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5

6 *Note: Revision 1 contains the following:

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

10 - Further guidance regarding technical aspects on the implementation of Regulation (EU) No
11 1235/2010 and Directive 2010/84/EU based on the experience gained since July 2012;

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

14 - Further instructions regarding the PSUR assessment process, product information and transitional
15 arrangements within the EU regulatory network in VII.C..

16

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Note for public consultation:

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

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VII.A. Introduction

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

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

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

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

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

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

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

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

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

[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/

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

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

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

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

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

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

VII.B. Structures and processes

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

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

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

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

A PSUR should not be used to provide initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted (see Module IX and XII).

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

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

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

The analysis of the risk-benefit balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available[2], with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.

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

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

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

The evaluation should involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.

2. Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the medicinal product.

3. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information.

[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..

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

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

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

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

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

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

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

VII.B.4. Reference information

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

The reference product information for the PSUR should include "core safety" and "authorised indications" components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PSUR, the reference product information document should list all authorised indications in ICH countries[3] or regions. When the PSUR is also submitted to other countries in which there are additional locally authorised indications, these indications may be either added to the reference product information or handled as a regional appendix as considered most appropriate by the marketing authorization holder. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarised in the PSUR section 17.1 ("Important baseline efficacy and effectiveness information").

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

[3] http://www.ich.org/

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

- Company core data sheet (CCDS)
  - It is common practice for marketing authorisation holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorised indications for which benefit is evaluated.
  - When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR.
- Other options for the reference product information
  - When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one country or region, or for established/generics products on the market for many years), the marketing authorisation holder should clearly specify the reference information being used. This may comprise national or regional product information such as the EU summary of product characteristics (SmPC).
  - Where the reference information for the authorised indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR (see VII.B.5.20.).

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

- changes to contraindications, warnings/precautions sections;
- addition to adverse reactions and interactions;
- addition of important new information on use in overdose; and
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

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

Where new information on safety that could warrant changes to the authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section 14 ("Late-breaking information"), if feasible.

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

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

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

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

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

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

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

- non-clinical studies;
- spontaneous reports (e.g. on the marketing authorisation holder's safety database);
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilisation information;
- clinical trials, including research in unauthorised indications or populations;
- observational studies, including registries;
- patient support programs;
- systematic reviews and meta-analysis;
- marketing authorisation holders sponsored websites[4];
- published scientific literature or reports from abstracts, including information presented at scientific meetings;
- unpublished manuscripts;
- licensing partners, other sponsors or academic institutions and research networks;
- competent authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorisation holder to present safety, efficacy and effectiveness in the PSUR and to

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

evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the marketing authorisation holder, a list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.

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

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

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

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

- Part I: Title page including signature[5]
- Part II: Executive Summary
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6. Data in summary tabulations
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   - 6.3. Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
   - 7.1. Completed clinical trials

[5] 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.

7.2. Ongoing clinical trials

7.3. Long-term follow-up

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20. Appendices to the PSUR

PSUR title page

The title page should include the name of the medicinal product(s)[6] and substance, international birth date (IBD) (the date of the first marketing authorisation for any product containing the active

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

substance granted to any company in any country in the world), reporting interval, date of the report, marketing authorisation holder details and statement of confidentiality of the information included in the PSUR.

The title page shall also contain the signature.

PSUR executive summary

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

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

PSUR table of contents

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

VII.B.5.1. PSUR section "Introduction"

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

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

VII.B.5.2. PSUR section "Worldwide marketing authorisation status"

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

VII.B.5.3. PSUR section "Actions taken in the reporting interval for safety reasons"

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

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

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

Examples of significant actions taken for safety reasons include:

Actions related to investigational uses:

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial[7] or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- recall of investigational drug or comparator;
- failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a marketing authorisation application;
- risk management activities, including:
  - protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
  - restrictions in study population or indications;
  - changes to the informed consent document relating to safety concerns;
  - formulation changes;
  - addition by regulators of a special safety-related reporting requirement;
  - issuance of a communication to investigators or healthcare professionals; and
  - plans for new studies to address safety concerns.

Actions related to marketing experience:

- failure to obtain or apply for a marketing authorisation renewal;
- withdrawal or suspension of a marketing authorisation;
- actions taken due to product defects and quality issues;
- suspension of supply by the marketing authorisation holder;

[7] "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).

- risk management activities including:
  - significant restrictions on distribution or introduction of other risk minimisation measures;
  - significant safety-related changes in labelling documents including restrictions on use or population treated;
  - communications to health care professionals; and
  - new post-marketing study requirement(s) imposed by competent authorities.

VII.B.5.4. PSUR section "Changes to reference safety information"

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

VII.B.5.5. PSUR section "Estimated exposure and use patterns"

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

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

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

VII.B.5.5.1. PSUR sub-section "Cumulative subject exposure in clinical trials"

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

- cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for "old products", detailed data might not available;
- more detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme);;
- important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
- if clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;

- when there are substantial differences in time of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);
- investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;
- if the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;
- for individual trials of particular importance, demographic characteristics should be provided separately.

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

VII.B.5.5.2. PSUR sub-section "Cumulative and interval patient exposure from marketing experience"

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

The data should be presented according to the following categories:

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

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

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

2. Post-authorisation use in special populations:

   Where post-authorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data would include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

   - paediatric population;
   - elderly population;
   - pregnant or lactating women;

- patients with hepatic and/or renal impairment;
- patients with other relevant co-morbidity;
- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- populations with specific racial and/or ethnic origins.

3. Other post-authorisation use:

   If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). If known, the marketing authorisation holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. If quantitative use information is available, it should be provided. For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorisation holder should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR (e.g. authorised indication, contraindications).

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

VII.B.5.6. PSUR section "Data in summary tabulations"

The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the marketing authorisation holder graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

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

The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A[8] (see Annex IV). When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSURs.

VII.B.5.6.1. PSUR sub-section "Reference information"

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

[8] ICH Topic E2A. Clinical safety data management: Definitions and standards for expedited reporting.

VII.B.5.6.2. PSUR sub-section "Cumulative summary tabulations of serious adverse events from clinical trials"

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

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

The following points should be considered:

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.
- In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and marketing authorisation holders should not unblind data for the specific purpose of preparing the PSUR.
- Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

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

VII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"

This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies[9]. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional

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

studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.

As described in ICH-E2D[10] (see Annex IV) guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.

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

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

VII.B.5.7. PSUR section "Summaries of significant findings from clinical trials during the reporting interval"

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

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

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

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

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

- study ID (e.g. protocol number or other identifier);
- study title (abbreviated study title, if applicable);
- study type (e.g. randomised clinical trial, cohort study, case-control study);
- population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);

[10] See footnote 8.

- study start (as defined by the marketing authorisation holder) and projected completion dates;
- status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

VII.B.5.7.1. PSUR sub-section "Completed clinical trials"

This sub-section of the PSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis[11]. It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

VII.B.5.7.2. PSUR sub-section "Ongoing clinical trials"

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

VII.B.5.7.3. PSUR sub-section "Long term follow-up"

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

VII.B.5.7.4. PSUR sub-section "Other therapeutic use of medicinal product"

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D[12] (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

VII.B.5.7.5. PSUR sub-section "New safety data related to fixed combination therapies"

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

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

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

[11] 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/.

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

VII.B.5.8. PSUR section "Findings from non-interventional studies"

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

The marketing authorisation holder should include an appendix listing marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval.

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

VII.B.5.9. PSUR section "Information for other clinical trials and sources"

Other sources of information may include data collection outside of a study environment. Information obtained from reports of events or patterns of use which do not result in suspected adverse reactions may be included in sub-sections VII.B.5.9.1. and VII.B.5.9.2. For example, this would include available information on reports of asymptomatic overdose, abuse, use beyond that recommended in the reference product information, or use in special populations (see Module VI). Such information may be received via spontaneous reports, medical information queries, customer's complaints, screening of digital media or via other information sources available to the marketing authorisation holder.

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

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

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

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

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

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

This PSUR section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns should be

included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR.

VII.B.5.11. PSUR section "Literature"

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

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

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

- pregnancy outcomes (including termination) with no adverse outcomes;
- use in paediatric populations;
- compassionate supply, named patient use;
- lack of efficacy;
- asymptomatic overdose, abuse or misuse;
- medication error where no adverse events occurred;
- important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class should be considered.

The publication reference should be provided in the style of the Vancouver Convention[13,14].

VII.B.5.12. PSUR section "Other periodic reports"

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

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

[13] 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

[14] 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

VII.B.5.13. PSUR section "Lack of efficacy in controlled clinical trials"

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

VII.B.5.14. PSUR section "Late-breaking information"

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

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

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

VII.B.5.15. PSUR section "Overview of signals: new, ongoing, or closed"

The general location for presentation of information on signals and risks within the PSUR is shown in figure 1 (see VII.B.21.). The purpose of this section is to provide a high level overview of signals[15] that were closed (i.e., evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PSUR, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorisation holder[16].It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicine/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide) (see Module IX).

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

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR, this would also be considered a new signal on the basis that a new aspect of a

[15] "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)].

[16] 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

previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR.

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

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

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

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

And example of tabulation of signals can be found in VII. Appendix 2.

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

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

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

VII.B.5.16. PSUR section "Signal and risk evaluation"

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

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

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

These evaluation sub-sections should not summarise or duplicate information presented in previous sections of the PSUR but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided (see VII.B.3.).

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

The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary[17] that is current at the start of the reporting interval of the PSUR. It should provide the following safety information:

- important identified risks;
- important potential risks; and
- important missing information.

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

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

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

- important adverse reactions;

[17] ICH-E2E – Pharmacovigilance planning (see Annex IV).

- interactions with other medicinal products;
- interactions with foods and other substances;
- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

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

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

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

1. Those signals that, following evaluation, have been refuted as "false" signals based on medical judgement and scientific evaluation of the currently available information.
2. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

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

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

- Closed and refuted signals.
- Closed signals that are categorised as important potential risks.
- Closed signals that are categorised as important identified risks.
- Closed signals that are potential risks not categorised as important.
- Closed signals that are identified risks not categorised as important.

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

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

- source or trigger of the signal;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed), and analytical approaches;

- results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
- discussion;
- conclusion.

VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information"

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

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

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

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

New information can be organised as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorised as important.
4. New information on other identified risks not categorised as important.
5. Update on important missing information.

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

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

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

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

VII.B.5.16.4. PSUR sub-section "Characterisation of risks"

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

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

- frequency;
- numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk and precision of estimate;
- estimate of absolute risk and precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- dose, route of administration;
- duration of treatment, risk period;
- preventability (i.e. predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PSURs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- risks relating to the active substance;
- risks related to a specific formulation or route of administration (including occupational exposure);
- risks relating to a specific population;
- risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products); and

VII.B.5.16.5. PSUR sub-section: "Effectiveness of risk minimisation (if applicable)"

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment [IR Art 34(3)].

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this sub-section of the PSUR.

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

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

VII.B.5.17. PSUR section "Benefit evaluation"

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

VII.B.5.17.1. PSUR sub-section "Important baseline efficacy and effectiveness information"

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

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

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

VII.B.5.17.2. PSUR sub-section "Newly identified information on efficacy and effectiveness"

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

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

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

VII.B.5.17.3. PSUR sub-section "Characterisation of benefits"

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

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

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

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

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

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

VII.B.5.18. PSUR section "Integrated benefit-risk analysis for authorised indications"

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

VII.B.5.18.1. PSUR sub-section "Benefit-risk context - medical need and important alternatives"

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

VII.B.5.18.2. PSUR sub-section "Benefit-risk analysis evaluation"

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

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

- Whereas previous sections/sub-sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section/sub-sections should be carried forward for integration in the benefit-risk evaluation.
- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).
- With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalisability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorised indications or populations, off-label use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

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

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
- Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis should be presented based on cumulative data . Conversely, where little new information

has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

VII.B.5.19. PSUR section "Conclusions and actions"

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

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

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

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

Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved summary of product characteristics (SmPC) for the product(s) for which the PSUR is submitted [IR Art 34(5)]. The regional appendix should include proposals for product information (SmPC and package leaflet) together with information on ongoing changes when applicable.

VII.B.5.20. Appendices to the PSUR

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

1. Reference information(see VII.B.4.).
2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
3. Tabular summary of safety signals (if not included in the body of the report)[18].
4. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.
5. List of the sources of information used to prepare the PSUR (when desired by the marketing authorisation holder).
6. Regional appendix:

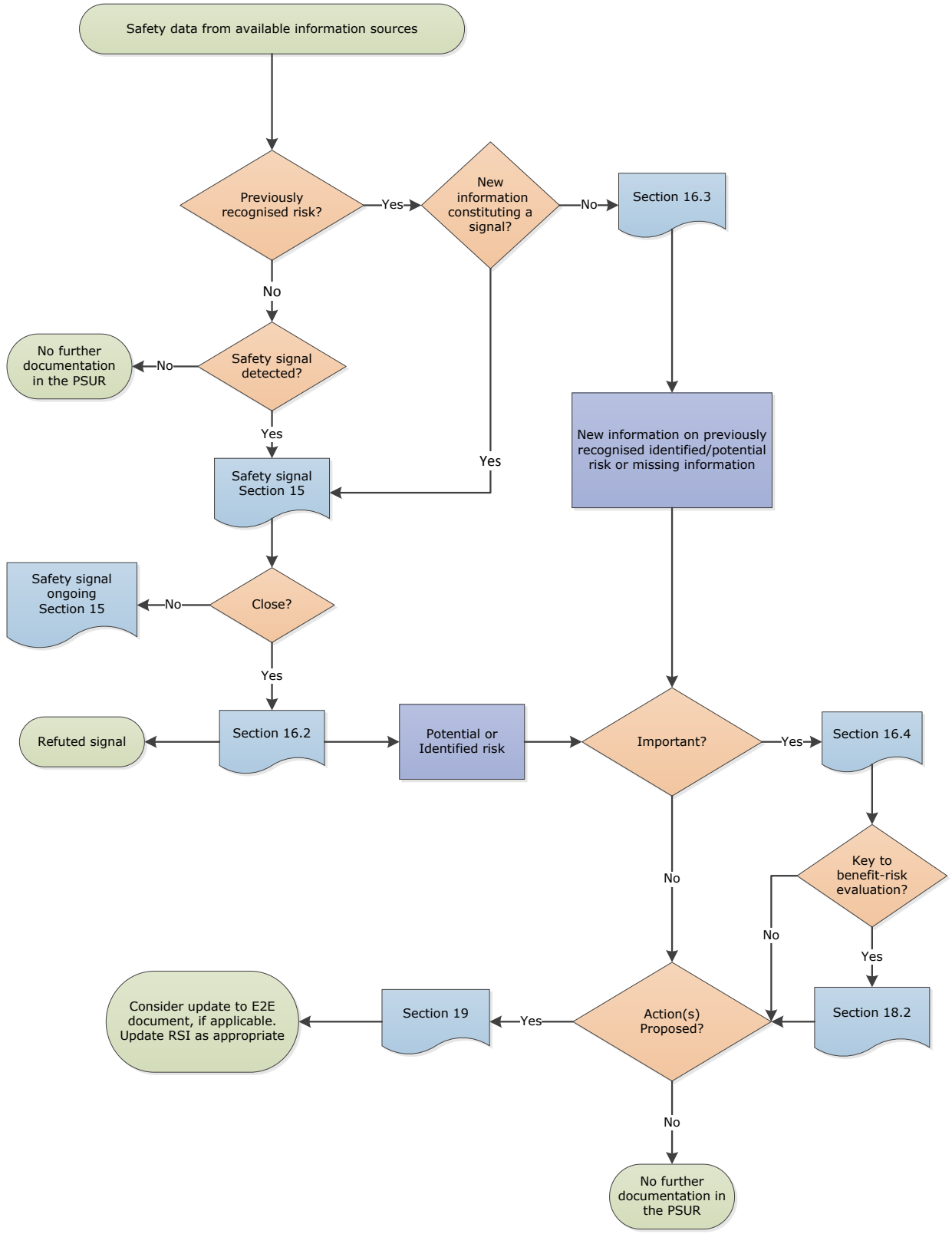
   The requirements for the regional appendix in the EU are provided in section VII.C.5..

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

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

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

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



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

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

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

The PSUR should also contain the assessment of specific safety issues requested to be addressed in the PSUR by competent authorities (worldwide). The marketing authorisation holder should have mechanisms in place to ensure that the requests made by competent authorities (worldwide) during the time of their PSUR assessment are properly addressed.

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

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

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

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

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

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

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

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

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

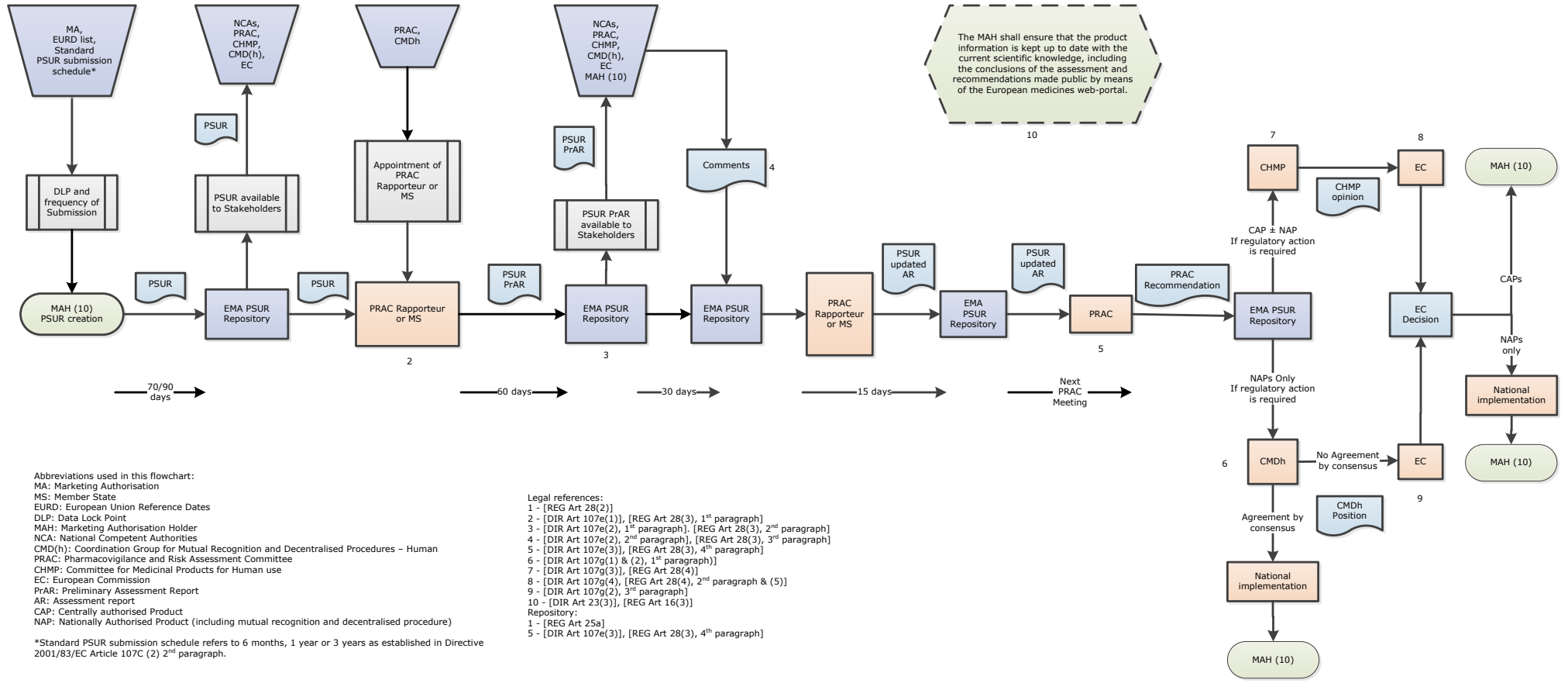
Training should cover legislation, guidelines, scientific evaluation and written procedures related to the PSUR process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

VII.C. Operation of the EU network

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

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

Figure VII.2. PSUR procedure - general process



Abbreviations used in this flowchart:
MA: Marketing Authorisation
MS: Member State
EURD: European Union Reference Dates
DLP: Data Lock Point
MAH: Marketing Authorisation Holder
NCA: National Competent Authorities
CMD(h): Coordination Group for Mutual Recognition and Decentralised Procedures – Human
PRAC: Pharmacovigilance and Risk Assessment Committee
CHMP: Committee for Medicinal Products for Human use
EC: European Commission
PrAR: Preliminary Assessment Report
AR: Assessment report
CAP: Centrally authorised Product
NAP: Nationally Authorised Product (including mutual recognition and decentralised procedure)

*Standard PSUR submission schedule refers to 6 months, 1 year or 3 years as established in Directive 2001/83/EC Article 107C (2) 2nd paragraph.

Legal references:
1 - [REG Art 28(2)]
2 - [DIR Art 107e(1)], [REG Art 28(3), 1st paragraph]
3 - [DIR Art 107e(2), 1st paragraph]. [REG Art 28(3), 2nd paragraph]
4 - [DIR Art 107e(2), 2nd paragraph], [REG Art 28(3), 3rd paragraph]
5 - [DIR Art 107e(3)], [REG Art 28(3), 4th paragraph]
6 - [DIR Art 107g(1) & (2), 1st paragraph)]
7 - [DIR Art 107g(3)], [REG Art 28(4)]
8 - [DIR Art 107g(4), [REG Art 28(4), 2nd paragraph & (5)]
9 - [DIR Art 107g(2), 3rd paragraph]
10 - [DIR Art 23(3)], [REG Art 16(3)]
Repository:
1 - [REG Art 25a]
5 - [DIR Art 107e(3)], [REG Art 28(3), 4th paragraph]

VII.C.2. Standard submission schedule of PSURs

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

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

VII.C.3. List of European Union reference dates and frequency of submission of PSURs[19]

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

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

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

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

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

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

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

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

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

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

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

[19] 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.

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

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

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

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

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

The EU reference dates list should contain the following information:

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

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

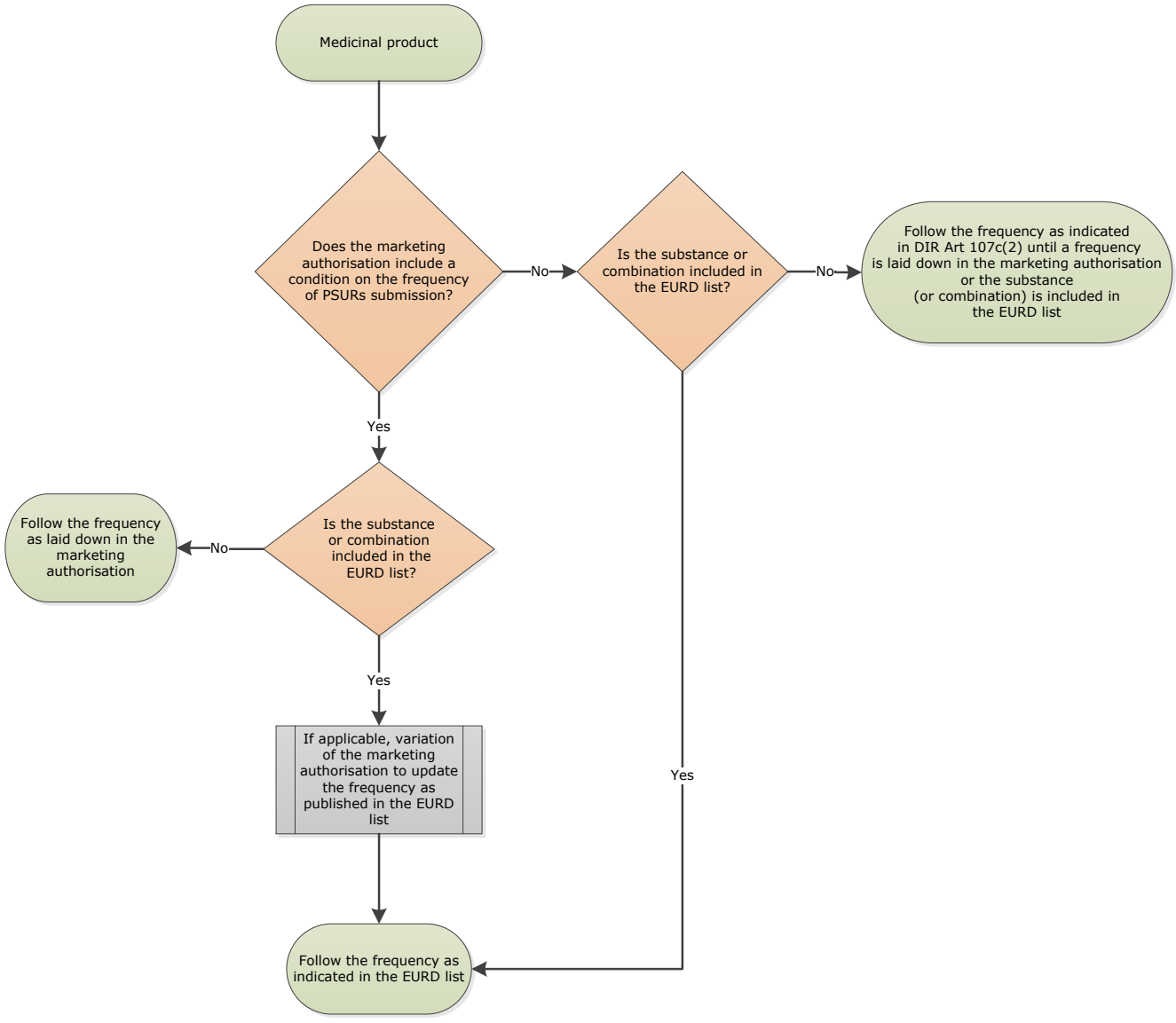
- whether or not it should cover all the indications of the substance or combination of active substances;
- whether or not it should cover all the formulations/routes of administration of the products containing a substance or combination of active substances;
- whether generic, well-established use,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

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

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

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

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



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

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

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

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

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

- 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 relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted (e.g. when the "reference" medicinal product is no longer marketed). The assessment reports of the requested PSURs shall be communicated to the PRAC, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the CMDh or CHMP accordingly, in order to apply the procedures laid down in DIR Art 107c(4) and 107e.

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

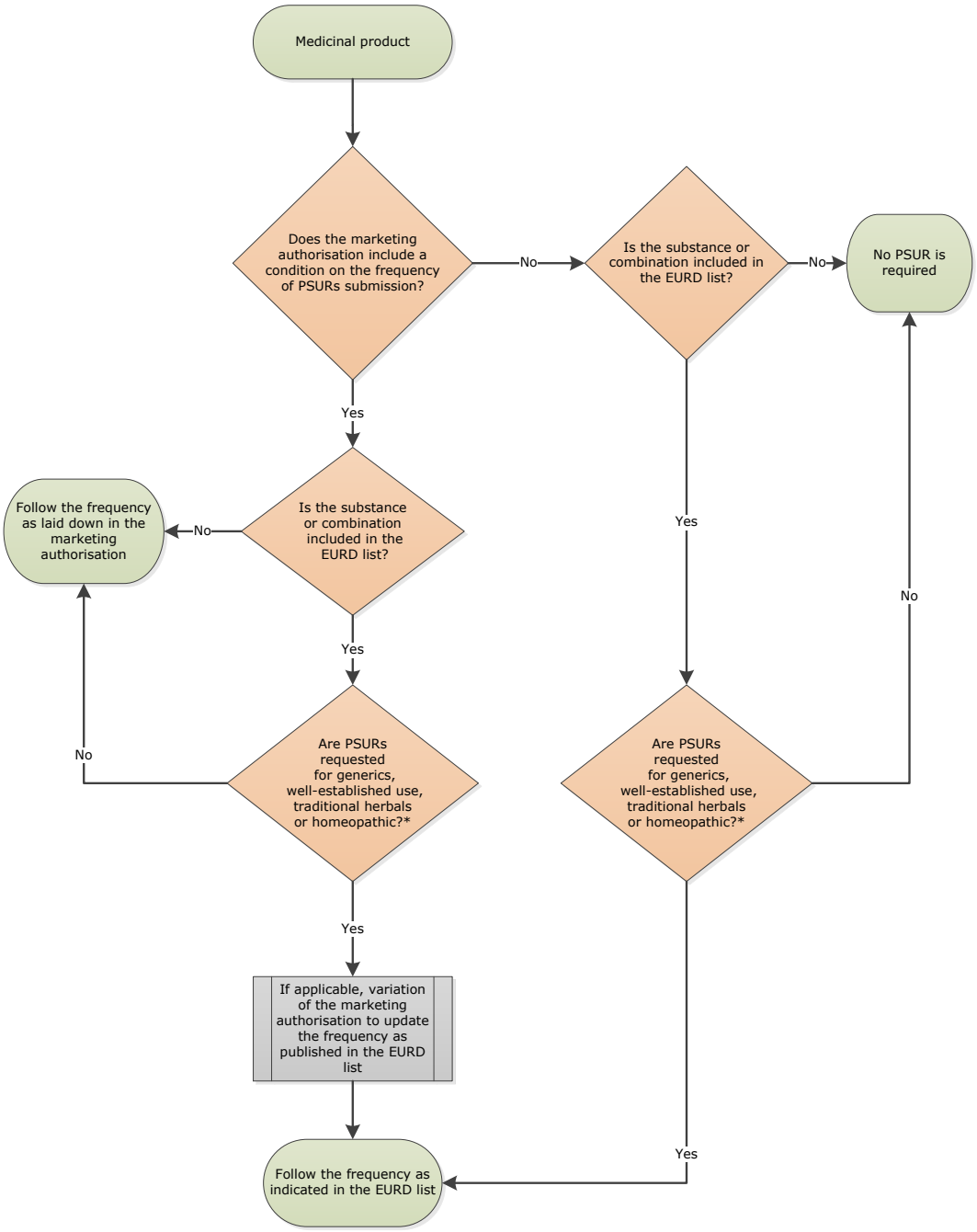
The harmonised frequency for the submission of the reports and the EU reference dates are determined by the CHMP and/or CMDh after consultation of the PRAC.

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

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

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

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



* 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.

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

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

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

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

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

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

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

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

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

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

VII.C.3.5.1. General principles

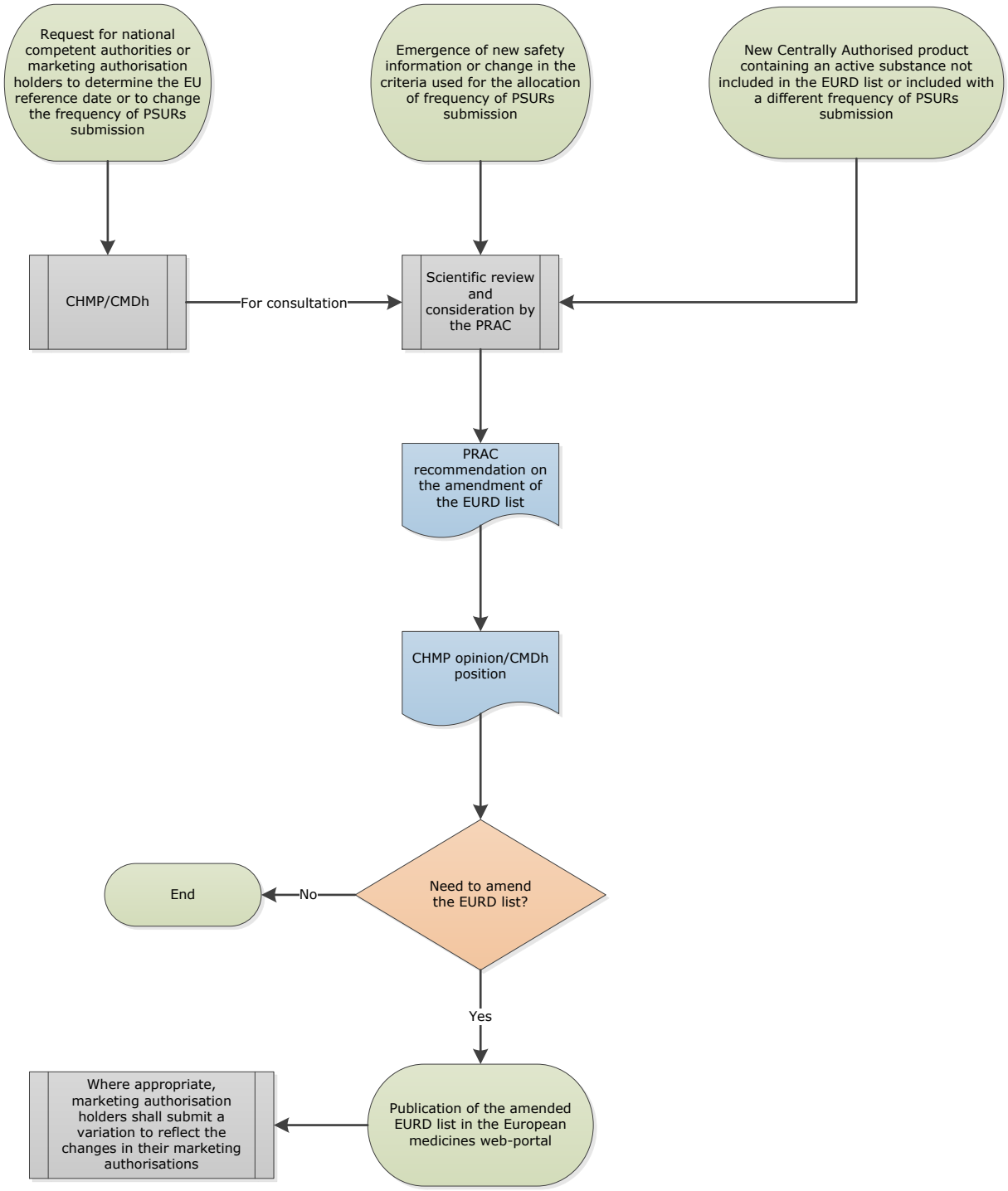
The maintenance of the list of EU reference dates should facilitate regulatory responsiveness to public health concerns identified within the EU and therefore the list will be subject to changes to reflect the decisions taken (e.g. by the Agency's committees following signal detection).

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

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

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

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



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

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

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

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

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

For details about how to submit requests for amendments to the list, refer to the EU reference dates cover note and the related template published on the European medicines web-portal[20]

VII.C.3.6. Publication of the list

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

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

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

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

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

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

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

[20] http://www.emea.europa.eu

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

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

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

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

When the proposals for the product information include new adverse reactions in section 4.8 ("Undesirable effects") of the SmPC, or modifications in the description, frequency and severity of the existing reactions, marketing authorisation holders should provide in the PSUR detailed information to allow the adequate description and classification of the frequency of the adverse reactions. If other sections of the SmPC (e.g. SmPC section 4.4 "Special warnings and precautions for use") are considered to be updated, clear proposals should be provided for the competent authorities in the Member States to consider during the PSUR assessment[21]. The proposals should be included in the PSUR regional appendix (VII.C.5.).

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

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

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

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

[21] 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

within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of cases classified as non-serious.

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

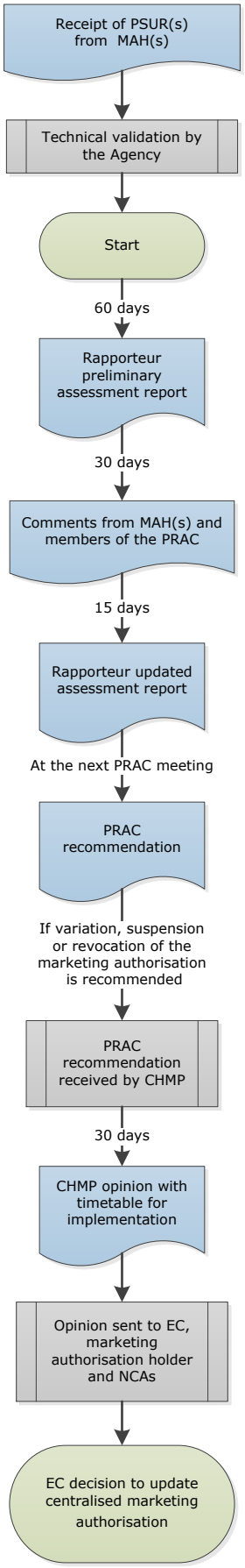
The assessment report and conclusions of the competent authority in the Member State should be provided to the marketing authorisation holder.

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

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

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

Figure VII.6. PSUR assessment procedure for a single centrally authorised medicinal product



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

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

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

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

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

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur through the Agency, for adverse reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of cases classified as non-serious.

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

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

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

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

Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG Art 28(3)] within 15 days (i.e. by Day 105). The updated assessment report is made available to the members of the PRAC.

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

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

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

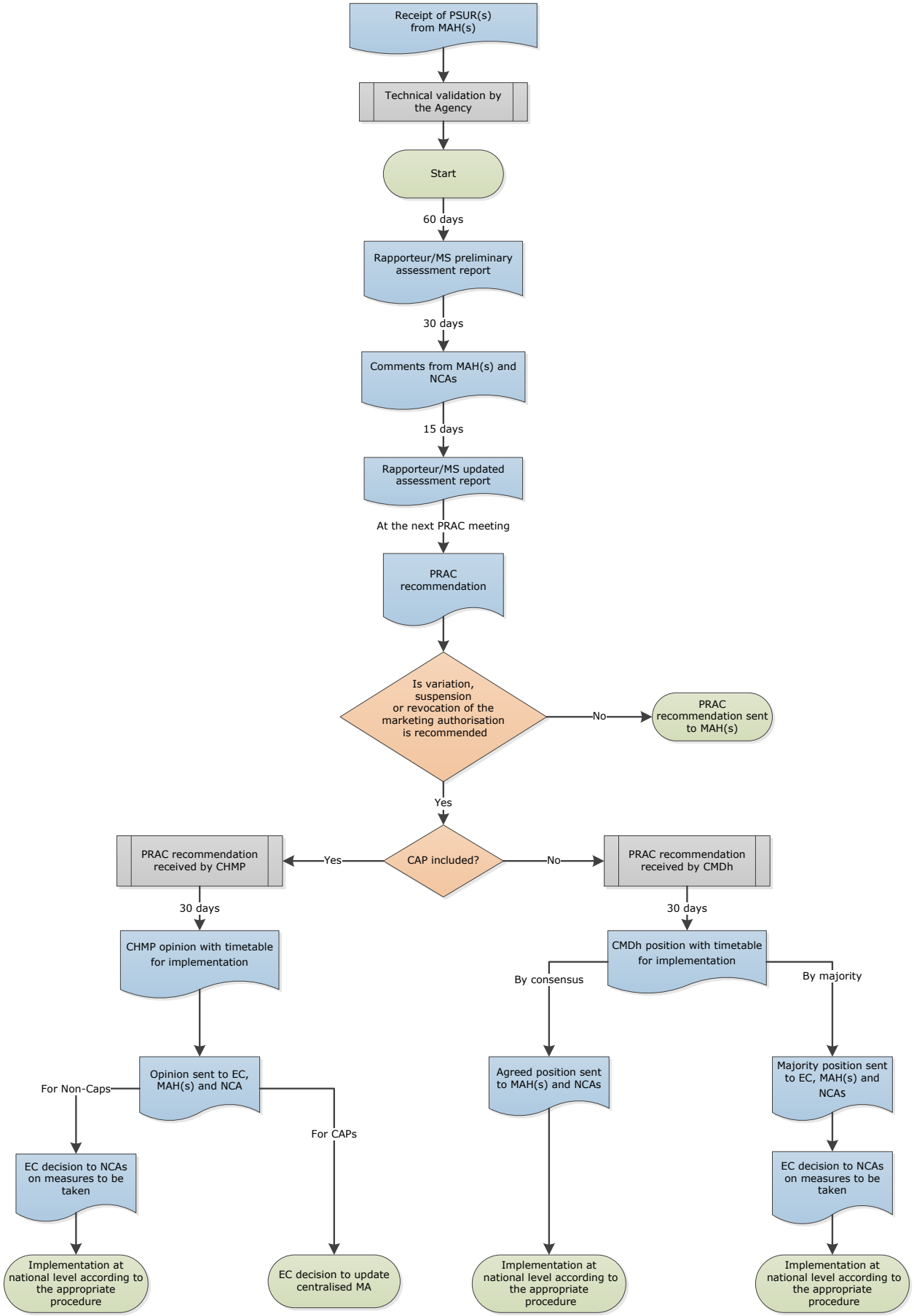
The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder [REG Art 28(3)].

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

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

This section describes the assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder and for which the frequency and dates of submission of PSUR have been harmonised in the list of EU reference dates. This could include a mixture of centrally authorised products, products authorised through the mutual recognition and decentralised procedures and purely nationally authorised products [DIR Art 107e to 107g] (so-called PSUR "EU single assessment" procedure).

Figure VII.7. PSUR assessment procedure for "EU single assessment"



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

- a "Member State" appointed by the CMDh where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure;
- a "Rapporteur" appointed by the PRAC, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure (hereinafter referred to as "PRAC Rapporteur").

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

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

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

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

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

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

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur or Member State through the Agency for adverse drug reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of cases classified as non-serious.

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

The Agency shall send the PRAC Rapporteur's/Member State preliminary assessment report to the concerned marketing authorisation holder(s) [DIR Art 107e(2)].

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

Following receipt of comments, the PRAC Rapporteur/Member State shall prepare an updated assessment report [DIR Art 107e (3)] within 15 days (i.e. by Day 105). The updated assessment report is forwarded to the members of the PRAC.

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

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

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

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

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

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

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

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

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

The opinion will contain the following:

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

- for centrally authorised products, revised product information and if applicable, conditions imposed to the marketing authorisation holder and where appropriate, the conditions or restrictions imposed to the Member States for the safe and effective used of the medicinal product, in accordance with the provision provided in DIR Art 127a;
- for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures, an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information as applicable.

- in the case of a CHMP opinion to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;
- in the case of a CHMP opinion to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- divergent positions of CHMP members, where applicable.

Further to adoption, the Agency should send the CHMP opinion together with its annexes and appendices to the European Commission, marketing authorisation holder(s) and competent authorities in Member States.

The final assessment conclusions and recommendations are published in the European medicines web-portal (VII.C.7.).

a. Post CHMP opinion - Centrally authorised products

Where the CHMP opinion states that the terms of the marketing authorisation(s) needs to be varied, the marketing authorisation holder(s) of centrally authorised products should provide the translations of the product information in all EU official languages, in accordance with the translation timetable adopted by the CHMP.

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt a decision addressed to marketing authorisation holders to vary, suspend or revoke the marketing authorisation(s) of centrally authorised product(s) [DIR Art 107g(4b)].

Further to adoption, the European Commission should notify the decisions amending the terms of the marketing authorisation of centrally authorised products to the marketing authorisation holder(s).

b. Post CHMP opinion - Nationally authorised products, including those authorised through the mutual recognition and decentralised procedures

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisations is necessary, the European Commission shall adopt a decision addressed to the competent authorities in Member States concerning the measures to be taken [DIR Art 107g(a)] in respect of nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

Further to the receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s) within 30 days [DIR Art 107g(4)].

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

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

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

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

The position will contain the following:

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

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

<u>If the CMDh position is reached by consensus:</u>

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

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

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

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

<u>If the CMDh position is reached by majority vote:</u>

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

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

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

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

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

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

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

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

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

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

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"

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

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

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

VII.C.5.1. PSUR EU regional appendix, sub-section "Proposed product information"

The assessment of the need for amendments to the product information is incorporated within the PSUR assessment procedure in the EU. The regulatory opinion/position should include recommendations for updates to product information where needed. Marketing authorisation holders should provide the necessary supportive documentation and references within the PSUR to facilitate this.

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

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

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

All the SmPCs and packages leaflets covered by the PSUR should be reviewed to ensure that they reflect the appropriate information accordingly to the cumulative data included and analysed in the PSUR.

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

~~**VII.C.5.2. PSUR EU regional appendix, sub-section "reference information comparison"**~~

~~In this sub-section, the marketing authorisation holder should highlight any important differences between the reference information in use and the proposals for product information in the EU. Examples of important differences may be those relating to adverse drug reactions, contraindications,~~

~~warnings, interactions and overdose. For the purposes of this comparison, the reference information in effect at the end of the reporting interval may be used but the marketing authorisation holder should highlight any important changes proposed/introduced in the time period between the data lock point and submission of the PSUR.~~

VII.C.5.2. PSUR EU regional appendix, sub-section "Proposed additional pharmacovigilance and risk minimisation activities"

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

VII.C.5.3. PSUR EU regional appendix, sub-section "Summary of ongoing safety concerns"

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

VII.C.5.4. PSUR EU regional appendix, sub-section "Reporting of results from post-authorisation safety studies"

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

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

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

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

VII.C.5.5. PSUR EU regional appendix, sub-section "Effectiveness of risk minimisation"

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The success of risk minimisation activities in delivering these objectives needs to be

evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised. In accordance with section VII.B.5.16.5., evaluation of broad global experience should be reflected in the body of the report.

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

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

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

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

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

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

- the list of EU reference dates and frequency of PSURs submission; or
- the conditions laid down in the marketing authorisation; or
- the standard PSUR submission schedule established according to DIR Art 107c(2) for products authorised before 2 July 2012 (for centrally authorised products) and 21 July 2012 (for nationally authorised products) as applicable (without any conditions in their marketing authorisation or not included in the list of EU references dates and frequency of submission or not affected by the derogation established in [DIR Art 107b(3)]); or
- ad hoc requests for PSURs by a competent authority in a Member State or the Agency.

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

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

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

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

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

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

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

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

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

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

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

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

All records related to PSURs created by the Agency's staff members, experts or consultants are the property of the Agency and all PSURs and related documents received are in the custody of the

Agency. Both types of PSURs records (created or received by the Agency) are subject to the Agency's overall control via the PSUR repository set up according to the provisions laid down in REG Art 25a.

The Agency's policy on records management (EMEA/590678/2007)[22], provides the basis for a consistent, sustainable and efficient records management program and it has been developed in accordance with the commonly recognised international standard for records management, "ISO 15489-1:2001 Information and documentation – Records management[23]". According to the records classification stated by the Agency's policy, PSURs would be considered business, legal, evidential and research/historical value records.

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

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

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

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

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

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

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

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

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

[22] www.ema.europa.eu
[23] www.ISO.org

VII.C.7. Transparency

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

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

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

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

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

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

VII.C.8. Renewal of marketing authorisations

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

No PSURs, addendum reports and summary bridging reports should be submitted within the renewal application. The clinical overview should include an addendum containing the relevant sections for the re-assessment of the risk-benefit balance of the medicinal product. These sections are identified in the above-mentioned guidelines for renewal. Marketing authorisation holders are advised to consider this GVP Module VII as guidance for the preparation of the addendum to the clinical overview.

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

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

VII.C.9. Transition and interim arrangements

VII.C.9.1. Submission and availability of documents before the Agency's repository is in place

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

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

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

The competent authorities in Member States requirements for the submission of PSURs during this transitional period are published in the Agency web-site[24].

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

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

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

- preliminary assessment report created by the PRAC Rapporteur/Member State within 60 days of the start of the procedure. The report should be circulated to the Agency and the members of the PRAC. The Agency should send the report to the concerned marketing authorisation holder(s);
- comments submitted by the marketing authorisation holders(s) and members of the PRAC by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report. These comments should also be circulated to all members of the PRAC by the marketing authorisation holder.

[24] www.ema.europa.eu

- updated PRAC Rapporteur/Member State assessment report created within 15 days (i.e. by Day 105) should be forwarded to the Agency and members of the PRAC.

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

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

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

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

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

VII.APPENDICES

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

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

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

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

Treatment	Number of Subjects
Medicinal product	
Comparator	
Placebo	

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

	Number of subjects		
Age range	Male	Female	Total

Data from completed trials as of [date]

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

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

Data from completed trials as of [date]

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																

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

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																

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

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

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

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 Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
<SOC 1>							
<PT>							
<PT>							
<PT>							
<SOC 2>							
<PT>							
<PT>							
<PT>							
<PT>							

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

** This does not include interventional clinical trials.

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

The tabular summary below is a fictitious example.

Table VII.9. Tabular summary of safety signals ongoing or closed during the reporting interval

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	Sportaneous 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 dermatologis t and literature searches	RSI updated with a warning and precaution DHPC sent Effectiveness survey planned 6 months post DHPC. RMP updated

Explanatory notes:

Signal term:

- A brief descriptive name of a medical concept for the signal. This may evolve and be refined as the signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s), depending on the source of signal.

Date detected:

- Month and year the marketing authorisation holder became aware of the signal.

Status:

- Ongoing: Signal under evaluation at the data lock point of the PSUR. Anticipated completion date, if known, should be provided.
- Closed: Signal for which evaluation was completed before the data lock point of the PSUR.

Note: A new signal of which the marketing authorisation holder became aware during the reporting interval may be classified as closed or ongoing, depending on the status of the signal evaluation at the end of the reporting interval of the PSUR.

Date closed:

- Month and year when the signal evaluation was completed.

Source of signal:

- Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous reports, clinical trial data, scientific literature, and non-clinical study results, or information request or inquiries from a competent authority (worldwide).

Reason for evaluation and summary of key data:

- A brief summary of key data and rationale for further evaluation.

Action(s) taken or planned:

State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed, otherwise leave blank for ongoing signals.