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3 Guideline on good pharmacovigilance practices (GVP)

4 Module VII – Periodic safety update report

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Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

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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 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC in respect of the format and content of electronic PSURs. 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".

This Module contains guidance for the preparation, submission and assessment of PSURs. The scope, objectives, format and content of the PSUR are described in VII.B., in accordance with the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)).

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.

Marketing authorisation holders should submit PSURs to the Agency according to the following timelines:

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

As a result of the new legal requirements for the electronic submission of suspected adverse reactions to the EudraVigilance database, it should be noted that detailed listings of individual cases should not be included routinely [IM Annex III.1(5)]. The PSUR should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.

Recital 23 of Directive 2010/84/EU newly establishes that the obligations imposed in respect of PSURs should be proportionate to the risks posed by medicinal products. PSURs reporting should therefore be linked to the risk management plans (RMPs) 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 RMP, by enabling the common content of particular sections to be utilised interchangeably across different PSURs, DSURs and RMPs.

The new legislation also waives the obligation to submit PSURs routinely for generic medicinal products, well-established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products [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

[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/

State on 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 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 shall 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 [DIR Art 107e]. 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 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 the 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 benefit-risk profile 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.

The PSUR should not be used to provide the 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 benefit-risk balance within PSURs

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

After marketing authorisation, it is necessary to evaluate, on an ongoing basis, the benefits and risks of medicinal products in actual use and/or long term use, to confirm that the benefit-risk profile remains favourable. This assessment may include evaluation of populations and/or endpoints that were not investigated in the registrational clinical trials.

The analysis of the risk-benefit balance should incorporate an evaluation of the available[2] safety, efficacy and effectiveness information collected during the reporting interval for the medicinal product in the context of what was known previously. This evaluation will include the following steps:

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 authorised indications based on the cumulative information available since the international birth date (IBD), the date of the first marketing authorisation in any country in the world / development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country.
4. Summarising any risk minimisation actions that may have been taken or are planned.
5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder should conclude the PSUR with considerations as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the product(s) for which the PSUR is submitted [IM Annex III.1(6)].

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

The marketing authorisation holder should prepare a single PSUR for all its medicinal products containing the same active substance with information on 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, should be presented in a separate section within the body of the PSUR and any safety concerns addressed accordingly, without preparing a separate PSUR [IM Annex III.1(7)]. 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 these cases, agreement from the competent authorities, preferably at the time of authorisation, should be obtained.

Case narratives must be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR [IM Annex III.1(5)].

[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.

Additional pharmacovigilance data, in particular, in relation to requests from competent authorities should be included in the PSUR. This may include analysis of cases classified as non-serious.

VII.B.4. Reference information

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

It is common practice for marketing authorisation holders to prepare their own company core data sheet (CCDS) which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The latest CCDS in effect at the end of the reporting interval should be used as the reference for both, the benefit and the risk sections of the PSUR. The core safety information contained within the CCDS is referred to as company core safety information (CCSI). For the definitions of CCDS and CCSI, see Annex I.

The marketing authorisation holder should discuss whether any revision of the CCDS/CCSI was needed during the reporting interval and ensure that all changes made over the interval are described in PSUR section 4 “Changes to the reference safety information” and/or PSUR section 16 “Signal and risk evaluation”. The marketing authorisation holder should provide a copy of all current versions of the CCDS (e.g. different formulations included in the same PSUR) referred in the PSUR as an appendix to the PSUR. The CCDS/CCSI should be dated, version controlled and it should state the version of the coding dictionary used.

The marketing authorisation holder should clearly highlight meaningful differences between the CCSI and their proposals for the local authorised product information. These meaningful differences should be included in PSUR regional appendix (see VII.B.5.20.).

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

A PSURs shall contain cumulative data starting from the granting of the marketing authorisation, though with the focus on new information emerging in the period since the data lock point of the last PSUR [IM Annex III.1(2)]. 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 non-authorised 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 should provide summaries of significant safety and efficacy information from all data sources, where relevant to the benefit-risk assessment and available to the marketing authorisation holder. These should include:

- summaries of information from marketing experience:
  - spontaneous data sources;
  - literature sources;
  - findings from active surveillance methodologies (e.g. data-mining in internal or external databases);
  - safety signals under evaluation by the marketing authorisation holders;
  - information from co-marketing or co-distribution partners, where relevant to the marketing authorisation holder’s approved product;

- summaries of information from clinical trials and studies:
  - ongoing clinical trials and other studies that the marketing authorisation holder or its representative is conducting or has completed during the reporting period (Phases I - IV);
  - therapeutic use of an investigational medicinal product;
  - observational or epidemiological studies;
  - drug utilisation studies;
  - non-clinical studies (toxicological and in vitro studies);
  - clinical trials conducted by a co-development or co-marketing partner;
  - clinical trials with results indicating lack of efficacy that could have a direct impact on the benefit-risk assessment;
- summaries of data from other sources:
  - any other source of relevant efficacy or safety findings for products in the same therapeutic class;
  - other PSURs or DSURs (e.g. from contractual partners or investigator initiated trials);
  - late-breaking information.

The PSUR shall be prepared following the full modular structure set out in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC [IM Annex III.2(1)]. When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on Periodic Benefit-Risk Evaluation Report (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.5.20.. When no relevant information is available for any of the sections, this should be stated

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PSUR title page

The title page should include the PSUR number (reports should be numbered sequentially), the name of the medicinal product(s), international birth date, 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, report number 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 post-authorisation exposure;
- 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 including significant changes to the investigator brochure and post-authorisation 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 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, reporting interval and sequential number of the report;
- 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;
- a brief description and explanation of any information that has not been included in the PSUR.

VII.B.5.2. PSUR section “Worldwide marketing approval status"

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

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 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.

The reason for each action should be provided, if known, and additional relevant information should be provided when 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 drugs:

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial[3] 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 marketed drugs:

- failure to obtain a marketing authorisation renewal;
- withdrawal or suspension of a marketing authorisation ;
- risk management activities including:
  - significant restrictions on distribution or introduction of other risk minimisation measures;
  - significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;
  - communications to health care professionals; and

[3] "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).

– 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, adverse events of special interest, and interactions; important findings from ongoing and 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. A tracked changes version of the reference document identifying the changes made during the reporting interval should be included as an appendix.

The marketing authorisation holder should also provide information on any final and ongoing changes to the national/local authorised product information based on the most recent version of the CCSI in the regional appendix, see VII.B.5.20..

VII.B.5.5. PSUR section "Estimated exposure and Use Patterns"

PSURs shall provide an accurate estimation of the population exposed to the medicinal product including all data relating to the volume of sales and volume of prescriptions. This estimation of exposure should be accompanied by a qualitative and quantitative analysis of actual use including how it may differ from indicated use based on all data available to the marketing authorisation holder including the results of observational or drug utilisation studies [IM Annex III.1(3)].

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.

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, if applicable presented in tabular formats[4]:

- 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 older products, detailed data might not be available;
- more detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial 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

[4] Examples of tables can be found in the ICH-E2C(R2) guideline, Appendix B, tables 1-3 (see Annex IV).

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.

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

When possible, separate estimations should be provided for cumulative exposure (since the IBD) and interval exposure (since the data lock point of the previous PSUR)[5]. Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. A justification should be provided if an estimate of the number of patients exposed is impossible to obtain. If an estimate of the number of patients is not available, alternative estimated measures 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;

[5] Examples of tables can be found in the ICH-E2C(R2) guideline, Appendix B, tables 4-5 (see Annex IV).

- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- patients of different racial and/or ethnic origins.

3. Pattern of use of the Medicinal Product

If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Such patterns may include, in particular, off-label use (e.g. an anti-epileptic drug used off-label for neuropathic pain and/or prophylaxis of migraine headaches). If known, the marketing authorisation holder may briefly comment on whether such use 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 which patterns of use are off-label, the marketing authorisation holder should reference the CCDS in the PSUR.

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

The objective of this PSUR section is to present clinical safety data through summary tabulations of adverse events/reactions. 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 the individual case safety reports (ICSRs) using the criteria established in ICH-E2A[6]. 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 analysis of adverse events/reactions.

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, for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. When useful and feasible, data can be presented by trial, indication, route of administration or other variables[7].

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

The following points should be considered:

[6] ICH Topic E2A. Clinical safety data management: Definitions and standards for expedited reporting.
[7] An example of summary tabulation can be found in the ICH-E2C(R2) guideline, Appendix B, table 6 (see Annex IV).

- 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; they should not include non-serious events.

- 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).

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 non-interventional studies, and spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and competent authorities. Serious and non-serious reactions should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC. For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables[8].

As described in ICH-E2D[9] guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter, although certain reports may need further evaluation (e.g. reports of hepatotoxicity).

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

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

The marketing authorisation holder should include as an appendix a listing of the sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during the reporting interval.

When possible and relevant, data categorized by sex and age (particularly children versus adult), indication, dose, and region should be presented.

[8] An example of summary tabulation can be found in the ICH-E2C (R2) guideline, Appendix B, table 7 (see Annex IV).
[9] ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

The signals arising from clinical trial sources should be tabulated in PSUR Section 15 ("Overview on Signals: New, Ongoing or Close"). For those that are considered to be either a potential or identified risk, the risk should be evaluated and characterised in PSUR Sections 16.3 ("Evaluation of risks and new information") and 16.4 ("Characterisation of risks"), respectively.

This PSUR section should provide a summary of the clinically important efficacy and safety findings obtained from the following sources during the reporting interval:

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. 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[10] (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 product 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.

[10] 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.

The marketing authorisation holder should include as an appendix a listing of any marketing authorisation holder-sponsored non-interventional study conducted with the 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 was completed or ongoing during the reporting interval (i.e. post-authorisation safety studies).

Progress or final study reports generated during the reporting interval for post-authorisation safety studies should also be included in the regional appendix of the PSUR (see VII.B.5.20.).

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

This PSUR section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources that is accessible[11] 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.5.10. 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. Implications of these findings should be discussed in the section 16 ("Signal and risk evaluation") and section 18 ("Integrated benefit-risk analysis for approved indications") 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, when relevant to the medicinal product that the marketing authorisation holder became aware during the reporting interval.

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.

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;

[11] See footnote 2

- medication error where no adverse events occurred, or “near misses”;
- important non-clinical safety results.

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

The publication reference should be provided in the style of the Vancouver Convention[12,13].

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 PSUR.

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

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

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 could reflect a significant risk to the treated population and should be summarised in this PSUR section.

When relevant to the benefit-risk evaluation, clinical trials demonstrating lack of efficacy for products not intended for treatment of life-threatening diseases in the approved indications should also be summarised in this section.

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 has taken for safety reasons. New individual case reports should not be 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.

These data 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 purpose of this PSUR section is to provide a high level overview of signals detected, under review and evaluated during the reporting interval.

[12] 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

[13] 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

The marketing authorisation holder should also provide a brief description on the specific signal detection methods used, as well as the sources screened for signals.

A newly identified signal refers to a signal that has been identified during the reporting interval. An ongoing signal refers to a signal that was still under evaluation at the data lock point. A closed signal refers to a signal for which an evaluation was completed during the reporting interval. Signals that are both newly identified and closed during the reporting interval should be handled in this section as closed signals (i.e., signals detected during the reporting period, with evaluation completed within the reporting period).

This section should consist of a tabulation of signals ongoing and closed during the reporting interval. The tabulation should be provided as an appendix to the PSUR and should conform to the template included in the ICH-E2C(R2) guideline, Appendix C (see Annex IV). At the discretion of the marketing authorisation holder, this tabulation may also provide cumulative signal data by including previously closed signals, in which case the starting point (date) for the cumulative data should be specified.

Detailed signal evaluations will not be included in this section but will instead be presented in the PSUR sections 16.2 (“Signal evaluation”) and 16.3 (“Evaluation of risks and new information”).

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

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

The purpose of this PSUR sub-section is to provide a baseline summary of important safety concerns against which new information and evaluations within the PSUR can be made. 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
- public perception of risk where it may impact public heath, (e.g. avoidance of vaccines).

The summaries should represent the best available knowledge of the product as of the beginning of the reporting interval of the current PSUR and should address:

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

For products with a safety specification (see Module V), the information included in this sub-section should be equal to the summaries provided in the version of the safety specification current at the beginning of the PSUR reporting interval.

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

- important adverse reactions;
- interactions with other medicinal products;
- identified medication error where no adverse events occurred, or near misses of medication errors;

- interactions with foods and other substances;
- occupational exposure;
- 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 PSUR sub-section should summarise the results of evaluations of safety signals that were closed during the reporting interval; there will be two main categories:

1. Signals that following evaluation have been categorised as a potential or identified risk, including lack of efficacy. These closed signals should be discussed in PSUR section 16.3 ("Evaluation of risks and new information").
2. Signals that following evaluation, have been rejected as false signals based on a scientific evaluation of the currently available information. For this category of signals, a description of each signal evaluation should be included in order to provide the basis upon which the signal was rejected. This description can be included in the PSUR body, or as an annex.

For signals that have had a completed evaluation during the reporting interval, it is recommended that the level of detail provided in the description of the signal evaluation be proportionate to the public health importance of the concern and the extent of the available evidence and should include the following information as appropriate:

- source or trigger of the signal;
- background relevant to the evaluation;
- methods of evaluation, including data sources, search criteria, and analytical approaches;
- results: a summary and critical analysis of the data considered in the signal evaluation;
- discussion;
- conclusion, including proposed actions.

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

Marketing authorisation holders should provide a critical appraisal of new information from the reporting interval on new or previously detected risks (important or other).

This PSUR sub-section should provide a description and evaluation of all risks detected during the reporting period, as well as an evaluation of the impact of new data on previously identified risks. This section should not summarise or repeat information presented in previous sections of the PSUR, but should provide an interpretation of the new information, with a view towards characterising the risk profile.

The new information can be organised as follows:

1. new potential risks;
2. new identified risks;
3. new information on previously detected risks (potential or identified);

4. update on important missing information.

Concise summaries of the evaluations of important risks should be provided. For "other" risks not classified as "important," for which new information has emerged during the reporting interval, the level of detail should be proportional to the available evidence on the risk and its public health relevance.

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 will characterise important identified risks and important potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe important missing information.

Where applicable, taking into account the data source, risk data should include the following:

- frequency;
- numbers of cases (numerator); 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 of life);
- public health impact;
- risk factors (e.g. patient factors (consider age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism, racial and/or ethnic origin), dose);
- duration of treatment, risk period;
- preventability (considering predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- reversibility;
- potential mechanism;
- strength of evidence and its uncertainties, including analysis of conflicting evidence if applicable.

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 the 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 active substances that are available as both prescription and non-prescription products);

- safety concerns regarding missing information.

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).

Result of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment shall be included [IM Annex III.1(4)].

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 that may be applicable across multiple regions are of particular interest. Information may be summarised by region, if applicable and relevant.

Results of evaluations that became available during the reporting interval should be provided in the regional appendix (see VII.B.5.20.), to comply with national or regional requirements.

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

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

This sub-section of the PSUR summarises baseline information on both efficacy and effectiveness of the medicinal product as of the beginning of the reporting interval. This information should relate to authorised indication(s) of the medicinal product, listed in the CCDS.

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

When there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, the summary should be succinct, essentially the content of the CCDS.

For medicinal products where there have been significant changes in either the risk or benefit profile, the sub-section should include sufficient information to support an updated characterisation of the benefit of the medicinal product in PSUR sub-section 17.3 ("Characterisation of benefits"). The type and extent of the information presented will vary by product, and may include the following, if available and relevant:

- the epidemiology and natural history of the disease;
- nature of the benefit (e.g. diagnostic, preventive, symptomatic , or disease modifying treatment);
- important endpoints that support the benefit (e.g. effects on mortality, symptoms, patient reported outcomes);
- evidence of efficacy and effectiveness by comparator (e.g. active-controlled trials, meta-analyses, observational studies); and

- when relevant to the benefit-risk evaluation; trends, patterns and/or evidence of benefit in important subgroups, (e.g. age, sex, ethnicity, disease severity, or genetic polymorphism).

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. Substantive information on evidence supporting use in non-authorised indications should not be included, unless relevant for the benefit-risk evaluation in the 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.

The type and extent of the information presented in this sub-section will vary by product, and could refer to PSUR sub-section 17.1 ("Important baseline efficacy and effectiveness information") if no new information became available.

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 became available during the reporting interval for authorised indications.

When there are no new relevant benefit data provided, and no significant change in risk profile, this sub-section should refer to PSUR 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 section should be succinct.

When there is significant change to the risk profile, or new evidence that suggests benefit is significantly less than originally demonstrated, this section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following, when applicable:

- 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. This section should provide a critical analysis and integration of the information in the previous sections with respect to benefit and risk, and should not duplicate the benefit and risk information presented in sections 16.3 ("Evaluation of risks and new information") and 17.3 ("Characterisation of benefits").

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

The benefit-risk evaluation should be presented in a structured manner, as described below:

- General points regarding benefits and risks:
  - Whereas previous sections will 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 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).
  - With respect to benefit, 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 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 off-label use, a new 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. For example, uncertainty in important benefits and/or risks may reduce their contribution(s) to 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.
- Comment on the feasibility of expressing benefits and risks in such a way as to facilitate their comparison.
- If a formal 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 based on cumulative data would be appropriate. 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"

The conclusion section of the PSUR should provide a conclusion about 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 CCDS/CCSI, and propose changes as appropriate.

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

For products with pharmacovigilance or risk management plan, the proposals should be incorporated into the pharmacovigilance plan and risk minimisation plan (see Module V).

VII.B.5.20. Appendices to the PSUR

The PSUR should contain the following appendices as appropriate:

1. Reference information
2. Cumulative summary tabulations of serious adverse events from clinical trials
3. Cumulative and interval summary tabulation of serious and non-serious adverse reactions from post-marketing data sources
4. Signal tabulation
5. Signals evaluation, when applicable
6. Listing of all post-authorisation safety studies
7. Regional appendix:

   The information included in this appendix should be used to comply with national or regional requirements[14].

[14] For the EU-specific requirements, see VII.C.5..

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 clinical study reports, literature screening, signal detection, validation and evaluation, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from available data sources and maintenance of product information. The quality system should describe the links within the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PSURs. There will 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.

As established in the content of the PSUR (see VII.B.5.), the PSUR should also contain the assessment of specific safety concerns requested by competent authorities. The marketing authorisation holder should have mechanisms in place to ensure that the requests made by the competent authority(ies) 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, safety 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 have not been addressed.

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 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 obligations provided by the

legislation. Explicit procedures and detailed agreements should exist between the marketing authorisation holder and the third parties.

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

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. 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. The 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. The PSUR process in the EU - General process

The following flowchart (Figure VII.1.) 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.

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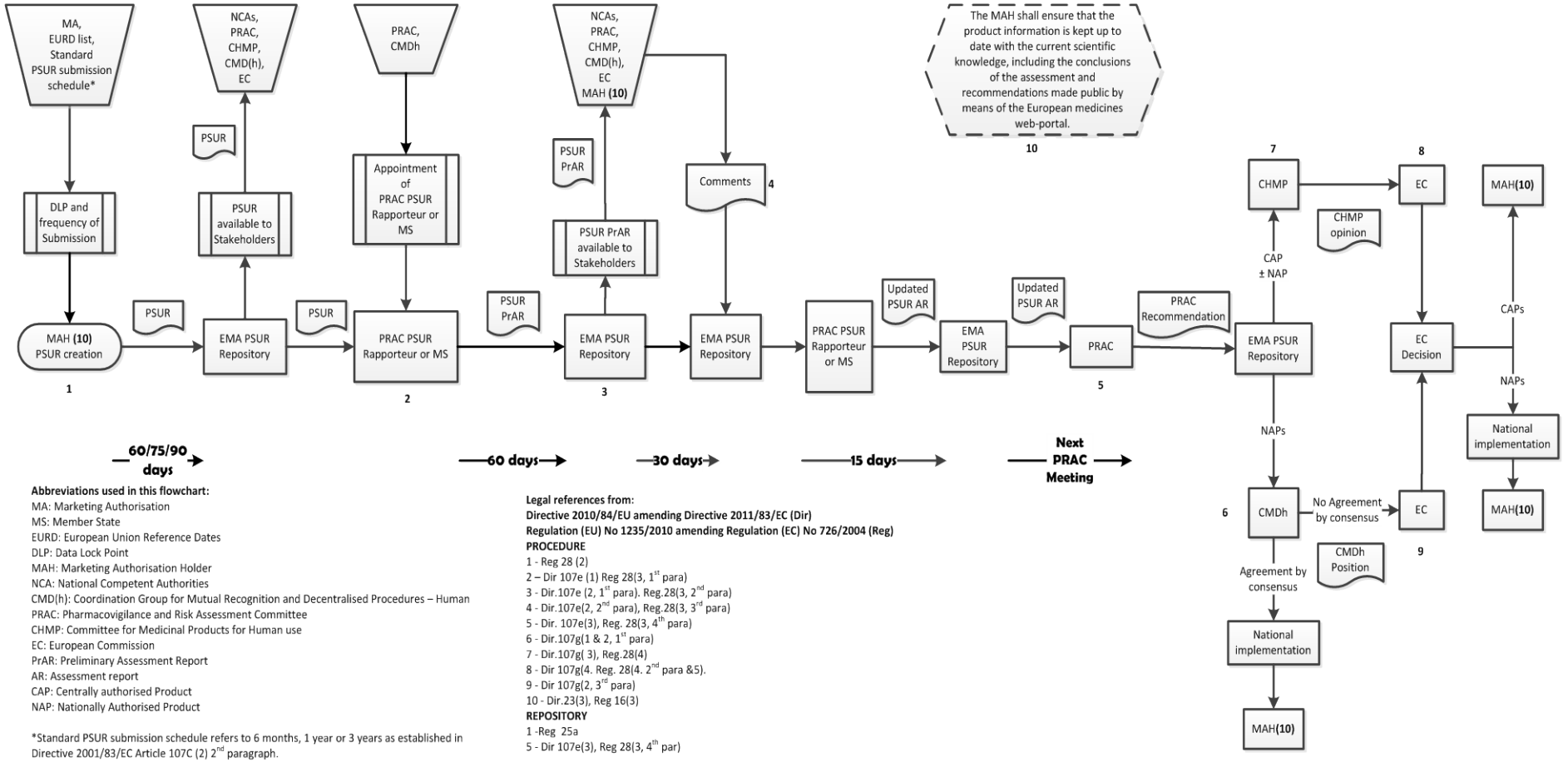

Abbreviations used in this flowchart:
MA: Marketing Authorisation
MS: Member State
EURD: European Union Reference Dates
DLP: Data Lock Point
MAH: Marketing Authorisation Holder
NCA: National Competent Authorities
CMD(h): Coordination Group for Mutual Recognition and Decentralised Procedures – Human
PRAC: 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

*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 from:
Directive 2010/84/EU amending Directive 2011/83/EC (Dir)
Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (Reg)
PROCEDURE
1 - Reg 28 (2)
2 – Dir 107e (1) Reg 28(3, 1st para)
3 - Dir.107e (2, 1st para). Reg.28(3, 2nd para)
4 - Dir.107e(2, 2nd para), Reg.28(3, 3rd para)
5 - Dir. 107e(3), Reg. 28(3, 4th para)
6 - Dir.107g(1 & 2, 1st para)
7 - Dir.107g(3), Reg.28(4)
8 - Dir 107g(4. Reg. 28(4. 2nd para &5).
9 - Dir 107g(2, 3rd para)
10 - Dir.23(3), Reg 16(3)
REPOSITORY
1 -Reg 25a
5 - Dir 107e(3), Reg 28(3, 4th par)

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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 the product is marketed, 6 monthly PSURs submission should be continued following initial placing on the market in the EU and until 2 years of marketing experience in the EU, then once a year for the following 2 years and thereafter at 3-yearly intervals.

PSURs shall also be submitted at any time immediately upon request by the national competent authority(ies) or the Agency.

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

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 will 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.

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 sorted 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 EU list will 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 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 the substance or combination of active substance;
- 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.).

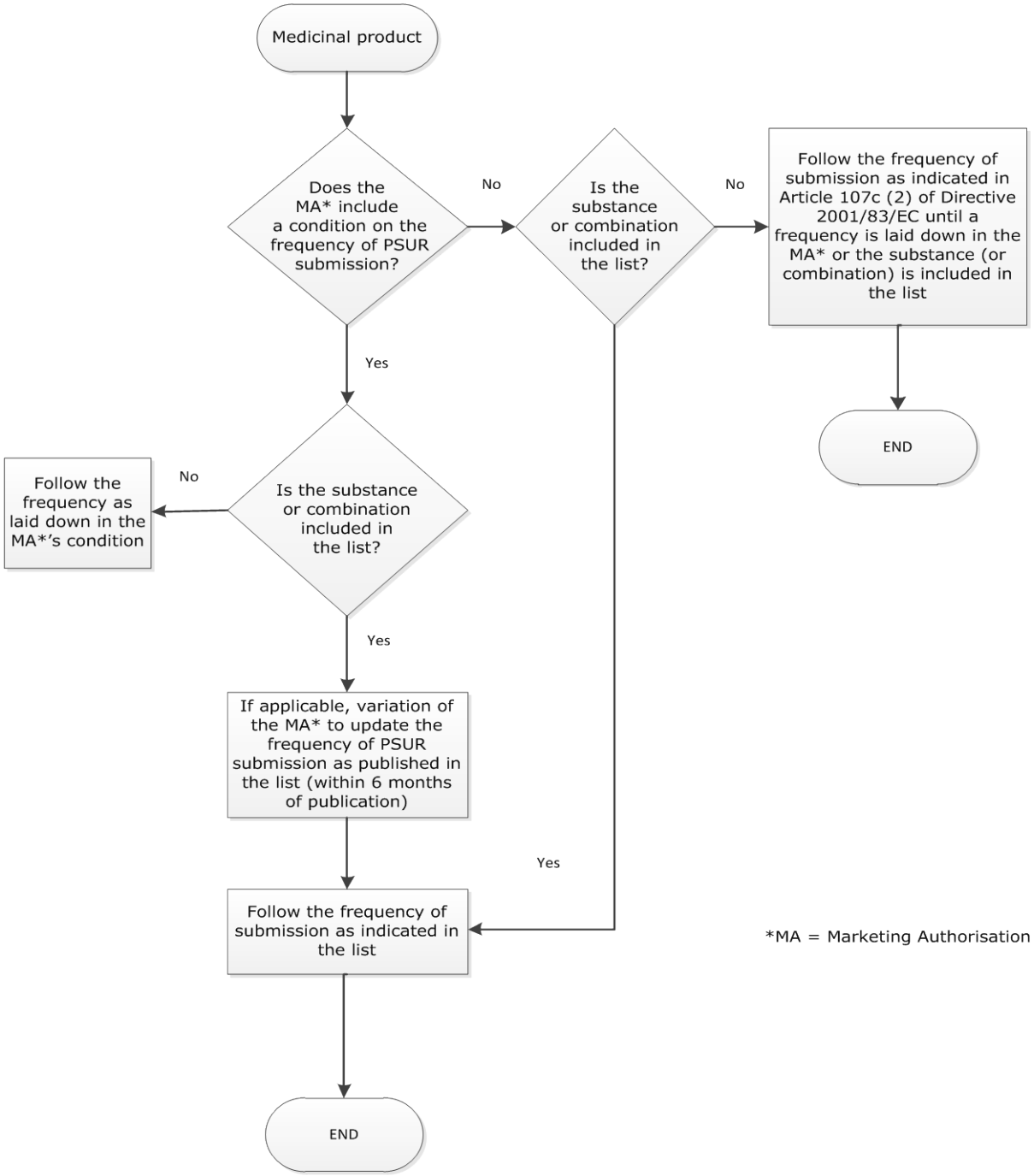
The list should be updated in line with the “list of all medicinal products for human use authorised in the Union” as referred to in [REG Art 57(b)].

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.2. presents the various potential scenarios as regard the submission of a PSUR as a general requirement.

Figure VII.2. Conditions for PSURs submission as general requirement



Unless otherwise specified in the list of EU reference dates and frequency of submission, a single PSUR should be prepared for all medicinal products containing the same active substance and authorised for one marketing authorisation holder, including all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures [IM Annex III.1(7)].

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), 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. 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].

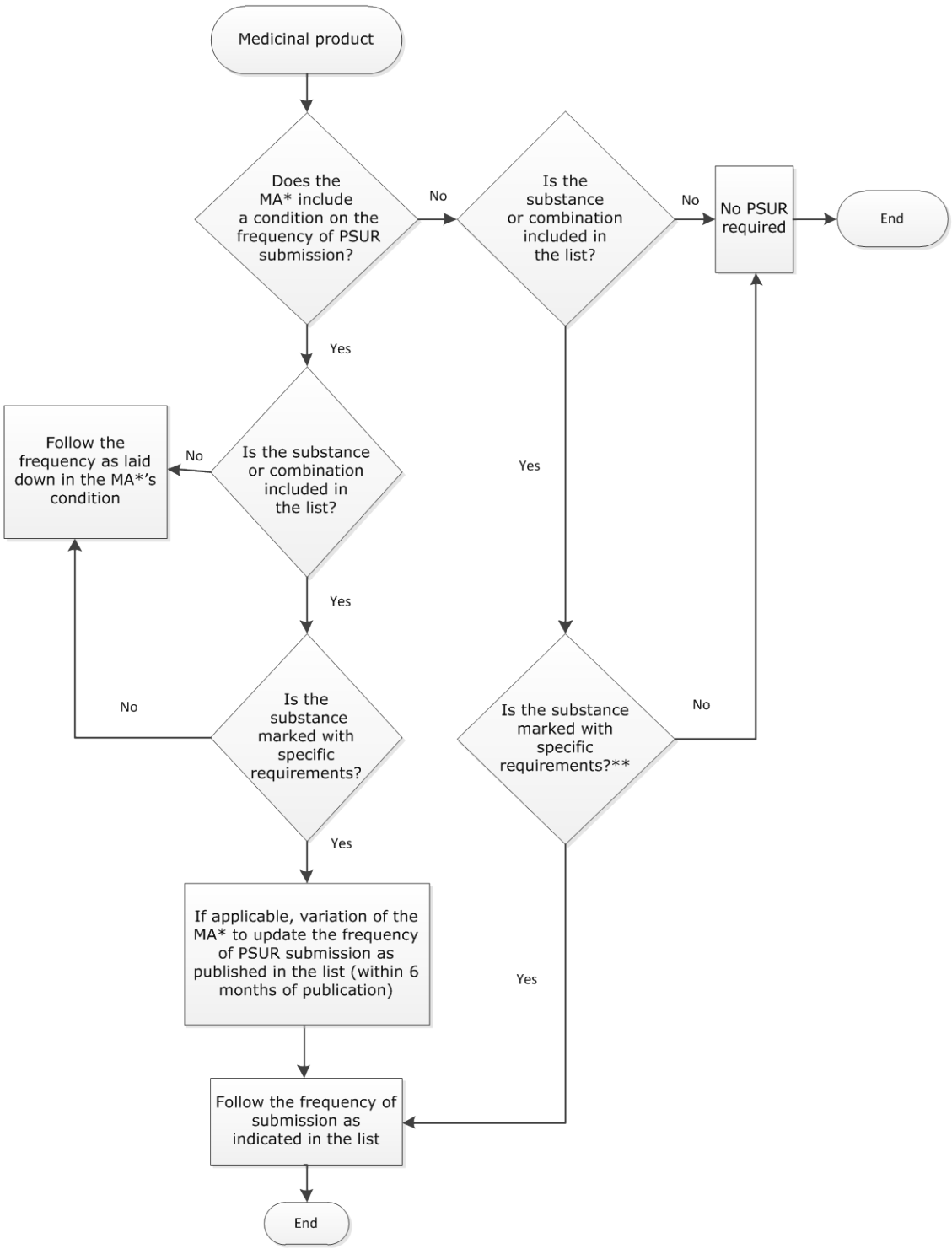
In order to facilitate and optimise the PSUR EU single assessment process, to avoid duplications of requests for PSURs and to provide transparency and predictability for the marketing authorisation holders, the legislative provision laid down in [DIR 107b(3)(b)] will be applied by specifying in the list 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 Union reference dates are determined by the CHMP and/or CMDh after consultation of the PRAC.

The application of the list of Union 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].

The flowchart in Figure VII.3. presents the various potential scenarios as regard the submission of a PSUR for generic, well-established use, traditional herbal and homeopathic medicinal products:

1148 **Figure VII.3.** Conditions for PSURs submission for generic, well-established use, traditional herbal
1149 and homeopathic medicinal products



*MA: Marketing Authorisation

**Specific requirements refer to:
- whether marketing authorisation holders for generic, 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 concerns relating to pharmacovigilance data or lack of PSUR submission and;
- whether or not the PSUR should cover all the indications, formulations, route of administrations.

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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, there are two options for products containing the same combination of active substances. The marketing authorisation holder shall either submit a stand-alone 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. [IM Annex III.1(8)].

As stated under VII.B.2., agreement with the competent authority(ies) in Member States or the Agency and the marketing authorisation holders should be reached as to the submission of a stand-alone PSUR for the combination of active substances, or to the possibility to analyse data on the combination within one of the single active substance's PSUR.

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 may make use of the list of EU reference dates to request the submission of PSURs.

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 (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

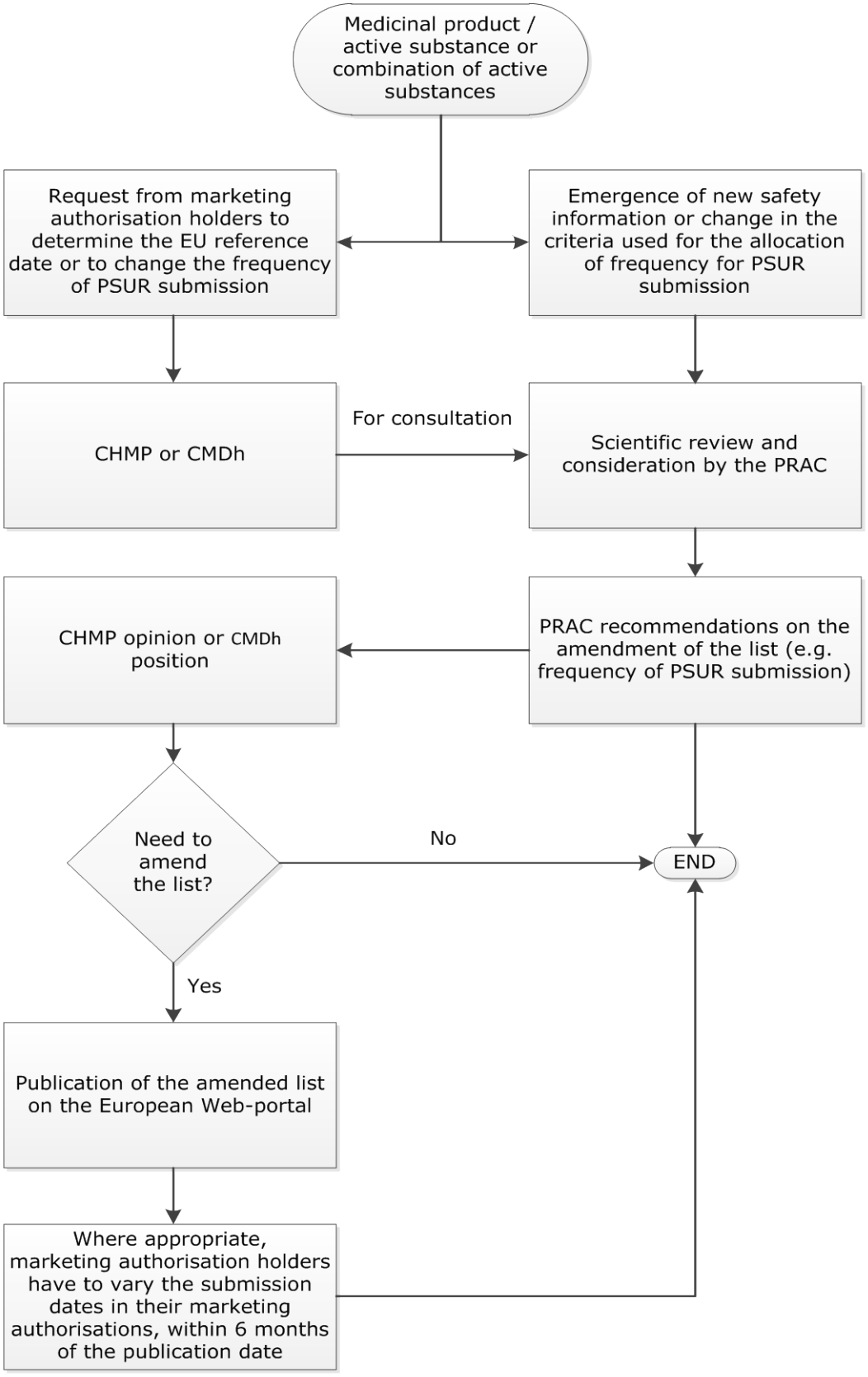
The maintenance of the list of EU reference dates should facilitate regulatory responsiveness to public health concerns identified within the EU and therefore the list will be subject to changes to reflect the decisions taken (e.g. by the Agency's committees following signal detection).

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

1205 **Figure VII.4.** Maintenance of the list of EU reference dates and frequency of submission of PSUR



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

The marketing authorisation holders shall be allowed to submit 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 sent via email <address> before it can 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.).

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 the week following its adoption by the CHMP or the CMDh. It is expected to be updated monthly.

Marketing authorisation holders shall continuously check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures [IM Art 14(e)].

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 PSUR 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 within these six months 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 and containing an active substance or combination of active substances for which an EU reference date and harmonised frequency has not been established, the assessment of PSUR is conducted by the competent authority in the Member State where the product is authorised (see VII.C.4.1.).

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, a 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 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 maintain, 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 is legally binding and can result in the marketing authorisations of the concerned medicinal products being varied, suspended or revoked on the basis of the position of the CMDh or the opinion of the CHMP following the recommendations from the PRAC. The recommendations are therefore implemented in a harmonised and timely manner for all products within the scope of the procedure across the EU.

VII.C.4.1. PSURs for purely nationally authorised medicinal products not on the list of EU reference dates

It is the responsibility of the competent authority in the Member State to evaluate PSURs for these medicinal products.

The assessment of the PSUR is conducted in accordance with the national legislation. Listings of individual case safety reports 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 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 shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary. They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate [DIR Art 107f] according to the appropriate procedure at national level.

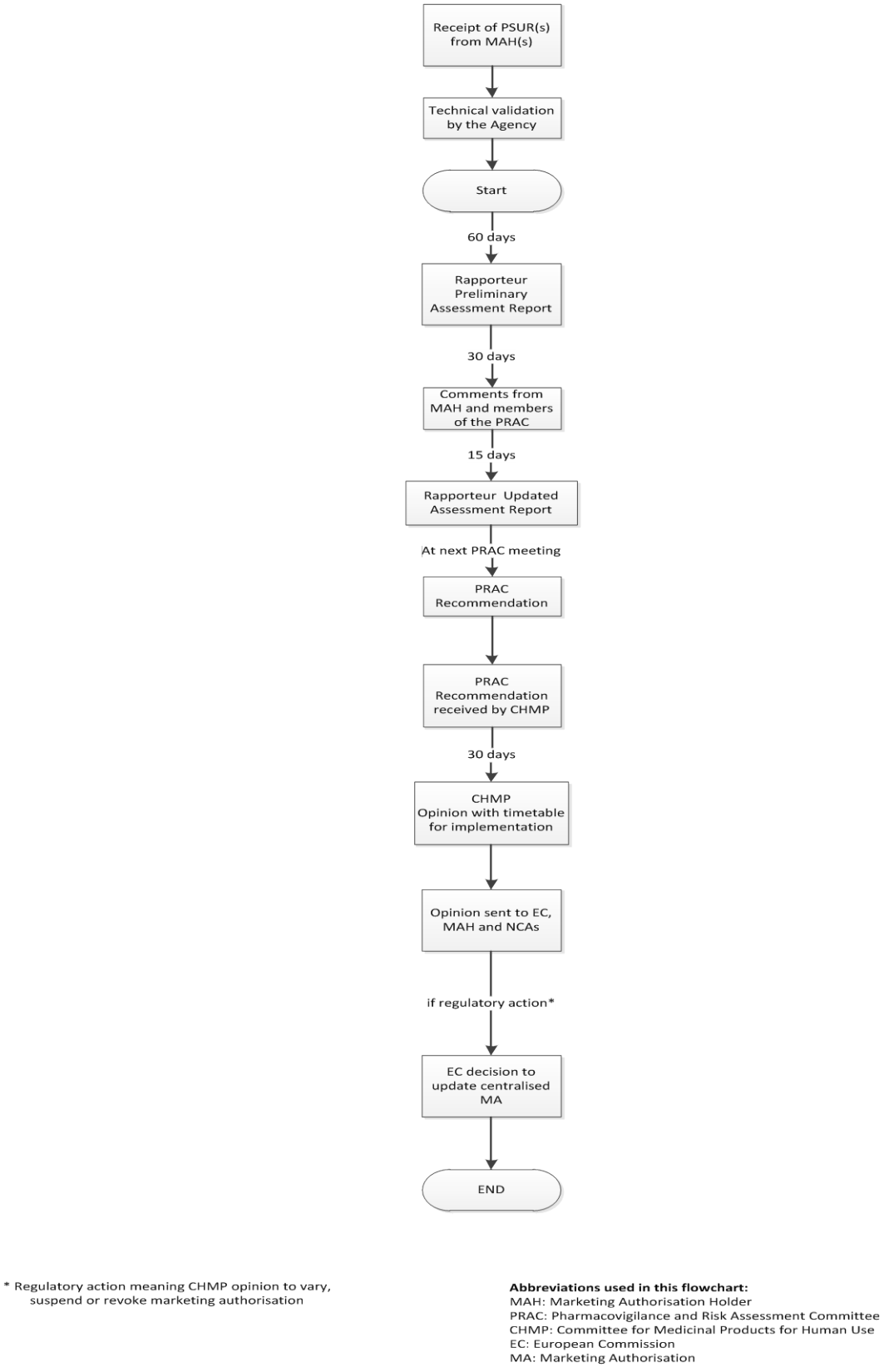
The assessment report and conclusions of the competent authority in the Member State should be provided to the marketing authorisation holder.

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.5.).

1279 **Figure VII.5.** PSUR assessment procedure for a single centrally authorised medicinal product



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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* retrieved from EudraVigilance database, and other relevant data, are created by the Agency and made available to the PRAC Rapporteur.

**Drafting note: this provision will be reviewed and implemented in light of the EudraVigilance implementation plan and reporting transitional arrangements.*

Further to the above verifications and provision of EudraVigilance data, 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 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.

During the drafting of the assessment report, the PRAC Rapporteur shall closely collaborate with the CHMP Rapporteur [REG Art 28(3)]. The PRAC Rapporteur’s assessment of the PSUR should be performed using the assessment report template available in Annex III.

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 from 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, using the template available in Annex III.

Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG Art 28(3)] using the template available in Annex III, 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 request an update of the RMP, the need to conduct a post-authorisation safety study, review of safety issues and close monitoring of events of interest. Templates to be used by the PRAC are available in Annex III.

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)].

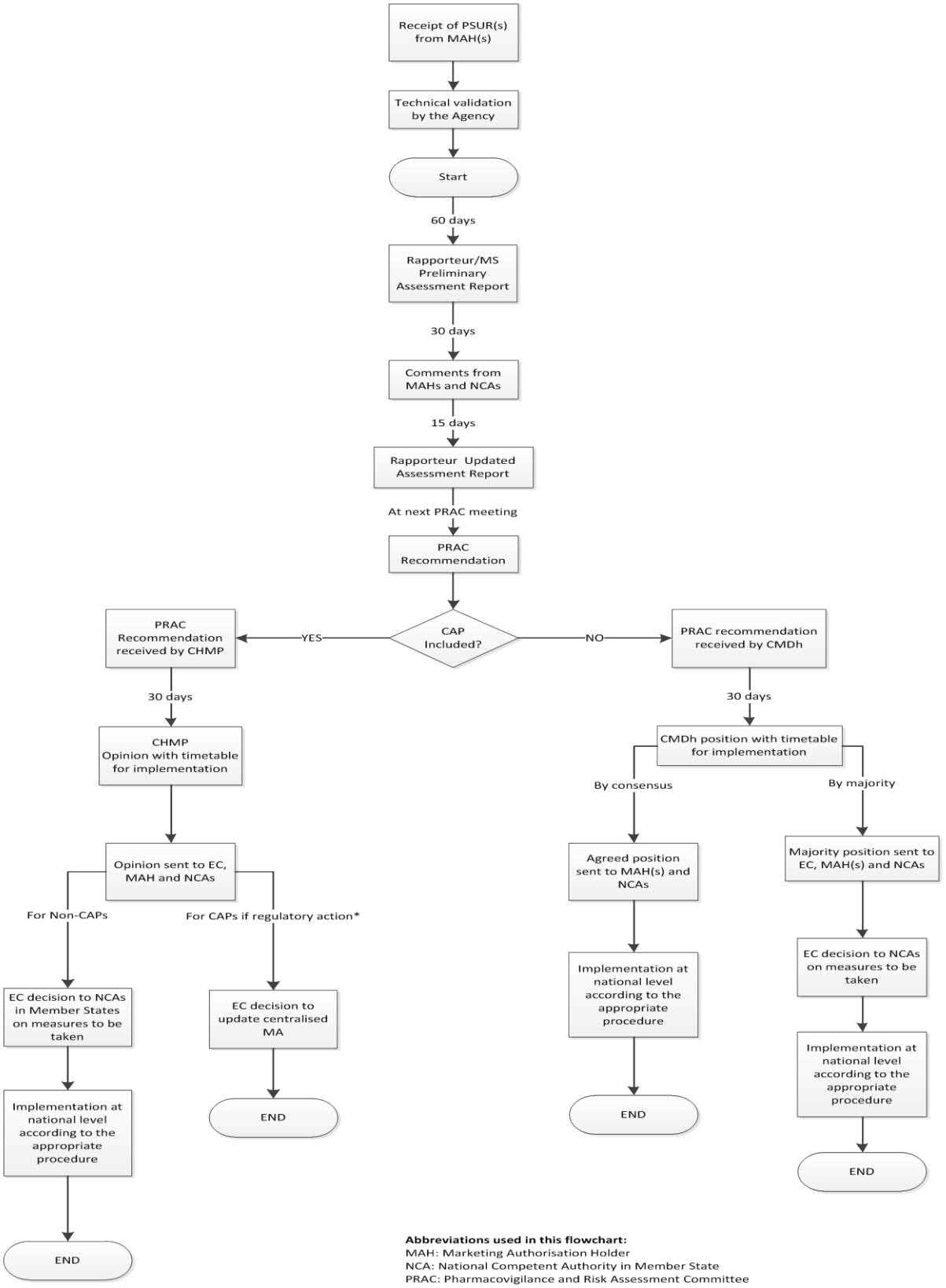
The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder [REG Art 28(3)].

Further to adoption at the PRAC meeting, 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 hold 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).

1339 **Figure VII.6.** PSUR assessment procedure for "EU single assessment"



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The assessment of the 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 also will 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 will 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, summary tabulations and other relevant data are created and retrieved from the EudraVigilance database by the Agency* and made available to the PRAC Rapporteur or Member State.

**Drafting note: this provision will be reviewed and implemented in light of the EudraVigilance implementation plan, reporting transitional arrangements and staff allocation.*

Further to the above verifications and provision of EudraVigilance data, 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. The PSUR assessment should be prepared using the assessment report template available in Annex III.

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 from 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, using the template available in Annex III.

Following receipt of comments, the PRAC Rapporteur/Member State shall prepare an updated assessment report [DIR Art 107e (3)] using the template available in Annex III, 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 request an update of the RMP, the need to conduct a post-authorisation safety study, review of safety issue and close monitoring of events of interest. Templates to be used by the PRAC are available in Annex III.

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, 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 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):
  - for centrally authorised products, revised product information and if applicable, 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. This annex should also include timelines for implementation by the competent authorities in Member States;

- 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. This annex should also include timelines for implementation by the competent authorities in Member States;
- in the case of a CHMP opinion to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation. This annex should also include timelines for implementation by the competent authorities in Member States;
- 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). The Agency and the competent authorities in Member States will also receive the decision in electronic form.

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 and further to consultation of the Standing Committee, 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 maintain, vary, suspend or revoke the marketing authorisation(s), within 30 days unless otherwise specified in the timetable for implementation as appended to the decision [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 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), 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. This annex should also include timelines for implementation by the marketing authorisation holder to submit a variation;
- 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. This annex should also include timelines for implementation by the competent authorities in Member States;
- in the case of a CMDh position to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation This annex should also include timelines for implementation by the competent authorities in Member States;
- divergent position(s) for the CMDh members, where applicable.

The final assessment conclusions and recommendations are published in the European medicines web-portal (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 maintain, 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.

If the CMDh position is reached by majority vote:

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 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 and further to consultation of the Standing Committee, the European Commission shall adopt decision(s) [DIR Art 107g(2)] addressed to the competent authorities in Member States in order for them to maintain, 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 unless otherwise specified in the timetable for implementation as appended to the agreed position [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, an updated 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 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 2 – "Worldwide marketing approval status" and EU marketing approval status included in the EU Regional Appendix	Sub-section of part I – "Product overview"
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 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 newly established by Article 107b of Directive 2001/83/EC and by the Implementing Measure [IM Annex III.1(1)].

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

VII.C.5.1. PSUR EU regional appendix, sub-section "Additional pharmacovigilance and risk minimisation activities"

For products without an RMP, the proposals for additional pharmacovigilance and additional risk minimisation activities based on the conclusions and actions should be included in this PSUR section, including the submission of an RMP when applicable.

VII.C.5.2. PSUR EU regional appendix, sub-section "EU marketing authorisation status"

Marketing authorisation holders should provide a detailed description of the marketing status for all Member States where marketing authorisation(s) have been granted. This information should contain the following:

- dates of marketing authorisation and subsequent renewal;
- any qualifications surrounding the authorisation, such as restrictions of indications if relevant to safety;
- indications and special populations covered by the marketing authorisation;

- lack of marketing authorisation, including explanation, by competent authorities in Member States;
- withdrawal by the marketing authorisation holder of an application for authorisation submission if related to safety or efficacy;
- dates of launch and cessation if any (where PSURs are common for identical products with different invented names or in the case of generics, the listing of the dates should cover separately all products);
- dates when the marketing authorisation has been revoked/withdrawn or dates when the marketing or marketing authorisation has been suspended either by a competent authority or voluntarily by the marketing authorisation holder;
- invented name(s).

Typically, indications, populations (e.g. children versus adults) and pharmaceutical forms will be the same in many or even most Member States where the product is authorised. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the new benefit and/or safety information that is related to such different exposures.

If more convenient and useful, separate regulatory status tables for different product uses or forms should be utilised.

Entries by Member States should be listed in chronological order of marketing authorisations.

VII.C.5.3. PSUR EU regional appendix, sub-section "Company core safety information and summary of product characteristics"

The marketing authorisation holder should include in this section the meaningful differences between the CCSI and their proposals for the summary of product characteristics (SmPC).

When the marketing authorisation holder considers that changes to the SmPC are required in line with the provisions established in Article 16(2) of Regulation (EC) No 726/2004 and Article 23(2) of Directive 2001/83/EC, the proposed amendments to the SmPC should be submitted with the PSUR provided these changes are in relation to the new safety information regarding the new interval covered. If not directly related to the new safety information, the amendments should not be delayed. 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.

The proposed SmPC and package leaflet should be included as an appendix to the PSUR.

VII.C.5.4. PSUR EU regional appendix, sub-section "Summary of ongoing safety concerns"

In order to support the information provided in PSUR section "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 section. This table will be extracted from the version of RMP available at the beginning of the PSUR reporting period (See Module V).

VII.C.5.5. PSUR EU regional appendix, sub-section "Reporting of results from post-authorisation safety studies"

Findings from both interventional and non interventional post-authorisation safety studies (PASS) (see Module VIII) 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.

Progress reports and final study reports generated during the reporting interval should be also included as an annex to the PSUR.

For studies ongoing during the reporting period, the content of the progress report should follow a logical sequence and should include all the available data which is judged relevant for the progress of the study, e.g. number of patients who have entered the study according to their status (e.g. exposure, outcome) and problems encountered and deviations from the expected plan. Any additional information requested by competent authorities in Member States should also be included in the progress report.

For those non-interventional post-authorisation safety studies being a condition to the marketing authorisation and for those included in the RMP the format and content of the final study report should follow the provisions of the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC on the format of protocols, abstracts and final study reports for the post-authorisation safety studies provided to in Article 87a(g) of Regulation (EC) No 726/2004 and Article 108(g) of Directive 2001/83/EC. For studies discontinued during the reporting period, 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. This information and the outcome of its evaluation should be discussed in the study progress report sent to the competent authorities in Member States which should be also included in the PSUR EU regional appendix.

PSURs should not be used as the initial communication method either for the submission of progress and 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.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

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
- 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

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

For those medicinal products where the submission of a RMP is not required, the marketing authorisation holder should maintain on file a specification of important identified risk, 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 will be created using validated reports by means of the EudraVigilance data analysis system. The validation of the reports should be documented together with a detailed description of the scope, production, quality control and storage of the line listings and summary tabulations from EudraVigilance.

Effective communication and circulation of PSURs and related documents will be 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 will establish the necessity for quality checks with the aim to remove any information of a personal or commercially confidential nature.

The list of EU references dates and frequency of submission of PSURs published by the Agency in the European medicines web-portal should undergo a quality control check during the update process in order to properly reflect the decisions regarding the frequency of PSURs submission. Written procedures should reflect the different steps to follow for the maintenance of the list and its version control (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)[15], provides the basis for a consistent, sustainable and efficient records management programs 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[16]". 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 product-related documents, i.e. the PSURs and related documents, including the 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. Furthermore competent authorities should exchange information in cases on 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 and containing an active substance for which a EU reference date and harmonised frequency has not been established; 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 authorised in more than one Member State 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 the effective

[15] www.ema.europa.eu
[16] www.ISO.org

communications 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 shall 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 product-related documents, i.e. the PSURs and related documents, including the assessment reports, the data retrieved from the EudraVigilance database or other data used to support the PSUR assessment

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 documents listed in section VII.C.7.1. with the exception to the European Commission decision, should be made publicly available at the latest two weeks following the CMDh and the CHMP plenaries.

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. This information is moreover necessary as it constitutes the temporal basis for the implementation of the required regulatory actions.

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. Transition and interim arrangements

VII.C.8.1. 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].

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 Member State only or more than one Member State 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 [DIR Art 2(7)]. 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 specific addresses to comply with this requirement are provided in Annex <no>.

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), IM Annex III.2(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, the 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:

- preliminary assessment report created by the Rapporteur within 60 days from the start of the procedure. The report will be circulated to the Agency and the members of the PRAC. The Agency will 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 Rapporteur's preliminary assessment report. The comments should be submitted using the template available in Annex III;
- updated Rapporteur's assessment report created within 15 days (i.e. by Day 105) will 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.8.2. 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.8.3. 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 will be published in the European medicines web-portal, nevertheless, the EU single assessment procedure detailed in VII.C.4.2.2., VII.C.4.2.3. and VII.C.4.2.4. will be delayed until funds are available.