EMA/544966/2020

Consideration on core requirements for RMPs of COVID-19 vaccines

coreRMP19 guidance

Introduction/Background

In addition to the EMA guidance on pharmacovigilance and vaccine development, the EMA will issue the "Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines" giving an overview of the monitoring activities to be carried out in the EU for COVID-19 vaccines, including the roles, responsibilities and interactions of the stakeholders involved. Further interactions between EMA, NCAs, and the vaccine manufacturers have identified the need to develop further guidance on RMP requirements for COVID-19 vaccines.

This guidance reflects the EMA recommendations based on current knowledge and experience. As the pandemic situation evolves and further evidence becomes available for the respective vaccine candidates, the manufacturers should take into account further guidance and experience that EMA will communicate, in the form of an updated guidance or through the scientific assessment already completed (e.g. EPARs for approved products, RMPs of approved products).

Scope

This coreRMP19 document addresses the planning for post-marketing surveillance for COVID-19 vaccines in the context of marketing authorisation in the EU.

Objective

- providing supplemental section-by-section guidance and requirements for drafting the RMPs of COVID-19 vaccines.

coreRMP19 requirements and guidance

These coreRMP19 requirements should be read in conjunction with existing relevant EMA guidance (including Guideline on good pharmacovigilance practices(GVP) - Module V –Risk management systems (Rev 2), Guidance on the format of the risk management plan (RMP) in the EU, Product-or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, Guideline on Influenza Vaccines - Non-clinical and Clinical Module, etc.) published on the EMA website; the requirements and

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

guidance they provide should be read and applied in the context of pandemic use of COVID-19 vaccines.

Part I – Overview

No additional requirements.

Part II – Safety Specification

Module SI - Epidemiology of the indication(s) and target population(s)

This should reflect the up-to-date information on COVID-19, acknowledging the existing uncertainties.

Module SII - Non-clinical part of the safety specification

This part could be available early in the submission plan, so, when available, it should be included in the earlier versions of the RMP.

Module SIII - Clinical trial exposure

It is acknowledged that final exposure and follow-up data will only be available at the finalisation of clinical trial reports. Information from protocols of ongoing trials should be submitted in an earlier round of the rolling review, to keep EMA up to date on the expected size of the safety database and the limitations in safety follow-up.

Module SIV - Populations not studied in clinical trials

SIII advice above applies

Module SV - Post-authorisation experience

If there is information available since the approval of the vaccine in other world regions, or from emergency use access in EU, this should be provided. It is acknowledged that it is likely that this experience will be unavailable at the time of initial submission.

Module SVI - Additional EU requirements for the safety specification

This section is not expected to be relevant for COVID-19 vaccines.

Module SVII - Identified and potential risks

It is acknowledged that only limited information may be available at early stages of regulatory submissions (e.g. first rolling reviews) while clinical trials are ongoing. A more complete safety specification in the RMP will only be available after preliminary clinical trials results are available (i.e. at the time of the efficacy endpoint analysis) with further data being generated from the same trials post-approval. In addition, the Applicants should consider for the generation of the safety specification:

- The vaccine construct and the formulation;
- The degradation of the active substance / antigen and potential impact on safety related to this; (e.g. for mRNA-based vaccines)
- The presence of an adjuvant;

- Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease[1]).

It is essential that each decision to classify a (potential) risk of a vaccine is evidence-based and adequately presented and justified in the RMP Module SVII, even if initial considerations are driven by previous clinical and non-clinical experience with vaccines in general, vaccines using the same construct/platform, or from other COVID-19 vaccines from the same or other manufacturers, as applicable.

When the clinical results do not raise particular safety concerns, it may be acceptable that no **important identified risks** are included in the RMP; this may be expected for a medicine that is to be used for prevention, where risks related to the administration procedure are expected to be adequately managed by vaccinators and have minimal impact on risk/benefit considerations for the product.

The list of **important potential risks** should include risks with potential impact on the risk/benefit balance, for which there is clinical and/or pre-clinical evidence suggesting a causal relationship with the vaccine, but for which the strength of the evidence does not (yet) allow to infer causality.

While some of the important potential risk may be derived from the experience with the vaccine construct/platforms, pre-clinical data, or clinical trials, some will derive from the global knowledge of the COVID-19 and any role vaccines could have, based on more theoretical considerations, (e.g. vaccine-associated enhanced respiratory disease, immune mediated disorders)

Applicants should include a well justified list of important potential risks for which evidence as described above exists, and not a comprehensive list of all theoretical risks for vaccines in general. Such theoretical risks could be included in the list of AESI to be followed up via routine and additional pharmacovigilance activities. The list of AESI should be described in section SVII.1.1., but not into the sections SVII.1.2 nor SVII.3. Relevant pharmacovigilance activities should be designed to be able to monitor existing and detect new safety concerns. Focused activities should prioritise, in addition to important risks (identified or potential) and missing information, the AESI (see below for further guidance).

It is understood that clinical trials may have exclusion criteria that might result in subpopulations not being included in the clinical investigations; not all these subpopulations will necessarily constitute missing information in the summary of the safety concerns in the RMP. Based on current evidence and concerns, the following missing information should be considered to be added in the RMP (unless clinical trials data - in these populations - is considered comprehensive):

- Safety in pregnant women;
- Safety in patients with severe co-morbidities (e.g. frail, vaccinees with auto-immune diseases);
- Safety in elderly;
- Safety in children;
- Interaction with other vaccines.

Further considerations for Module SVII for COVID-19 vaccines:

- Reactogenicity:
    - If the vaccine in clinical trials shows a higher reactogenicity profile than the control (especially if the control is another vaccine with an already elevated reactogenicity

[1] Including considerations for antibody dependent enhancement

profile), the RMP should include a discussion on this high reactogenicity, its impact on the safety profile and necessary risk minimisation measures;

    - Reactogenicity in subgroups such as frail vaccinees and the risk of flares in patients with chronic inflammatory conditions needs to be discussed;
    - Differences in reactogenicity with a second (or subsequent) dose should be discussed, when applicable;

- Aspects of the formulation and preparation of the vaccine should be discussed when they may increase the risk of ADRs. e.g. a formulation where a diluent for reconstitution needs to be added may affect sterility, leading to clinical reactions such as increased local reactions, abscesses;
- In case two (or more) doses are recommended, the risk of vaccine drop out e.g. due to reactogenicity should be evaluated as well as the risk of disease enhancement;
- Any early signal from clinical trials should be adequately documented and discussed in this section;
- The relevance of the long-term follow-up should be discussed, and adequate pharmacovigilance activities should be considered. Challenges of using the ongoing CTs for this should be presented (e.g. maintaining blinding).

Topics that require further considerations from the Applicants, but are not required to be discussed in the RMP by default:

- Risks of vaccination errors in a context of mass vaccination campaigns – to be followed up post-marketing and reported in the monthly safety reports and PSURs;
- Safety effects of mixed schedule (possible in real life during a pandemic with travel/contact restrictions) – to be followed up in post-marketing and reported in the PSURs;
- Antibody waning, the need for a booster dose or revaccination – should be included in the efficacy discussion with the MA application, and with the PSURs rather than in the RMP.

Part III - Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

This section should include the planning in the context of the pandemic, even for activities not routinely included in the RMP: signal detection and ICSR reporting. Challenges related to restrictions during the pandemic (e.g. due to social distancing or limited medical resources) or to the volume of ADR reports to be processed (e.g. associated with a mass vaccination campaign) should be considered and reflected into the planning document.

Signal detection methodological considerations and requirements are described in GVP Module IX, which should be read in conjunction with GVP P.I. Signal management; further considerations related to the description in the RMP include:

- Data sources for signal detection should be specified; MAHs should perform signal detection using every means available to them. This would include their own database and EudraVigilance (EV), other publicly available or private databases, screening of literature etc. While there is currently no obligation for MAHs to continuously monitor EudraVigilance data

outside the context of the ongoing pilot[2], MAHs are expected to use the database to strengthen their signal management activities, for instance to further investigate signals detected in their own database. The use of a single data source for signal detection and evaluation is not considered appropriate;

- Routine signal detection methods and practices may be insufficient to efficiently screen the expected high volumes of ADR reports also taking into consideration the situation of a mass vaccination campaign. Limitations when performing and interpreting signal detection methods of disproportionality of reporting on the whole safety database (e.g. EudraViglance) should be taken into account in any situation where health care professionals and the public are actively encouraged to report defined adverse reactions for defined medicinal products, due to the weights given to these adverse reactions and products in comparison to the background information available in the database. The reporting pattern for a vaccination campaign during a pandemic is likely to differ qualitatively from other reporting, which need to be taken into account when performing the analysis;
- Leveraging the infrastructure and results of global efforts to define lists of AESI and background rates (e.g. ACCESS, CONSIGN, ConcePTION), observed versus expected (O/E) analyses should be part of MAHs' signal detection activities. These are expected to be described in the RMP, and reported in the summary safety reports. Coverage data sources, periodicity for frequent analyses and periodic reporting to EMA should also be defined and submitted for assessment;
- The list of AESI proposed should also consider the SPEAC list (see https://brightoncollaboration.us/priority-list-aesi-covid/).

Methods that should be considered by the MAHs for signal detection activities include, but are not limited to:

- Time-to-onset (TTO) analysis;
- Time series analyses and algorithms that may be useful to help detecting batch issues and spurious reports;
- Cluster analyses to help identify groups of ICSRs that may point to syndromes (e.g. narcolepsy and A/H1N1 pandemic vaccines).

ICSR reporting requirements are described in GVP Module VI, which should be read in conjunction with GVP P.I. and Detailed guidance on ICSRs in the context of COVID-19[3].

Specific follow-up questionnaire(s) should also be considered by applicants to obtain additional structured information for reports of safety concerns in the RMP and suspected AESI; the forms should be provided in RMP Annex 4 for evaluation. Applicants are advised to reuse the content of already approved forms, as published on EMA website as part of the EPAR documents (envisaged publication of RMP, including Annex 4), or request them from other MAHs, who are strongly encouraged to share the content of their questionnaire(s) upon request. To decrease the burden on healthcare professionals, the questionnaire should use the language of the reporter and not ask for information already provided in the initial report. When specific follow-up questionnaire(s) are implemented, the MAH should provide

[2] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management#transitional-arrangements-for-mahs-section
[3] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/detailed-guidance-icsrs-context-covid-19-validity-coding-icsrs_en.pdf

with the PSURs process data (e.g. response rate, the need for corrective actions), and reassess the need for continuing this routine pharmacovigilance activity.

During the pandemic the MAHs are expected to submit **Summary Monthly Safety Reports** to EMA; the submission of such reports does not replace but complements the submission of PSURs. The need and periodicity of continuing the submission of such reports will be re-evaluated by EMA based on the available evidence from post-marketing for each vaccine. The table of contents should be agreed with the regulators and should include as a minimum:

- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Reports per EU country
- Exposure data, stratified by EU country, age groups
- Changes to reference safety information in the interval
- Ongoing and closed signals in the interval
- AESI and RMP safety concerns: reports – numbers and relevant cases, including O/E analyses
- Fatal reports – numbers and relevant cases, including O/E analyses
- Risk/benefit considerations

The use of **enhanced passive surveillance** (EPS) could be considered by the applicants. Key elements for a good EPS design would be the ability to rapidly estimate vaccine usage (number of vaccinees, or doses administered), and to facilitate passive ADR reporting, in order to derive reporting rates of important risks and selected AESI.

Caution should be taken if considering using EPS based on vaccination report cards distributed to a limited number of vaccinees. Such design has been previously used for seasonal flu vaccines to identify a different reactogenicity as compared with previous years. For the COVID-19 pandemic, considering the absence of data previously collected using the same system and the safety data from randomised controlled trials available at the time of the submission of the marketing authorisation, the limitations of such design to provide added value to the safety characterisation of COVID-19 vaccines should be carefully considered.

Traceability using the provision of stickers with brand name and batch numbers to the vaccinators is considered useful for pharmacovigilance needs, acknowledging that the circumstances in each Member State for vaccination might not allow their optimal use in all cases. The use of such tools for traceability should be described in this section of the RMP. Additionally, recording of brand name and batch numbers information using electronic tools may be facilitated by the existence of a QR or bar code.

III.2 - Additional pharmacovigilance activities

Continuation of safety surveillance from **ongoing clinical trials** should be a priority and included as additional pharmacovigilance activities. Protocol review of long-term follow-up should be performed early in the RMP assessment, before the Opinion, acknowledging that changes at that stage might be limited in scope. The final safety results from pivotal trials are expected to be submitted for assessment.

Given the potential challenges, both logistic and ethical, on continuing the clinical trials as initially designed once sufficient efficacy and safety data to support approval have been collected, the manufacturers should plan of pharmacovigilance activities early. Considerations should be given whether routine activities will be sufficient to provide adequate data to further characterise important identified and potential risks and investigate missing information or if, in addition to ongoing or planned clinical trials, an observational **post-authorisation safety study (PASS)** is required. The RMP assessment will specify what safety concerns should be the focus of a PASS; additionally, it may be suitable to add secondary safety endpoints based on the list of AESI. Protocols should take into account the recommendations from ENCePP Guide on Methodological Standards in Pharmacoepidemiology (http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml), and ACCESS and CONSIGN projects results, once available.

If an observational PASS is considered needed, the following considerations apply:

- As the date of marketing in different regions of the world might differ considerably, the PASS should include an EU cohort, and not rely solely on non-EU databases. Studies already planned in Member States (e.g. by public health authorities) or by consortia or cross-EU initiative (e.g. Vac4EU, CONSIGN) could be used if the MAH can obtain access to the safety data in a way that brand-specific analyses can be used for risk/benefit monitoring.
- Key elements for a desirable suitable PASS design would be the ability to start data collection shortly immediately after the vaccine's approval and distribution, the ability to perform rapid analyses of safety and deliver frequent reporting to EMA for regulatory purposes (i.e. interim results).

While recognising that depending on vaccination policies, the enrolment of pregnancies in the early phases of the vaccination and recruitment of women who may become pregnant shortly after vaccination will be challenging, a study to further investigate the safety in pregnant women and pregnancy outcomes may be warranted e.g. using existing **pregnancy registries** such as INOSS and Covi-PREG. CONSIGN[4] project recommendations should be taken into consideration. Ensuring pregnant women are adequately followed in the PASS may also be a way to gather further data on safety.

Effectiveness studies should be included in this section of the RMP. It is recommended that the MAHs make use the existing/established EU efforts that could provide brand-specific data reliably and timely (e.g. from public health institutes networks, real-time risk/benefit monitoring network initiatives using databases, etc.).

Part IV: Plans for post-authorisation efficacy studies

No specific/additional requirements related to RMP presentation.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

[4] Link to be updated to results page; further updates expected at https://www.ema.europa.eu/en/news/covid-19-ema-sets-infrastructure-real-world-monitoring-treatments-vaccines

It is agreed that in principle routine risk minimisation in the form of the product information could be sufficient to minimise the risks of the product. MAHs should consider facilitating the dissemination of the product information via publicly available on-line communication channels.

Given the EMA review role in time-constrained procedures, it is considered useful that EMA and the MAHs agree "key messages to the public health authorities that may be used for inclusion in national educational material" to facilitate national efforts for communication and risk management.

Part VI: Summary of the risk management plan

It is expected that the entire RMP will be published on EMA website at the time of the authorisation, as part of the EPAR.

No additional requirements for the Summary of the RMP.

Annexes

Where applicable, no additional requirements.