lymphatic system disorders</u>	Anaemia				
	Bone marrow necrosis				
	<u>Cardiac disorders</u>				
	Tachycardia				
	Ischaemic cardiomyopathy				

2232

2233 **Table VII.8.** Numbers of adverse reactions by preferred term from post-authorisation sources*

SOC MedDRA PT	Spontaneous, including competent authorities (worldwide) and literature				Non-interventional post-marketing study and reports from other solicited sources **		
	Serious		Non-serious		Total	Serious	
	Interval	Cumulative	Interval	Cumulative	Spontaneous Cumulative	Interval	Cumulative
<SOC 1>							
<PT>							
<PT>							
<PT>							
<SOC 2>							
<PT>							
<PT>							
<PT>							
<PT>							

2234 * Non-interventional post-authorisation studies, reports from other solicited sources and spontaneous ICSRs (i.e.,
2235 reports from healthcare professionals, consumers, competent authorities (worldwide), and scientific literature)

2236 ** This does not include interventional clinical trials.

2237 **VII. Appendix 2. Example of tabular summary of safety signals that were**
 2238 **ongoing or closed during the reporting interval**

2239 **Table VII.9.** The tabular summary below is a fictitious example of a tabular summary of safety signals
 2240 ongoing or closed during the reporting interval

2241 Reporting interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYYY	Ongoing	MMM/YYYY	meta-analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; plausible time to onset and no possible alternative causes.	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologists and literature searches	RSI updated with a warning and precaution DHPc sent Effectiveness survey planned 6 months post DHPc. RMP updated

2242

- 2243 Explanatory notes:
- 2244 Signal term:
- 2245 • A brief descriptive name of a medical concept for the signal. This may evolve and be refined as the
2246 signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s),
2247 depending on the source of signal.
- 2248 Date detected:
- 2249 • Month and year **the marketing authorisation holder became aware of the signal.**
- 2250 Status:
- 2251 • Ongoing: Signal under evaluation at the data lock point of the PSUR. Anticipated completion date,
2252 if known, should be provided.
- 2253 • Closed: Signal for which evaluation was completed **before the data lock point of the PSUR.**
- 2254 Note: A **new signal** of which the marketing authorisation holder became aware during the reporting
2255 interval may be classified as closed or ongoing, depending on the status of the signal evaluation at the
2256 end of the reporting interval of the PSUR.
- 2257 Date closed:
- 2258 • Month and year when the signal evaluation was completed.
- 2259 Source of signal:
- 2260 • Data or information source from which a signal arose. Examples include, but may not be limited to,
2261 spontaneous reports, clinical trial data, scientific literature, and non-clinical study results, **or**
2262 **information request or inquiries from a competent authority (worldwide).**
- 2263 Reason for evaluation and summary of key data:
- 2264 • A brief summary of key data and rationale for further evaluation.
- 2265 Action(s) taken or planned:
- 2266 State whether or not a specific action has been taken or is planned for all closed signals that have been
2267 classified as potential or identified risks. If any further actions are planned for newly or previously
2268 identified signals under evaluation at the data lock point, these should be listed, otherwise leave blank
2269 for ongoing signals.