What is an ideal PSUR? – A new focus based on aligned expectations

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PSUR Road Map elements

PRAC/CMDh workshop & recommendations

Explanatory note to EMA PSUR Q&A

Consultation/finalisation via joint industry/assessor webinar

GVP VII update

Standard written consultation process

AR template update & proactive publication

CMDh template updates, Q&A

Training, industry meetings

Joint industry/assessor training envisaged; 7th Industry platform meeting, DIA PSUR info day

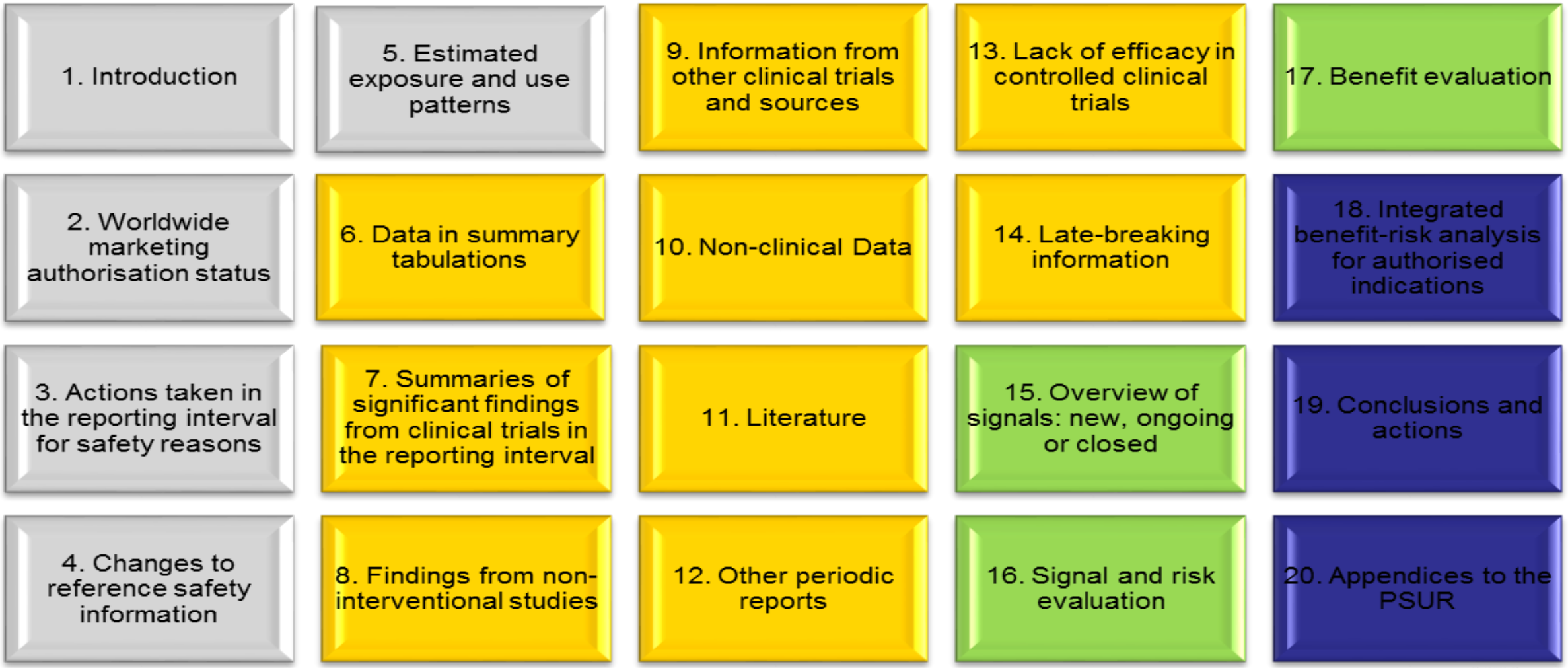
Industry involvement

DIA

Explanatory Note to GVP Module VII – background

- PSUSA - number of challenges
- Aims at complementing GVP VII
- Experience gained during the 2 years of running the PSUSA process
- Basis for the update of the GVP VII
- Preparation of PSURs for single assessment
- Divided into sections identified as key issues for development of further guidance
- Aimed at limiting the number of issues or clarifications given/time constraints

Explanatory Note to GVP Module VII – background



Explanatory Note to GVP Module VII – general principles

- Clarification of the purpose of a PSUR
- Provide the adequate level and quality of the information needed
- PSUR is not intended for the notification of significant new safety or efficacy information, which may have an important public health impact.

Explanatory Note to GVP Module VII – changes to the indication

- At the beginning of the PSUR cycle, the B/R is positive
- PI updates:
  - driven by PSUR data
  - based on a review of safety
- Only changes to an indication which are justified based on safety and efficacy concerns presented in the PSUR can be implemented as an outcome of a PSUR assessment
- A PRAC recommendation that the B/R for a certain indication that is authorised only in MSs is unchanged, cannot be used as a basis for extensions of indications to other MSs, where the indication is not authorised

Explanatory Note to GVP Module VII – assessment and outcome

- Requests to the MAH in the PAR or for the next PSUR will be risk-based, and both the request and its timing will be well justified in the AR
- Requests for Line Listings and CIOMS reports will in principle be avoided unless duly justified
- Harmonisation of the product information is not the scope of PSURs

Explanatory Note to GVP Module VII – reference information

- The reference safety information should be provided in English. Where appropriate, section 4 of the PSUR (Changes to reference safety information) should be completed by a brief description of ongoing procedures (e.g. variations) to update the product information
- It is essential that any discussions and considerations with regards to the RSI are always also put into the context of the PI that are authorised in the EU. For example, if a well-known adverse reaction is effectively managed via a contraindication, the expectation is that this is not only reflected in the RSI, but that the MAH provides confirmation that this is also the case for the relevant EU texts. Accordingly, a statement should be provided in which the MAH has considered the impact of the PSUR data on the EU PI
- Based on the evaluation of the cumulative safety data and the B/R analysis – MAH - need for changes and/or actions, including any implications for the approved PI
- Amendments not related to the information presented in the PSUR, should not be proposed in this framework
- MAHs of authorisations under Article 10 of the Directive should ensure that they have aligned their PI in full to their reference medicinal product prior to submission date

Explanatory Note to GVP Module VII – actions taken for safety reasons

- If significant actions have been taken in any country of the world in the reporting interval for safety reasons, it should be accompanied by an adequate description and explanation that will allow the assessor to understand the safety impact or absence of impact on the B/R

- Simply stating “interruption of the placing on the market” would not be considered as sufficiently informative

- Examples of actions taken in the reporting interval for safety reasons include: details about safety related variations, variations filed in the EU, contents of Direct Healthcare Professional Communications (DHPCs) / any action / inspection of (non-)EU Health Authorities etc.

Explanatory Note to GVP Module VII – patient exposure

- Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should preferably be provided alongside the exposure length (preferably number of patients or patient/year).
- The method should be explained.
- Where a discrepancy exists (e.g. information provided per trial, when added together, does not match with the total provided) this should be explained
- Discrepancies of the patient exposure reported from one PSUR to another should be justified and elaborated upon with an adequate level of detail

Explanatory Note to GVP Module VII – overview of signals

- The MAH should provide a high level overview of signals for which the evaluation was completed during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. These signal evaluations should always include cumulative data with the appropriate level of details

- Template of a tabular format

- The assessment of the data presented in the PSUR is the basis for any decision, and will lead to agreement on closure of the signal or maintaining it open. If, on the other hand the signal cannot be refuted, then it should be followed-up in the next PSUR, or in a different procedure based on the signal seriousness or urgency. When repeated requests are made to closely monitor a safety issue, consideration should be given to adding this issue as an important identified/potential risk

- It is reminded that when safety issues (not considered a signal) are followed-up in subsequent PSURs, the interval data should be put in the context of the cumulative data

- When a competent authority has requested that a specific topic (not considered a signal) be monitored and reported in the PSUR, the MAH should summarise the result of the analysis in section 15 of the PSUR, if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sub-section 16.2 (“Signal evaluation”).

Explanatory Note to GVP Module VII – signal evaluation

- A structured analysis of causality should be performed in line with accepted. The most important factors for classification of causality (time to onset, positive de- and re-challenge) and overall result of causality assessment should be presented
- When a signal evaluation is finalised and the signal closed on the MAH´s own initiative, the respective rationale should be presented as to why a signal/concern will or will not impact on the B/R
- In principle, a refuted signal should not lead to additional follow up for precautionary reasons, provided the PRAC agrees with this assessment. The assessment of the data is the basis for any decision, and will lead to agreement on closure of the signal or maintaining it open. Routine pharmacovigilance will apply from this moment on.
- Apart from the information already provided in the signal tabulation, the section on the evaluation (Section 16.2) should provide the minimum information
- In certain situations, it would be important for the MAH to provide, or for the assessor to request, a detailed description of pivotal or illustrative cases including a summary of the case narratives
- In this context, the term “case narratives” refers to clinical evaluations of individual cases rather than the CIOMS narratives. It should not be necessary to provide the actual CIOMS narrative text included in the ICSR but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal

Explanatory Note to GVP Module VII – summary of safety concerns

- A proposed set of safety concerns should be provided. For a product, for which there is an RMP in place, the summary of safety concerns outlined in the RMP is expected to be included. Differences or additional safety concerns in the PSUR compared to the EU RMP should be highlighted and explained
- Focus should be given to those identified/potential risks that are critical to the B/R and may profit from further characterisation
- Not all the adverse events listed in the PI are to be stated among these safety concerns
- Based on information arising from the evaluation period (e.g. successful RMM in place), the MAH may propose changes to the list
- It is expected to see in each PSUR, the outcomes of the safety monitoring (e.g. routine pharmacovigilance) for the safety concerns classified as important potential risk
- Summary of safety concerns for a generic medicinal product should be the same as that of the reference product or of other generic products for which an RMP is in place
- PSUR is not a tool for harmonisation of the safety specification per se

Explanatory Note to GVP Module VII – evaluation of risks and new info

- The aim of this section is to provide new information (e.g. information arising from studies to further characterize an important potential risk) and not to present all the information related to the list of safety concerns

- MAHs should consider the impact of the new information on the B/R of their product(s), namely in the list of safety concerns, PhV/RM activities and provide a level of detail proportionate to the level of risk

- Special attention should be given to the potential risks and whether the new data could confirm those risks. Although focus is given to the analysis of new data, the assessment has to be carried out in the context of known and cumulative information (i.e. the cases received during the reporting interval should be analysed in the context of cumulative numbers and previous analysis)

Explanatory Note to GVP Module VII – characterisation of risks

- Reflect a characterization of the important identified and/or potential risks for the product based on cumulative data (i.e. not solely based on information received during the reporting period)
- Describe important missing information associated with the use of the product
- Based on information arising from the evaluation period (e.g. successful RMM in place), the MAH may propose changes to the list of safety concerns
- When an important risk or missing information is re-classified or removed, a justification should be provided in this section as well as a proposal to update the RMP accordingly

Explanatory Note to GVP Module VII – effectiveness of RM

- The results of the evaluation of the effectiveness of risk minimisation activities in place should be presented in this section

- Based on this evaluation, the MAH should propose the implementation of further measures/amendments to the existing ones and/or consider the relevance of maintaining or removing the related safety concern

Explanatory Note to GVP Module VII – B/R analysis evaluation

- Focus of the PSUR should be on whether there are new risks or whether risks have changed, or whether there are changes to the B/R
- When there is new positive benefit information and no significant change in the risk profile in the reporting interval, the integration of baseline and new information should be succinct. In this situation, a full re-evaluation of the baseline efficacy data is not warranted, only changes in the reporting period should be taken into account
- Lack of efficacy or studies challenging the established efficacy profile should be discussed within the PSUR
- Although PSURs have the appropriate regulatory scope to restrict/suspend/revoke a marketing authorisation based on safety grounds, when there is need for a wider engagement in a rigorous scientific analysis, then an alternative procedure (e.g. referral) might be more appropriate
- At the beginning of the PSUR period the B/R balance profile is positive, based on the data evaluated at the time of initial MA and subsequent assessments of its B/R profile such as renewal, and upcoming PSURs

Explanatory Note to GVP Module VII – QMS for PSURs - MAHs

- Submit PSURs containing summaries of data relevant to the benefits and risks of the medicinal product and a scientific evaluation of the B/R balance of the medicinal product taking into account all available data
- To allow for an adequate assessment of the PSUR - critical that the information provided is of sufficiently good quality
- Provide the adequate level and quality of the information and analyses during the procedure when necessary such as in response to the RSI in the PAR or as requested as a follow-up to a previous PSUR
- An appropriate quality system should be in place in order to avoid failure to comply with the PSUR requirements such as the failure to provide adequate answers to competent authorities' requests
- Significant concerns about the quality of the PSUR data may also be flagged for follow up as a Quality and Compliance issue which has to be improved in the next PSUR submission and can be the reason for a further PhV Inspection and any non-compliance detected will be highlighted in the evaluation of the PSUR and further actions will be discussed at EU level

In summary

What is an ideal PSUR?

- Follow the purpose
- Provide the adequate level and quality of the information needed

Ask