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Consideration on core requirements for PSURs of COVID-19 vaccines

corePSUR19 guidance

Introduction/ Background

This guidance reflects the EMA recommendations on PSURs for COVID-19 vaccines based on current knowledge and experience. As the pandemic situation evolves and further evidence on the benefits and risks becomes available for the vaccines, the Marketing authorisation holders (MAHs) should take into account current guidance and experience communicated by EMA , in the form of updated guidelines or through the scientific assessments already completed (e.g. PSUR assessment reports, monthly summary safety reports assessment reports).

MAHs are reminded that the Monthly Summary Safety Reports (MSSRs) are not meant to replace the PSURs. Therefore, all relevant information (safety signals evaluations, regulatory requests…) in scope of the reporting period should be provided in the PSURs. However, all those safety evaluations or regulatory requests that have been closed during the reporting period in the context of another regulatory procedure should provide a cross reference to the corresponding procedure.

Scope

This corePSUR19 document addresses the planning for post-marketing safety surveillance for COVID-19 vaccines in the context of periodic safety update reports.

Objective

To provide guidance and highlight requirements when drafting the PSURs of COVID-19 vaccines.

CorePSUR19 requirements and guidance

This guidance should be read in conjunction with existing relevant EMA guidance (including Good Pharmacovigilance practices (GVP)- Module VII- Periodic Safety update Reports, Explanatory Note to GVP Module VII , Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1) Product-or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, Product- or Population-Specific Considerations III: Pregnant and breastfeeding women, Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. coreRMP19 guidance Good practice guide on recording, coding, reporting and assessment of medication errors, Detailed guidance on ICSRs in the context of COVID-19 Validity 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

coding of ICSRs) published on the EMA website; the requirements and guidance provided should be read and applied in the context of pandemic use of COVID-19 vaccines.

This guidance will be updated once vaccines with multiple or different strains are authorized to provide guidance on how to best present the data, if considered necessary.

CONTENT OF THE PSUR:

1. Introduction

No additional requirement.

2. Worldwide marketing authorisation status

No additional requirement.

3. Actions taken in the reporting interval for safety reasons

No additional requirement.

4. Changes to the reference safety information

No additional requirement.

5. Estimated exposure and use patterns

5.1 Cumulative Subject Exposure in Clinical Trials

No additional requirement.

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

Cumulative and interval exposure data should be based on administered doses rather than distributed doses whenever possible, and stratified by region (and within the EU, also by country), age groups, gender and by dose (when applicable/available).

MAHs are requested to use publicly available data (when available):

Europe:

COVID-19 vaccine tracker

COVID-19 Vaccine rollout overview

US:

CDC COVID data tracker

6. Data in summary tabulations

6.1 Reference information

No additional requirement.

6.2 Cumulative summary tabulations of serious adverse events form clinical trials

No additional requirement.

6. 3 Cumulative and interval summary tabulations from post-marketing data sources

No additional requirement.

7. Summaries of significant safety findings from clinical trials during the reporting interval

7.1 Completed clinical trials

No additional requirement.

7.2 Ongoing clinical trials

No additional requirement.

7.3 Long term follow-up

No additional requirement.

7.4 Other therapeutic use of medicinal product

No additional requirement.

7.5 New safety data related to fixed combination therapies

Not applicable for vaccines.

8. Findings from non-interventional studies

No additional requirement.

9. Information from other clinical trials and sources

9.1 Other clinical trials

In addition to standard requirements, a summary of clinical trial data providing data on mixed dose schedules, antibody waning, booster dose or revaccination provided by other clinical trial sources initiated externally and that are available to the MAH (e.g. co-development partners, investigator initiated trials…etc) should be presented. MAHs are reminded that the PSUR is not the tool to assess final clinical study reports (CSR). Final CSRs will be assessed in the relevant regulatory procedure, as appropriate (refer to Explanatory Note to GVP Module VII).

9.2 Medication errors

In the context of mass vaccination, medication errors are anticipated, including errors arising from the use of multi-dose vials. Acknowledging the amount of information gathered in the mass vaccination setting, a summary of medication errors with harm should be prioritised.

10. Non-clinical data

No additional requirement.

11. Literature

This section should critically discuss new important information (benefits, efficacy, antibody waning, revaccination, need of a booster dose, mixed dose schedule, safety concerns, AESIs…etc) available in the literature regarding the COVID-19 vaccine. New important information refers to new information on associations (either adverse or beneficial) that have not been assessed before or on news aspects of known associations.

12. Other periodic reports

No additional requirement.

13. Lack of efficacy in controlled clinical trials

If available, information of differing efficacy or lack of efficacy in controlled clinical trials due to emergent variants should be reflected in this section.

14. Late breaking information

No additional requirement.

15. Overview of signals: new, ongoing or closed

All validated signals which are ongoing or closed during the reporting period should be summarised high level in this section as detailed in GVP VII. As part of the summary/tabulations, it should be indicated which signal has been assessed in another regulatory procedure (i.e. MSSR or a variation) and which signals have not been subject to regulatory assessment before. Closed signals that have been assessed during the reporting period as part of another regulatory procedure will not be re-assessed in the PSUR.

Post-approval regulatory requests (worldwide)

When a regulatory authority has requested for a specific topic (not initially considered a signal) to be monitored and reported in a PSUR (e.g. in the context of the monthly summary safety reports), the MAH should summarize the result of the analysis in PSUR Section 15 if the conclusion of the evaluation is that the requested topic does not constitute a validated signal. If, however, the conclusion of the evaluation is that a signal is validated and warrants further evaluation, it should be discussed in section 16.2.

It should be clearly stated whether the regulatory request has been assessed in another regulatory procedure (i.e. MSSR or a variation) and which signals have not been subject to regulatory assessment before.

16. Signal and risk evaluation

16.1 Summary of safety concerns

No additional requirement.

16.2 Signal evaluation

The description(s) of the signal evaluations can be included in this sub-section of the PSUR or in an appendix.

Two different categories of closed signals are acknowledged:

- For signals closed during the reporting period which have been assessed in another regulatory procedure, a brief abstract including background information, source, data and outcome should be provided. Each signal should have a cross-reference to the procedure where it was assessed.
- For signals closed during the reporting period which have not been assessed as part of any regulatory procedure a detailed evaluation is expected, there's no additional requirement to those detailed in the GVP VII.

16.3 Evaluation of risks and new information

When applicable, full evaluation documents of the risks provided in this section including observed versus expected analysis can be provided in an appendix.

As per the coreRMP19 guideline, for those events for which follow-up questionnaires are implemented (e.g. anaphylaxis, VAED/VAERD) the MAH should provide a summary of experience with the FuQs (e.g. response rate, completeness of returned follow-up questionnaires) and reassess the need for improvement of the follow-up questionnaire(s) or its handling as well as the need for continuing this routine pharmacovigilance activity.

New information can be organised as follows:

- ***new information on important identified risks;***

No additional requirement.

- ***new information on important potential risks;***

No additional requirement.

- ***new information on other potential risks not categorized as important;***

Information on all AESIs for the COVID-19 vaccines that has not been already included in section 16.2 (signals) or in section 15 (post-approval requests) should be summarised in this section as described in GVP VII. Supporting documentation, such as complete evaluations or observed/expected analysis should be provided in an appendix.

Lack of efficacy: MAHs are encouraged to follow the definitions of confirmed lack of efficacy and suspected lack of efficacy as per CIOMS/WHO working group definitions. Overall, in the classification of confirmed or suspected vaccination failure, it is necessary to take into account the incubation period and the normal delay for the protection to be acquired as a result of immunization (in alignment with **authorised indication**, **CCDS**) and whether the occurrence of the disease has been confirmed by laboratory tests or not. Limitations inherent to the spontaneous reporting setting are acknowledged. The definition should be aligned **with the authorised indication and posology rather than country recommendations** Nevertheless, MAHs should provide the definition of vaccination failure that they are following.

The following are examples of general definitions provided as a guidance:

Confirmed vaccination failure*: occurrence of the specific vaccine preventable-disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.*

This definition requires clinical and laboratory confirmation that the disease is the specifically targeted by the vaccine (e.g. COVID-19 PCR positive test, antigen test....)

Suspected vaccination failure*: occurrence of the disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine preventable-disease.*

This definition requires that the incubation period and the normal delay for the protection to be acquired as a result of immunization is taken into account.

The limitation of the spontaneous data is acknowledged. MAHs should follow-up the AEs as per routine pharmacovigilance to ensure appropriate documentation.

Not a vaccination failure*: occurrence of the disease in patients who have not received the full dose schedule or occurrence of the disease during the incubation period.*

The classification on the above categories may depend on the company code conventions and search strategy for retrieving cases of lack of efficacy.

- ***new information on other identified risks not categorized as important;***

The following topics are considered relevant for vaccines:

- vaccination anxiety related reactions, such as syncope

- potential for local and systemic adverse reactions should be analysed for by dose of the vaccine and across vaccination schedules. If possible, data should be presented stratified by age strata.
- Impact of reactogenicity: i.e. decreased mobility of the vaccinated arm, extensive limb swelling

- ***update on missing information***

In addition to the clinical data (efficacy, immunogenicity, safety) obtained through the additional pharmacovigilance activities in the RMP, relevant information can be obtained from the post-marketing monitoring. The limitation inherent to spontaneous data is acknowledged.

Below there's a non-exhaustive list of considerations to take into account for the presentation/interpretation of the missing information (as per coreRMP19) data from spontaneous sources. It's acknowledged that there may be some overlap between populations (i.e. use in immunocompromised patients, autoimmune or inflammatory disorders, frail patients with comorbidities). Criteria for inclusion of case reports in each category should be clearly mentioned.

- Use in pregnancy and while breastfeeding:

For pregnancy outcomes, data should be classified into prospective and retrospective reports to decrease the recall bias. Pregnancy outcomes should be classified by trimester of exposure and any congenital anomaly reported should be further described.

For guidance on how to report pregnancy outcomes in the PSUR refer to Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data, GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women for additional guidance

- Use in immunocompromised patients:

Description of the criteria to which spontaneous reports are to be included for this subpopulation should be provided (i.e. manual screening of medical condition). An overall summary of the adverse events reported, seriousness, case outcome, gender, age and interpretation of the data is required. Any relevant difference on the pattern of ADR reported in immunocompromised patients that differs from the know safety profile for the vaccine in the general population should be discussed.

- Use in patients with auto-immune or inflammatory disorders

Description of the criteria to which spontaneous reports are to be included for this subpopulation should be provided (i.e. which conditions in the medical history are considered). An overall summary of the adverse events reported, seriousness, case outcome, age, gender and interpretation of the data is required. In particular, MAHs should comment whether data allows any increase on the risk of exacerbation/flares of the underlying disease following vaccination. Any relevant difference on the pattern of ADR reported in patients with autoimmune or inflammatory disorders that differs from the know safety profile for the vaccine in the general population should be discussed.

- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder):

Description of the criteria to which spontaneous reports are to be included for this sub population should be provided (i.e. which conditions in the medical history are considered). An overall summary of the adverse events reported, seriousness, case outcome, age, gender and interpretation of the data is required. Any relevant difference on the pattern of ADR reported in frail patients with co-morbidities that differs from the know safety profile for the vaccine in the general population should be discussed.

- Interactions with other vaccine(s):

Considering the ongoing mass vaccination programs in different countries, it is acknowledged that the number reports of vaccine co-administration reported from post-marketing setting could be limited. If concomitant administration of the COVID-19 vaccine with other vaccines has been reported in the spontaneous data, MAHs are encouraged to comment whether the pattern of ADR(s) reported is different than when the COVID-19 vaccine is administered as a stand-alone vaccine.

- Long-term safety:

Available post-marketing data should be evaluated to address long term safety.

16.4 Characterisation of risks

No additional requirement.

16.5 Effectiveness of risk minimisation (if applicable)

No additional requirement.

17. Benefit evaluation

17.1 Important baseline efficacy/effectiveness information

No additional requirement.

17.2 Newly identified information on efficacy/effectiveness

New information about efficacy/effectiveness from any source (e.g. MAH data, literature, public health agencies (ECDC, CDC)… etc) should be discussed in this section, including available data about efficacy against any of the circulating strains, antibody waning, the need for a booster dose or revaccination, impact of mixed dose schedule on efficacy/effectiveness. New data on immunogenicity or efficacy in the populations classified as missing information is to be discussed in this section.

17.3 Characterisation of benefits

No additional requirement.

18. Integrated benefit-risk analysis for authorised indications

18.1. Benefit-risk context- medical need and important alternatives

No additional requirement.

18.2 Benefit-risk analysis evaluation

No additional requirement.

19. Conclusions and actions

No additional requirement.

20. Appendices to PSUR:

1. Reference Information;

2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical trials and Interval and Cumulative Summary Tabulations from post-marketing Experience;

3. Tabular Summary of Safety Signals, including a reference whether the signal has been assessed in another regulatory procedure (i.e. MSSR or a variation) or not

(if not included in the body of the report);

4. Listing of interventional and non-interventional studies with a primary objective of post authorization safety monitoring;

5. List of the Sources of Information Used to Prepare the PSUR (when desired by the MAH).

The PSUR may also be accompanied by regional appendices, as needed, to fulfil national and regional requirements.

6. Regional appendices to fulfil regional requirements.

- Regulatory authorities request(s) following review of MSSR(s) (not considered as a signal)
- As an outcome of the MSSR(s) assessment or any other regulatory procedure, MAHs may have been requested to closely monitor events in the PSUR. Therefore, cumulative reviews are expected to be provided with a DLP aligned with that from the PSUR.
- Other safety evaluations:
    - Supporting documentation for evaluations provided in the PSUR (e.g. signal evaluations, observed expected analysis for AESIs…)
    - Interval and Cumulative review of **fatal reports** – number and relevant cases (considering co-morbidities and frailty), including O/E analyses, stratified by age groups, cause of death, autopsy results (if available)
    - Safety effects of mixed schedules
    - Issues related to batch(es) (if applicable)

General consideration for all safety evaluations:

For all safety evaluations (including signals, AESI,…etc), search criteria, case definitions (standardised case definitions available by Brighton Collaboration criteria to be prioritised, if available (e.g. anaphylaxis: Rüggeberg et al 2007), risk periods considered for temporal association with vaccination should be provided.

Justification should be given for cases not meeting case ascertainment criteria (e.g. no laboratory results reported) or causal association with vaccination (no biological plausibility, no plausible time to onset, event could be explained by alternative aetiology/ concomitant medication, etc…)

If safety evaluations by age are required, age stratification should follow the same age group than the available source of vaccine administration data, unless otherwise requested or justified.

General considerations for observed-expected (O/E) analysis:

Any O/E analyses should be performed cumulatively, using appropriate and justified background rates, an appropriate and justified risk window and when applicable, should be stratified by age group or presented per region (e.g. if background rates vary), and complemented with a sensitivity analysis. Case definitions for both observed and expected cases should be included.

Priority should be given to background rates provided by ACCESS available from Dashboard background rates of Adverse Events of Special Interest for COVID-19 vaccines – VAC4EU, when available. When not available via ACCESS, other data sources can be referenced. The selection of background rates used in the analysis should be thoroughly justified. Methodological aspects of the O/E analyses, including limitations, should be presented and discussed as part of the report.

If an increased O/E ratio is detected, a discussion on the need for further evaluation of the concern should be presented.

Methodological considerations of O/E analyses:

- GVP Module P.I: Vaccines for prophylaxis against infectious diseases

- (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

- Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines (Pharmacoepidemiol Drug Saf. 2016;25(2):215–222)