DCVMN
Risk Management Plan (RMP) Project

List of general issues

General Comments

- The RMP is a complex regulatory document, use the RMP template as it structures the information in a clear manner.
- Knowledge exchange and communication within the company (manufacturing team, regulatory team, clinical team) is crucial as the source of information for various sections is with other functions (e.g., plan for risk minimization, post authorization safety studies etc.).
- A lot of information to be provided in the RMP is included in other regulatory documents (e.g., CTD, (D)PSUR, IB, SmPC); therefore, consistency of the information provided in the various documents at the time of submission is key.
- PV should have a good understanding of the manufacturing process to be able to assess potential safety risks from manufacturing (e.g., egg-based production could give problems with people having an egg allergy).
- Scientific / regulatory writing expertise is helpful in compiling the information.
- Use appropriate tables, esp. use the table templates from the EU RMP template
- Have documentation quality assurance and quality control processes in place (e.g., according to GVP Module 1 "Pharmacovigilance system and their quality systems").

1. Product overview

- Clarify if the vaccine is a new product using a new in-house developed technology or the result of a technology transfer and make the difference between new and novel (e.g., mRNA vaccines are novel and will need a more stringent RMP).
- Briefly describe the product, indication, posology, and pharmaceutical forms: Provide clear information consistent with the respective sections of other regulatory documents (CTD, SmPC)
- Provide a short, but clear description of the chemical class, mode of action and important information on the origin of active substance (e.g., biotechnological construct), relevant immunogenic adjuvants, stabilizers, preservatives, excipients, and residual material from the manufacturing process (e.g., adventitious agents, Sf-rhabdovirus when using a baculovirus expression system, host cells, etc.) and explore any information of competition.

2. Part II Safety Specification

Part II SI: Epidemiology, Indication, Target Population

- Differences in the epidemiology in different geographical regions / country settings should be discused – epdemiology of the indication may vary geographically, think about age:

    - in Cameroun 80% of the people is less than 35 years, for a COVID-19 vaccine the benefit/risk is completely different compared to a country like Belgium.
    - Be aware of age related risks: women of child bearing age can take oral contra-ceptives, having a higher risk of thrombosis, this might be an important background for the benefit/risk analysis.

- Use publicly accessable information, published literature and secondary data sources(e.g., WHO documents, position papers etc.).
- Explain what events occur as part of the disease and what events can be expected in the target population (and why), risk factors for the disease, treatment options, information on important co-morbidties of the target population.
- Use tables as as much as possible to display the data / information.
- Seek support in writing clinical / scientific overviews / summaries – ensure consistency with other regulatory regulatory documents (e.g. CTD)

PartII SII Non-clinical part of the safety specification

- This section is a summary of all non-clinical studies and should be consistent with other regulatory documents at the time (e.g., CTD / (D)PSUR). Where the non-clinical safety finding could constitute an important risk in human, it should be discussed in Part II Module SVII and carried forward to Module SVIII and in other relevant sections where the list of safety concerns is listed.
- There should be a short descripton of all non-clinical studies, e.g., animals / number of animals, methodology, safety parameters tested, results of the studies.
- All important non-clinical safety findings (e.g., tox / repeat tox studies, reactogenicity, reprotoxicity studies and information on vaccine quality related aspects such as host cells, genotoxic impurties etc.) with relevance to human safety should be presented in a Table.
- A justification of inclusion or exclusion of the non-clinical findings with relevance to human as well as missing information from non-clinical studies (e.g., no DART study) should be added.
- Ensure that the nomenclatue used for important safety concerns is carried throughout the RMP where the safety concerns are listed.

Part II SIII Clinical Trial Exposure

- This section is to assess the limitations of the human safety database based on exposure data in completed clinical data. The information in this section should be consistent with other regulatory documents at the time (e.g., CTD / (D)PSUR)
- This section may start with an overview of the clinical development; a table displaying the clinical development program would be helpful.
- Subject exposure, age, gender, dose, and ethnic origin in all completed clinical trials should be displayed in Tables as laid down in the EU RMP template. A summary table should show the total exposure.
- If a significant level of exposure is in ongoing trials, a brief summary of these trials should be added in the text.

Part II SIV Population not studied in clinical trials

- The limitations of the clinical trial population in relation to predicting the safety in the target population should be discussed. (e.g.: age, lack of underlying disease, etc.).
- The information in this section should be consistent with other regulatory documents at the time (e.g., CTD, SmPC).
- All exclusion criteria relevant to safety in the pivotal clinical trials across the development program should be listed with an explanation for a) reason for exclusion in the CTs, b) / c) is this criterion to be included as "missing information" and if yes, rationale for adding this criterion to "missing information" (inclusion in Module SVII / SVIII).
- Discuss the limitations to detect AEFIs in the clinical development program (e.g., "rule of three," size of database, long-term effects).
- Add a summary table regarding the exposure of special populations included / not included in the clinical development program (e.g., per table in the EU RMP template).

Part II SV Post-authorization experience

- This section is usually empty before granting authorization, unless post-marketing data are available from post-authorization experience in countries where market authorization has been granted.
- The section should only provide exposure overview in the post-authorization phase; no duplication or post-authorization experience from PSURs.
- However, if the vaccine has already been used in practice in special populations mentioned in Module SIV (e.g., in pregnancy), the information can be used for risk identification discussion in Module SVII.

Part II SVI Additional requirements for the safety specification

- Check if / what is relevant for the respective NRA. The EU requirement concerns only the potential for "misuse for illegal purposes."

Part II SVII Identified and potential risks

- This section should be concise and not a "data dump" of tables or lists with AEFIs from clinical trials or the proposed / actual contents of Section 4.8 of the SmPC.
- Section on vaccine construct, formulation and potential degradation of the active substance / antigen and the potential impact on safety can be placed here. Information needs to come from the manufacturing / quality team.
- Section on "risks not considered important for inclusion in the list of safety concerns in the RMP" should contain a summary of known risks that do not impact the benefit-risk profile such as injection site reactions and frequently reported systemic AEFIs with low-grade severity and self-limiting (reactogenicity), and adverse events of special interest.

- Section on risks considered "important for inclusion in the list of safety concerns" should contain information on identified or potential risks that could have an impact on the benefit-risk balance of the vaccine or have implications for public health.
    - Definitions on identified and potential risks can be found in GVP Annex I Definitions.
    - Any risk which is clinically important and likely to be included in the contraindications or warnings and precaution section of the SmPC should be included here, i.e., risks already characterized and confirmed to have an impact in the B/R balance and risks, when further characterized and if confirmed to be associated, would have an impact on the B/R balance.
    - Generally the following risks should be considered for vaccines: potential risks anticipated from the experience with similar vaccines and vaccine ingredients, potential risks associated with concomitant administration of vaccines, potential interactions with medicinal products usually given to target population, syndromes resembling wild-type disease, waning immunity, accidental iv administration, risks associated with a significant change to the manufacturing process, risks associated with medication error.
    - Add missing information from Module SIV and SV, if applicable.
    - For each important identified risk and identified potential risk the potential mechanism, evidence, characterization, risk factors, preventability, impact on the B/R balance and on public heath should be described.
    - Missing information: only include information which has been selected in Module SIV. Include information on evidence, population in need for further characterization and anticipated risk / consequences of the missing information.

Part II SVIII Summary of safety concerns

- Safety concerns identified in Modules SII, SIV, SVI and SVII should be compiled in a Summary Table (Important identified risks, Important potential risks, Missing information).
- Each risk listed in the SmPC sections 4.3 "Contraindications," and 4.4 "Special warnings and precautions" should be regarded as an important risk.
- AEFIs mentioned in section 4.8 "Undesirable effects" should not be included as important identified risks as they are unlikely to change the B/R balance.
- Ensure that terminology, sequence, and presentation of safety concerns are consistent throughout all applicable modules.

Part III Pharmacovigilance Plan

- For each safety concern summarized in Module SVIII the planned activities must be listed.
- For safety concerns well characterized "Routine Pharmacovigilance Activities" are generally sufficient. A brief description of the PV activities should be included (details as included in the PSMF are not required). The activities should include information beyond AEFI reporting and signal detection (e.g., use of specific AEFI F/U forms, targeted safety surveillance, cumulative reviews of specific AEFIs, etc.)
- "Additional Pharmacovigilance Activities" may include e.g., non-clinical studies, observational studies, clinical trials, and a justification should be added for proposing respective activities (e.g., long-term safety follow-up, evaluation of missing data etc.).

- A complete overview of all on-going and planned Additional Pharmacovigilance Activities should be presented and compiled in Tables as laid down in the EU RMP template (study name/ number, status, summary of objective, safety concern addressed, milestones, due dates).

Part V Risk minimization measures

- The safety information in this risk minimization plan must be aligned with the proposed product safety information (SmPC).
- The routine risk minimization measures should be listed and addressed by each safety concern identified in Module SVIII (important identified, important potential risk and missing information).
- For each safety concern the respective routine risk minimization activities must be provided (from Part II Module SVIII): a) refer to respective section of the SmPC, b) mention if specific clinical measures will be recommended (yes/no) and c) other routine risk minimization measures beyond SmPC (yes/no).
- A summary t able including each safety concern with the respective risk minimization measures and the respective pharmacovigilance activities (Part III.1 / III.2) should be added.

Part VI Summary of the Risk Management Plan

- This should be a summary of all displayed sections according to the RMP template. Part VI is made publicly available in the EU, a requirement of EU legislation.
- This scientific summary, written for the lay reader should present a balanced picture of the vaccine. The document should be a clear, concise summary with risks put in context of the benefit.

10. February 2022

KH/BH/PN

Consistency with CTD

RMP Module	eCTD
Part I Product(s) overview	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5 Clinical overview
Module SII Non-clinical part of the safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorisation experience	Module 2.5 Clinical overview
Module SVI "Additional EU requirements for the safety specification"	Data not presented elsewhere in eCTD
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance plan (including post-authorisation safety studies)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post-authorisation efficacy studies	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Module 2.5 Clinical overview Module 2.7 Clinical summary

Consistency with (D)PSUR

RMP section	PSUR section
Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part II, module SV – "Post-authorisation experience", section "Non-study post-authorisation exposure"	Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"
Part II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterisation of risks"
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 16.1 – "Summary of safety concerns"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"