الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

SFDA Guidance for Periodic Safety Update Reports of COVID-19 Vaccines

Version 1.0

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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Table of Content:

1. INTRODUCTION 6
   1.1. Scope 6
   1.2. Objective 6
   1.3. PSUR requirements and guidance for COVID-19 vaccines 6
2. CONTENT OF THE PSUR: 7
   1. Introduction 7
   2. Worldwide marketing authorization status 7
   3. Actions taken in the reporting interval for safety reasons 7
   4. Changes to the reference safety information 7
   5. Estimated exposure and use patterns 7
   6. Data in summary tabulations 7
   7. Summaries of significant safety findings from clinical trials during the reporting interval 8
   8. Findings from non-interventional studies 8
   9. Information from other clinical trials and sources 8
   10. Non-clinical data 9
   11. Literature 9
   12. Other periodic reports 9
   13. Lack of efficacy in controlled clinical trials 9
   14. Late breaking information 9
   15. Overview of signals: new, ongoing or closed 9
   16. Signal and risk evaluation 10
   17. Benefit evaluation 13
   18. Integrated benefit-risk analysis for authorized indications 14
   19. Conclusions and actions 14
   20. Appendices to PSUR: 14

   General consideration for all safety evaluations: 16

   General considerations for observed-expected analysis: 16

1. INTRODUCTION

This guidance was mainly adopted from the European Medicines Agency (EMA) document "Consideration on core requirements for PSURs of COVID19 vaccines". This guidance is a supplemental to the Saudi Food and Drug Authority (SFDA) guideline on good pharmacovigilance practices to provide further section-by-section guidance and requirements for Periodic Safety Update Reports (PSURs) of COVID-19 vaccines approved in the Saudi market. Moreover, Market Authorization holders (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.

1.1. Scope

This document addresses the PSURs for COVID-19 vaccines approved in the Saudi market.

1.2. Objective

This document aims to provide guidance and requirements for MAHs of COVID-19 vaccines for drafting the PSURs.

1.3. PSUR requirements and guidance for COVID-19 vaccines

This guidance should be read in conjunction with existing relevant SFDA guidance (including, Guideline on good pharmacovigilance practices (GVP), Guideline on GVP – Definition, GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases and National Manual for Surveillance of Adverse Events Following Immunization in Saudi Arabia) published on the SFDA website. The provided guidance and requirements should be read and applied in the circumstances 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 needed.

2. CONTENT OF THE PSUR:

1. Introduction

No additional requirement

2. Worldwide marketing authorization 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

No additional requirement

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

The exposure data (cumulative and interval) should be based on administered doses rather than distributed doses whenever possible, and stratified by age groups, gender, region and by dose (when applicable).

6. Data in summary tabulations

6.1 Reference information

No additional requirement

6.2 Cumulative summary tabulations of serious adverse events from clinical trials

No additional requirement

6.3 Cumulative and interval summary tabulations from post-marketing data sources

The following tabulations are requested along with the standard tabulations:

- Interval and cumulative number of reports, overall and by age groups, and in special populations (e.g. elderly and pregnant women)
- Interval and cumulative number of reports per High Level Terms (HLT) in addition to the MedDRA "System Organ Class (SOC)

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 therapeutics use of medicinal product

No additional requirement

7.5 New safety data related to fixed combination therapies

No additional requirement

8. Findings from non-interventional studies

No additional requirement

9. Information from other clinical trials and sources

9.1 Other clinical trials

This PSUR sub-section should summarize information relevant to the benefit-risk assessment of the COVID-19 vaccine from other clinical trial/study sources, which are accessible by the MAH during the reporting interval. In addition, a summary of clinical trial data providing information on booster dose or revaccination, antibody waning, and mixed dose schedules should be presented.

The SFDA will utilize any relevant regulatory procedure to assess the final clinical study reports (CSR), as appropriate because the PSUR is not the final tool to assess the CSR.

9.2 Medication errors

When mass vaccination occur, medication errors are expected, including errors from the use of multi-dose vials. The acknowledgement of the amount of the information gathered in a mass vaccination setting, medication errors with harm should be prioritized

10. Non-clinical data

No additional requirement.

11. Literature

The MAH should summarize the new important information (benefits, efficacy, antibody waning, revaccination, need of a booster dose, mixed dose schedule, safety concerns, Adverse events of special interest (AESIs) …etc.) either published in the peer-reviewed scientific literature or unpublished manuscripts that the MAH became aware of during the reporting interval, when relevant to the COVID-19 vaccines. New important information refers to new information on issues that have not been assessed before or news aspects of known issues.

12. Other periodic reports

No additional requirement.

13. Lack of efficacy in controlled clinical trials

The information of lack of efficacy or changes in the efficacy should be illustrated in this section (when applicable).

14. Late breaking information

No additional requirement.

15. Overview of signals: new, ongoing or closed

All signals (ongoing or closed) that is identified during the reporting period should be summarized in this section as detailed in GVP related to (overview of signals: new, ongoing or closed) section, should provide a full evaluations of those signals that have been discussed in the MSSRs.

Post-approval regulatory requests (worldwide)

If a regulatory authority has requested further evaluation for a specific safety topic (not initially considered a signal) and requested to be monitored and reported in a PSUR (e.g. in the context of the MSSR), the MAH should summarize the result of the analysis based on the conclusion:

- If the conclusion of the evaluation does not constitute a validated signal, then the result of the analysis should be summarize in PSUR Section 15.
- 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.

16. Signal and risk evaluation

16.1 Summary of safety concerns

No additional requirement

16.2 Signal evaluation

No additional requirement. Full evaluations can be included in appendix.

16.3 Evaluation of risks and new information

Full evaluation documentation for the risk should be presented in this section, including observed versus expected analysis, can be included as an appendix when applicable.

New information can be organized 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 AESIs: the section should summary of the AESIs included in section 16.2 (signals) or in section 15 (post-approval requests) with a supporting documentation, such as complete evaluations or observed/expected analysis should be provided in an appendix.

Lack of efficacy: SFDA encourages the MAHs to follow the definitions of confirmed lack of efficacy and suspected lack of efficacy as per CIOMS/WHO working group definitions. The MAHs should provide the definition of vaccination failure that they are following. Moreover, the definition should describe the following terms***:*** *Confirmed vaccination failure, suspected vaccination failure, and not a vaccination failure*

- ***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. MAHs are also strongly encouraged to present available data following each dose in individuals previously exposed or not to SARS-COV-2.
- 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, and safety) gathered through the additional pharmacovigilance activities in the risk minimization plan (RMP), relevant information can be obtained from the post-marketing monitoring. The inherent limitations of spontaneous data are acknowledged.

Below there is 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:

- ***Use in pregnancy and while breastfeeding:***

  To reduce the recall bias, data for pregnancy outcome should be classified into prospective and retrospective reports. Pregnancy outcomes should be categorised according to the trimester of exposure, and any congenital anomalies should be recorded in detail.

- ***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, and interpretation of the data is required. Any relevant difference on the pattern of adverse drug reaction (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 general description of underlying disease:***

  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, 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):***

  MAHs are encouraged to comment on whether the pattern of ADR(s) reported is different when the COVID-19 vaccine is administered as a stand-alone vaccination if co-administration of the COVID-19 vaccine with other vaccines has been documented in the spontaneous data. Considering the mass vaccination programs in different countries, it is acknowledged that the number reports of vaccine co-administration can be limited.

- ***Long – term safety:***

  Additional pharmacovigilance activities in the RMP are intended to acquire long-term safety data.

16.4 Characterization of risks

No additional requirement.

16.5 Effectiveness of risk minimization (if applicable)

Based on the RMP guideline, for the events of which follow-up questionnaires are implemented (e.g. anaphylaxis), the indicator process data (e.g. response rate, need for corrective actions) should be provided by the MAH and reassess the need for continuing this routine pharmacovigilance activity in the PSURs.

17. Benefit evaluation

17.1 Important baseline efficacy/effectiveness information

No additional requirement

17.2 Newly identified information on efficacy/effectiveness

In this section, new information about efficacy/effectiveness from any source 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 should be discussed. 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 authorized 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 (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).

6. Regulatory authorities request(s) following review of MSSR(s) (not considered as a signal)
7. 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 data lock point (DLP) aligned with that from the PSUR.
8. Signal evaluation (closed signals during the reporting period)
9. Other safety evaluations:
    - Supporting documentation for evaluations provided in the PSUR (i.e. Observed expected analysis for AESIs…)
    - Interval and Cumulative review of **fatal reports** – number and relevant cases (considering co-morbidities and frailty), including Observed expected analysis analyses, stratified by age groups, autopsy results (if available)
    - Safety effects of mixed schedules
    - Issues related to batch(es) (if applicable)

KSA specific requirements for PSURs

MAHs should submit below additional requirements:

1- KSA-approved product information

This sub-section should contain the latest approved version of COVID-19 vaccine product information

2- Proposed product information :

This sub-section should include the proposed amendments to the product information with track changes feature based on the assessment of the current PSUR or requested by SFDA. All necessary documentation that support such amendments should be provided.

3- Proposed additional pharmacovigilance and/or risk minimization activities :

This sub-section should include any proposal for additional pharmacovigilance and/or additional risk minimization activities based on PSUR assessment or requested by SFDA.

4- Patient exposure in the KSA

This section should provide information about the cumulative and interval patient exposure of COVID-19 vaccine in the KSA only.

5- ADRs reporting in the KSA

This sub-section should provide a summary tabulation of all received ADRs reports, including fatal case, in the KSA (from all available sources) related to COVID-19 vaccine during the reporting interval and cumulatively.

6- Safety signals evaluation

This sub-section should provide a tabular summary of all safety signals requested by SFDA related to COVID-19 vaccine during the reporting interval and cumulatively.

7- Clinical trials in the KSA

This section should list all clinical trials during the reporting interval and cumulatively, either planned, ongoing or completed.

General consideration for all safety evaluations:

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

Cases that do not meet case ascertainment criteria (e.g., no laboratory results reported) or that do not show a causal link to vaccination (e.g., no biological plausibility, no plausible time to onset, event could be explained by alternative aetiology/concomitant medication, etc...) should be justified.

General considerations for observed-expected analysis:

Any Observed expected analysis analyses should be performed both for interval cases and cumulatively, using appropriate 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.

Methodological aspects of the Observed expected analysis analyses, including limitations, should be presented and discussed as part of the report.

A discussion on the need for further evaluation of the concern should be present when an increased in the O/E ratio is detected

Methodological considerations of Observed expected analysis analyses:

- GVP Module P.I: Vaccines for prophylaxis against infectious diseases
- Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines (Pharmacoepidemiol Drug Saf. 2016;25(2):215–222)