Annex 12
to Pharmacovigilance Procedure
(item 1 of chapter 3 of part V)

STRUCTURE of periodic safety update report

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REQUIREMENTS FOR COMPLETION OF PERIODIC SAFETY UPDATE REPORT

Title page

The title page should include the name(s) of the medicinal product(s), vaccine(s), tuberculin (hereinafter – medicinal product) (for periodic safety update reports (hereinafter – PSUR), which cover several medicinal products, this information may be placed to title page of the PSUR) and active pharmaceutical ingredient (hereinafter – API), international birth date of the medicinal

product, reporting interval, date of drawing up the report, applicant details and statement of confidentiality of the information included in the periodic safety report.

The title page shall be attested by the signature of the person, who drew up the PSUR.

Executive Summary

A concise summary of the content and the most important information in the PSUR should be provided:

introduction and reporting interval;

medicinal product(s), therapeutic chemical or pharmacological class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;

estimated cumulative clinical trials exposure;

estimated cumulative and interval exposure from post-registration experience;

number of countries in which the medicinal product is registered;

summary of the overall benefit-risk analysis evaluation (based on data given in sub-section XVIII.2 "Benefit-risk analysis evaluation" of the PSUR);

actions taken and proposed for safety reasons, (e.g. significant changes to the medicinal product information, or other risk minimisation activities);

conclusions.

Table of contents of the PSUR

Section I. Introduction

The PSUR shall be a stand-alone document but it is also placed in perspective relative to previous periodic safety report by means of a concise description of medicinal product(s), vaccine, tuberculin and other important data. The introduction should contain the following information:

International birth date of the medicinal product, and reporting interval;

medicinal product(s), therapeutic chemical or pharmacological class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;

a brief description of the population(s) being treated and studied.

Section II. Worldwide registration status

A brief narrative overview, including date of the first registration worldwide, indications(s), registered dose(s), countries, where the medicinal product is registered, shall be provided.

Section III. Actions taken in the reporting interval for safety reasons

A description shall be provided for significant actions related to safety that have been taken worldwide during the reporting interval by the registration certificate holder, sponsors of clinical trial(s), ethics committees or authorized bodies, related to either investigational uses or post-

registration experience (regardless of their relation to the use of medicinal product) that had either a significant influence on the risk-benefit balance of the registered medicinal product; and/or an impact on the conduct of a specific clinical trial(s) or on the overall clinical trial programme.

The reason for each action should be provided and any additional relevant information should be included in the PSUR as appropriate. Relevant updates to previous actions for safety reasons should also be summarised in this section (for example, actions related to investigational uses of the medicinal product (refusal to authorize a clinical trial for ethical or safety reasons); partial (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) or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy; recall of investigational medicinal product or comparator; refusal of registration for tested indications, including voluntary withdrawal of an application for registration; risk management activities; actions related to marketing experience (refusal of a re-registration or failure to apply for a re-registration; withdrawal or suspension of a registration certificate; actions taken due to quality issues; suspension of supply of the medicinal product by the registration certificate holder; risk management activities)).

Section IV. Changes to reference safety information

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

Section V. “Estimated exposure and use patterns

An accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and number of prescriptions shall be provided. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use of the medicinal product, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the registration certificate holder, including the results of observational or drug utilisation studies. 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 all PSURs for the same medicinal product. If a change in the method is made for objective reasons, both methods and calculations shall be provided in the PSUR specifying the change and any important difference between the results using the two methods.

Sub-section V.1. Cumulative subject exposure in clinical trials

This section should contain information on the subjects of clinical trials sponsored by the registration certificate holder, if applicable presented in tabular formats, namely:

cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the Development International Birth Date of the medicinal product;

more detailed cumulative subject exposure in clinical trials should be presented (e.g. data 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 shoud be noted in the tables, if applicable, or separate tables can be used;

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 different clinical trials, it can be useful to express medicinal product exposure in subject-time (subject-days, -months, or -years);

investigational medicinal product exposure in healthy volunteers might be less relevant to the assessment of 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.

Sub-section V.2. Cumulative and interval patient exposure from post-registration experience

Estimates should be provided for cumulative exposure (since the international birth date), and interval exposure (since the data lock point of the previous PSUR). Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, shall be presented along with the method(s) used to derive them. The concept of a defined daily dose (DDD) may also be used to arrive at estimates of exposure to the medicinal product.

The data shall be presented according to the following categories:

Post-registration (non-interventional study) exposure (an overall estimation of patient exposure should be provided. The data should be presented by sex, age, indication, dose, formulation, etc., where applicable. Depending upon the medicinal product, other variables may be relevant - number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports on adverse reactions indicating a safety signal, exposure data within relevant subgroups should be presented, if possible);

Post-registration use in special populations (where post-registration use of the medicinal product has occurred in special populations, information regarding cumulative patient numbers exposed and the method of calculation shall be provided. Sources of such data may include non-interventional studies performed to obtain this information, including registries, data collection outside a study environment including information collected through spontaneous reporting (e.g. information on reports of pregnancy exposure to medicinal product without an associated adverse reactions may be summarised in this item). Populations to be considered include (but might not be limited to): paediatric population; elderly population; pregnant or lactating women; patients with hepatic and/or renal impairment; patients with other relevant co-morbidity; patients with disease severity different from that studied in clinical trials; sub-populations carrying relevant genetic polymorphism(s); populations with specific racial and/or ethnic origins);

Other post-registration use of the medicinal product (if the registration certificate holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, a brief description thereof should be provided. Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without

reference to adverse reactions should be summarised in this section. Such information may be received via spontaneous reporting systems, medical information queries, patient's complaints, or via other information sources. If quantitative information on the above data is available, it should be provided in this sub-section. If known, the registration certificate holder shall briefly comment on whether other use beyond the recommendation(s) in the reference information on medicinal product may be linked to clinical guidelines, results of clinical trial results, or it is caused by an absence of registered alternative treatments. For purposes of identifying patterns of use outside the reference information on medicinal product, the registration certificate holder should use the appropriate sections of the reference information on medicinal product that was in effect at the end of the reporting interval of the PSUR (e.g. registered indication, route of administration, contraindications). Signals or risks identified from such data or information source should be presented and evaluated in the relevant sections of the PSUR.

Section VI. Data in summary tabulations

Safety data shall be presented through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific and medical literature, authorized bodies (worldwide) and serious reactions from non-interventional studies and other non-interventional sources of information on adverse reactions. When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations. The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the individual case safety reports using the criteria established in ICH-E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). When serious and non-serious events/reactions are included in the same the individual case safety report, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness of adverse event/reaction should not be changed specifically for the preparation of the PSUR.

Sub-section VI.1. Reference information

The version(s) of the reference information (dictionary) used for presentation of adverse events/reactions shall be specified.

Sub-section VI.2. Cumulative summary tabulations of serious adverse events from clinical trials

Background should be provided for the appendix that contains a cumulative summary tabulation of serious adverse events reported in the registration certificate holder's clinical trials, from the development international birth date to the data lock point of the current PSUR. The registration holder should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational medicinal product, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. When useful and feasible, data can be presented by trial, indication, route of administration or other variables. This sub-section should not serve to provide analyses or conclusions based on the serious adverse events.

The following points should be considered during preparation of this sub-section:

Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. This 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 product, comparators and placebo. It may be useful to give rates by dose;

In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports;

The tabulations should include blinded and unblinded clinical trial data. Information on serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting). Sponsors of clinical trials and registration cetificate 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 substantiated 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 clinical trial endpoints (e.g. deaths reported in a trial of a product for congestive heart failure where all-cause mortality is the primary efficacy endpoint, or disease progression in cancer trials)).

Sub-section VI.3. Cumulative and interval summary tabulations from post-registration safety data sources

Background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the international birth date of the medicinal product to the data lock point of the current PSUR, should be given. These adverse reactions are derived from spontaneous reports including reports from workers with medical and pharmaceutical qualification, consumers, scientific literature, authorized bodies (worldwide) and reports from solicited non-interventional studies (ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting). Data on serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC (listed in the internationally agreed order). Data for special safety issues or concerns can be presented in additional tabulations by indication, route of administration, or other variables. Analysis or conclusions based on the summary tabulations should not be provided in this subsection of PSUR.

Section VII. Summaries of significant findings from clinical trials during the reporting interval

A brief description of the clinically important emerging efficacy and safety findings obtained from the registration certificate holder's sponsored clinical trials during the reporting interval, from the sources specified in the sub-sections listed below, shall be provided. When possible and relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and administrative territorial unit shall be provided.

Signals arising from clinical trial sources should be tabulated in section XV "Overview of signals: new, ongoing or closed" of the PSUR. Evaluation of the signals, whether or not categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in sub-section XVI.2 "Signal evaluation" of the PSUR. New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in sub-sections XVI.3 "Evaluation of risks and new information" and XVI.4 "Characterisation of risks" respectively.

Findings from clinical trials not sponsored by the registration certificate holder shall be described in the relevant sections of the PSUR.

When relevant to the benefit/risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in registered indications shall also be summarised in this section.

Information on lack of efficacy from clinical trials with medicinal products intended to treat or prevent serious or life-threatening illness shall be summarised in section XIII "Lack of efficacy in controlled clinical trials" of the PSUR.

Information from other clinical trials shall be included in sub-section IX.1 of the PSUR.

In addition, the registration certificate holder shall include an appendix listing the post-registration interventional trials sponsored by him with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval.

The listing should include the following information for each trial:

study identifier (e.g. protocol number or other identifier);

study title (abbreviated study title, if applicable);

study type (e.g. randomised clinical trial, cohort study, case-control study);

population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);

study start (as defined by the registration certificate holder) and projected completion dates;

status of clinical trial (ongoing (clinical trial has begun) or completed (preparation of the clinical study report is finalised)).

Sub-section VII.1. Completed clinical trials

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

Sub-section VII.2. Ongoing clinical trials

If the registration certificate holder is aware of clinically important efficacy and safety findings detected in ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), they shall be briefly summarized in this sub-section. It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

Sub-section VII.3. Long term follow-up

Information from long-term follow-up of subjects from clinical trials of investigational products, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products) shall be given.

Sub-section VII.4. Other therapeutic use of medicinal product

Clinically important safety information from other programmes conducted by the registration certificate holder that follow a specific protocol, with solicited adverse reactions reporting (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection) shall be given.

Sub-section VII.5. New safety data related to fixed combination therapies

The following options shall be considered:

If the active substance that is the subject of the PSUR is also registered or under development as a component of a fixed combination product or a multi-drug regimen, important safety findings from use of the combination therapy shall be summarized;

If the product itself, which is the subject of the periodic safety report is a fixed combination product, important safety information arising from the individual components (whether registred or under development) shall be summarised.

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

Section VIII. Findings from non-interventional studies

Relevant safety information or information with potential impact in the benefit-risk assessment from registration certificate holder-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active pharmacovigilance programmes) shall be summarized. This section shall also include relevant information from drug utilisation studies when relevant to multiple administrative territorial units. The registration certificate holder should include an appendix listing registration certificate holder sponsored non-interventional studies conducted with the primary aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, which were completed or ongoing during the reporting interval.

Final study reports completed during the reporting interval for the studies mentioned in the section VII of this annex shall be included in the appropriate appendix of the PSUR. Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the periodic safety report. The registration certificate holder should present signals or risks identified from other information sources in the relevant sections of the periodic safety report.

Section IX. Information from other clinical trials and sources

Sub-section IX.1. Other clinical trials

Information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources, which are accessible by the registration certificate 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) shall be summarized.

Sub-section IX.2. Medication errors relating to medicinal product

Information on medication errors relating to the medicinal product and potential medication errors, even when not associated with adverse outcomes shall be summarised. A potential medication error relating to the medicinal product is the recognition of circumstances that could lead to a medication error relating to the medicinal product, and may or may not be made by a patient. Errors relating to prescription or use of the medicinal product may be made by patients, consumers, or medical workers. This information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product.

Section X. Non-clinical data

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 shall be summarised. Results from studies designated to address specific safety concerns shall be included in the PSUR, regardless of the outcome. Implications of these findings shall be discussed in the relevant sections of the PSUR.

Розділ XI. Literature

New and significant safety findings concerning the medicinal product, either published in scientific medical literature or made available as unpublished manuscripts that the registration certificate holder became aware of during the reporting interval, when relevant to the medicinal product, shall be demonstrated.

Literature search for PSUR shall be wider than those for adverse reaction cases as it shall also include studies reporting safety outcomes in groups of patients and other products containing the same active substance. E.g. safety information that should be included in the PSUR, but which may not be found by a literature search constructed specifically to identify individual cases of adverse reactions, include namely:

pregnancy outcomes (including termination) with no adverse outcomes;

use in paediatric populations;

compassionate supply or named patient use;

lack of efficacy;

asymptomatic overdose, abuse or misuse;

medication error where no adverse reactions occurred;

important non-clinical safety results.

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

Section XII. Other periodic safety update reports

This section shall only apply concerning fixed combination products or medicinal products with multiple indications and/or formulations where multiple periodic safety reports are prepared in agreement with the authorized body. In such case this section shall also provide significant findings from other PSURs if they are not presented elsewhere within the PSUR. When available, based on the contractual agreements, the registration certificate holder should summarise significant findings

from PSURs provided during the reporting interval by other parties (e.g. sponsors or other contractual partners).

Section XIII. Lack of efficacy in controlled clinical trials

This section shall summarise data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses that could reflect a significant risk to the treated population.

Section XIV. Late-breaking information

The potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the periodic safety report shall be summarised. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the registration certificate holder or authorised body (worldwide) has taken for safety reasons. New case reports of adverse reactions should not be routinely included in PSUR unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR. Any significant change in the reference information on medicinal product (e.g. new adverse reaction, warning or contraindication) which has been introduced during this period, shall also be included.

The data presented should also be taken into account in the evaluation of risks and new information.

Section XV. Overview of signals (new, ongoing or closed)

A general description of signals that were closed (i.e. their evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval shall be given. A signal should be included in the PSUR once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the registration certificate holder. Signals may be qualitative or quantitative. Signals may arise in the form of an information request or inquiry on a safety issue from authorized bodies (worldwide). Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data. A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval, this would be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval and submission of the PSUR.

Within this section, or as an appendix all signals ongoing or closed at the end of the reporting interval shall be provided in the form of a tabulation. This tabulation should include a brief description of the signal; date when the signal became known; status of the signal at the end of the reporting interval (close or ongoing); date when the signal was closed; source of the signal; a brief summary of the key data; plans for further evaluation; actions taken or planned. The detailed signal assessments for closed signals are not to be provided.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in sub-section XVI.3 “Evaluation of risks and new information” of the PSUR.

When an authorised body has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR, the results of the analysis shall be summarised in this section if they are

negative. If the specific topic becomes a signal, it should be included in the signal tabulation and analysed in sub-section XVI.2 “Signal evaluation” of the PSUR.

Any significant changes made to the reference information on the medicinal product (e.g. new adverse reaction, warnings or contraindications) within the interval shall be listed (section IV of the PSUR). The data presented in this section shall be considered in the evaluation of risks and new information (sub-section XVI.3 of the PSUR).

Section XVI. Signal and risk evaluation

Provided should be a succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the PSUR; an evaluation of all signals closed during the reporting interval; an evaluation of new information with respect to previously recognised identified and potential risks; an updated characterisation of important potential and identified risks; a summary of the effectiveness of risk minimisation activities in any country or administrative territorial unit, which may have utility in other countries or administrative territorial units. Information in sub-sections below should not duplicate information presented in previous sections but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. It is not necessary to include individual case narratives in the risk evaluation sections of the PSUR (but where they are integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases should be provided).

Sub-section XVI.1. Summaries of safety concerns

Important safety concerns, which are known at the beginning of the reporting interval, against which new information and evaluations can be made, shall be summarised. For medicinal products with an existing safety specification, the data presented in this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR. Information on the important identified and potential risks and missing information shall be provided.

For medicinal products without an existing safety specification, information on the important identified and potential risks and missing information associated with their use, based on pre- and post-registration experience shall be provided.

Sub-section XVI.2. Signal evaluation

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

those signals that, following evaluation, have been refuted as “false” signals based on scientific evaluation of the currently available information;

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

Where multiple evaluations are included under both categories of closed signals, they can be presented in the following order:

closed and refuted signals;

closed signals that are categorised as important potential risks;

closed signals that are categorised as important identified risks;

closed signals that are potential risks not categorised as important;

closed signals that are identified risks not categorised as important.

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

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

source or trigger of the signal;

background relevant to the evaluation;

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

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

discussion;

conclusion.

Registration certificate holder’s evaluations and conclusions for refuted signals shall be presented.

Sub-section XVI.3. Evaluation of risks and new information

A critical appraisal of new information relevant to previously recognised risks that is not already included in sub-section XVI.2 of the PSUR shall be provided.

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal shall be presented in the signals tabulation and evaluated in subsection XVI.2 of the PSUR, if the signal is also closed during the reporting interval.

Updated information on a previously recognised risk that does not constitute a signal shall be included. New information can be organised as follows:

new information on important potential risks;

new information on important identified risks;

new information on other potential risks not categorised as important;

new information on other identified risks not categorised as important;

update on missing information.

The focus of the evaluation(s) is on new information, which has emerged during the reporting interval. Such evaluation will form the basis for an updated characterisation of important potential and identified risks in sub-section XVI.4 of the PSUR. The level of detail of the evaluation included in this subsection shall be proportional to the available evidence on the risk and its medical significance and public health relevance.

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

source of the new information;

background relevant to the evaluation;

method(s) of evaluation, including data sources, search criteria, and analytical approaches;

results (a summary and critical analysis of the data considered in the risk evaluation);

discussion;

conclusion, including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in sub-section XVI.4 “Characterisation of risks” of the PSUR.

Any new information on populations exposed to the medicinal product or data generated to address previously missing information should be critically assessed. Unresolved concerns and uncertainties should be described.

Sub-section XVI.4. Characterisation of risks

Important identified and potential risks shall be characterised based on cumulative data (i.e. not restricted to the reporting interval), and missing information shall be described.

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

For PSUR for medicinal products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration.

Sub-section XVI.5. Effectiveness of risk minimisation (if applicable)

The results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment shall be presented. Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important risks identified in any country or administrative territorial unit that has become available during the reporting interval shall be summarised.

Information may be summarised by administrative territorial unit, if applicable and relevant.

When required for submitting the results of assessments of the effectiveness of risk minimisation activities in the reporting interval, which refer to an individual administrative territorial unit, they shall be provided in the regional appendix to the PSUR.

Section XVII. Benefit evaluation

Sub-section XVII.1. Important baseline efficacy and effectiveness information

Information on both efficacy and effectiveness of the medicinal product, which is available at the beginning of the reporting interval and provides the basis for the benefit evaluation, shall be summarised. This information shall correspond to registered indication(s) of the medicinal product listed in the reference information on the medicinal product.

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant. If there is no significant change in the benefit and risk profile of the medicinal product in the reporting interval the summary shall be succinct (this should preferably be the contents of the reference information or indications listed in the introduction of the PSUR). The level of detail provided in this sub-section should be sufficient to support the characterisation of benefit in the sub-section XVII.3 "Characterisation of benefits" of the PSUR and the benefit/risk assessment in section XVIII "Integrated benefit/risk analysis for registered indications" of the PSUR.

Sub-section XVII.2. Newly identified information on efficacy and effectiveness

Additional information on efficacy or effectiveness in registered indications, which may have become available during the reporting interval, shall be provided. For registered indications, new information on efficacy and effectiveness under conditions of actual use should also be given, if available. New information on efficacy and effectiveness in non-registered indications should not be included unless relevant for the benefit/risk evaluation in the registered indications. Information on indications newly registered during the reporting interval should also be included. The level of detail provided in this section should be sufficient to support the characterisation of benefit and the benefit-risk assessment.

Particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may have an impact on efficacy/effectiveness over time.

Sub-section XVII.3. Characterisation of benefits

An integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for registered indications shall be provided. The level of detail should be sufficient to support the assessment of benefit/risk. When there are no new relevant benefit data, a characterisation of the information presented in sub-section XVII.1 of the PSUR shall be provided. 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 should be succinct.

This sub-section shall provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness of the medicinal product.

Section XVIII. Integrated benefit-risk analysis for registered indications

An overall appraisal of the benefit and risk of the medicinal product as used in clinical practice shall be given. An information on the benefit and risk given in the sub-sections XVI.2 "Signal evaluation", XVI.3 "Evaluation of risks and new information" and XVII.3 "Characterisation of benefits" shall not be duplicated but a critical analysis and integration of the key information on benefit and risk from these sections shall be given.

Sub-section XVIII.1. Benefit-risk context (medical need and important alternatives)

A brief description of the medical need for the medicinal product in the registered indications and summarised alternatives (medical, surgical or other; including no treatment) shall be presented.

Sub-section XVIII.2. Benefit-risk analysis evaluation

The benefit/risk profile shall be evaluated and presented by each indication individually. If there are important differences in the benefit/risk profile among different populations within an indication, the benefit/risk evaluation shall be presented by population, if possible.

The benefit/risk evaluation should be presented and analysed in a way that facilitates the comparison of benefits and risks. The key benefits and risks shall be specified in the evaluation, the key information on benefit and risks presented in the previous section/sub-sections shall be integrated, the context of use of the medicinal product shall be considered, the effect size, all elements of benefit, clinical importance of the risk and circumstances of its detection shall be taken into account.

A clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation shall be provided.

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

Section XIX. Conclusions and actions

The implications on any new information obtained during the reporting interval in terms of the overall evaluation of benefit-risk for each registered indication, as well as for relevant subgroups of patients, shall be dicussed. The need for changes to the reference information shall be assessed, and changes shall be proposed as appropriate. As applicable, preliminary proposal(s) shall be included to optimise or further evaluate the benefit-risk balance for further discussion with the relevant authorized body(ies). Proposals for additional risk minimisation activities may be also included. For medicinal products with a pharmacovigilance or risk management plan, the proposals concerning them should also be considered. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, conclusions as to the need for changes and/or actions, including changes in the approved summary of product characteristics ofthe medicinal product(s), shall be provided.

XX. Appendices to the periodic safety update report

1. Reference information.

2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval tabulations of serious and non-serious adverse reactions according to post-registration surveillance data.

3. Tabular summary of safety signals (if tabular summary of safety signals is not included in the appropriate section of the periodic safety report it is recommended to include it in the appropriate section of the periodic safety report).

4. Listing of all the registration certificate holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product.

5. List of the sources of information used to prepare the PSUR (when desired by the registration certificate holder).

6. Regional appendix: