Risk Management Plans

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Risk Management Plans (RMP)

- Definition
- Legislation
- Content – what to include
- Requirements for COVID-19 vaccines RMPs
- Examples

RMP is…

- a regulatory requirement established by **pharmaceutical companies**
- has to be included in new request for marketing authorization, bad RMP can delay approval!
- Tool for communication between industry and regulators
- a key document defining any necessary activities around the safety of the medicinal product during launch and post-marketing
- Evolving document, has to be systematically updated during post-marketing follow-up

PSUR: periodic safety update report/ PBRER: periodic benefit-risk evaluation report

Definitions

Risk Management Plan

- *A detailed description of the risk management system [DIR Art 1(28c)].*

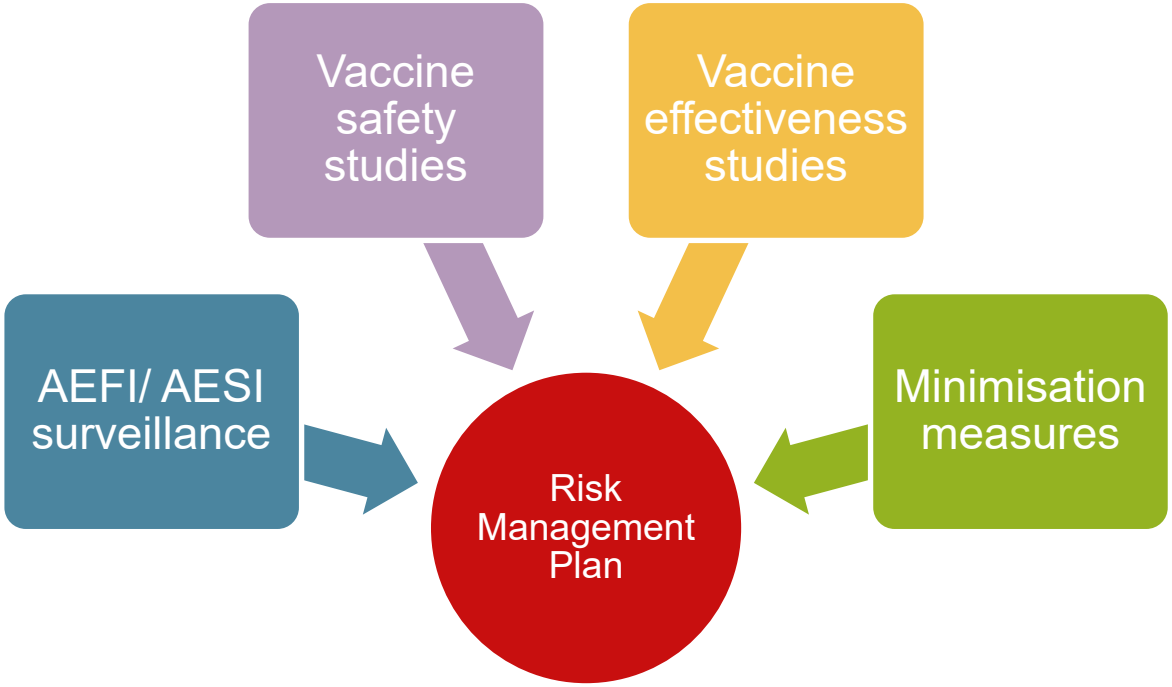
Risk management system

- *A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [DIR Art 1(28b)].*

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

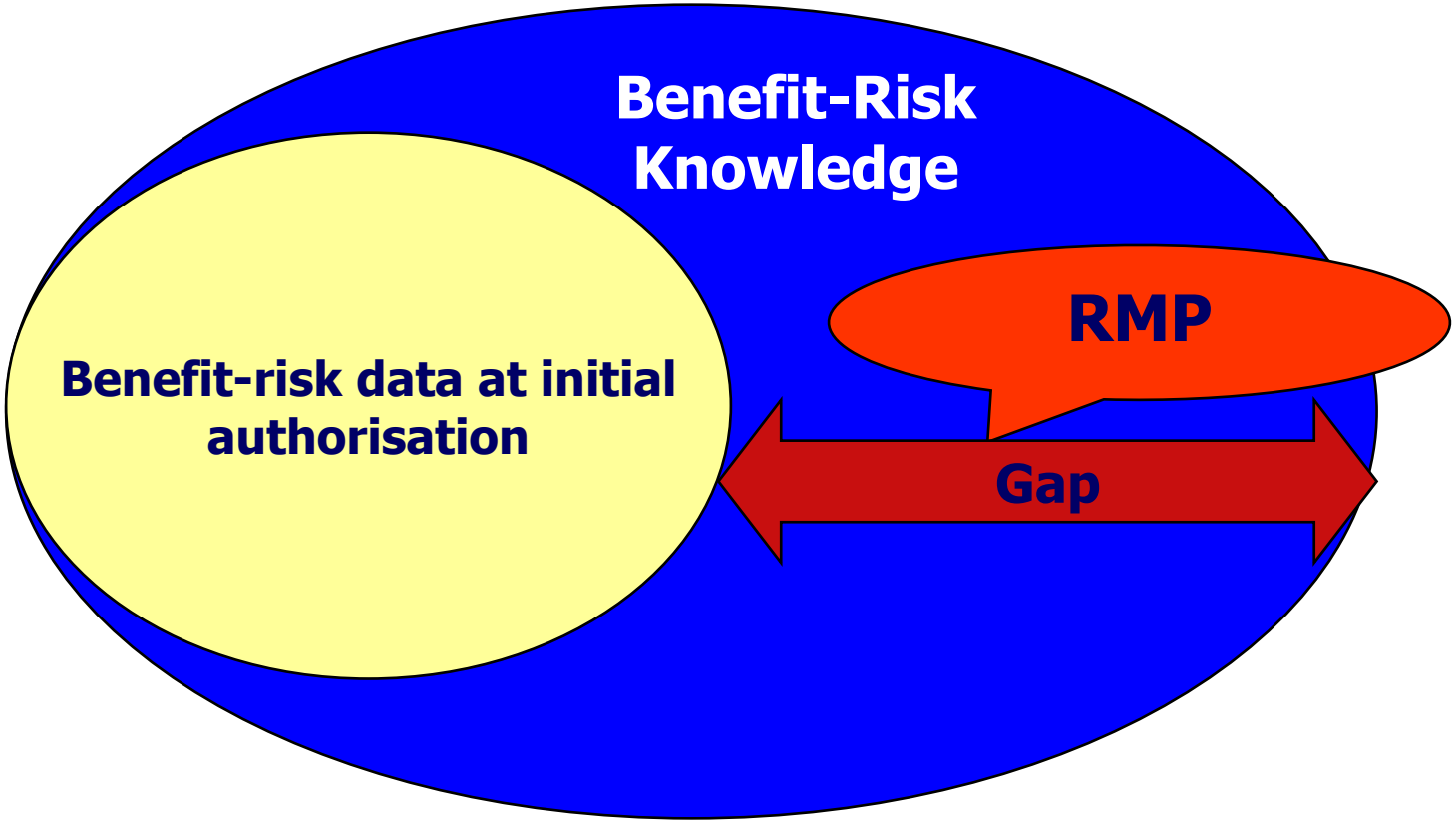
Risk Management Principles

- The overall aim of risk management is to ensure that the benefits of a medicinal product exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole



https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

Why do we need RMPs?



Legislation

EU

- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)[1]

US

- Format and Content of a Risk Evaluation and Mitigation Strategies (REMS) Document Guidance for Industry[2]

Other countries

- Many countries accept the EU-RMP format +/- local specificities (e.g., a region-specific annex, local studies…)
- WHO PQ: EU-RMP format
- WHO safety manual for COVID-19 vaccines: “manufacturers are encouraged to adopt existing formats, such as the EU-RMP format”[3]

[1] *https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf*

[2] *https://www.fda.gov/files/drugs/published/Format-and-Content-of-a-REMS-Document-Guidance-for-Industry.pdf*

[3] *https://apps.who.int/iris/bitstream/handle/10665/338400/9789240018280-eng.pdf?sequence=1&isAllowed=y*

Objectives of the RMP

- Identify or characterise safety profile
- How to characterise further the safety profile
- Measures to prevent or minimise risks including assessment of the effectiveness of those measures
- Document post-authorisation obligations

Content of the EU-RMP[1]

Safety specification

Medicinal product safety profile with emphasis on:

- important identified and potential risks and missing information
- which safety concerns need to be managed proactively or further studied

Pharmacovigilance plan

Pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions

Risk minimization plan

How risks will be prevented or minimised in patients

- risk minimization measures
- evaluation of the effectiveness of these activities

safety profile knowledge increase over time => RMP changes

[1]Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev 2) - 28 March 2017 EMA/838713/2011 Rev 2
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

Safety specifications

Identify what is known!
what is unknown?

VACCINE
Pre-Clinical data
Immunogenicity
How will it be used?
Adverse events profile
Class effects?
Interactions?

TARGET POPULATION
Who was studied?
Who wasn't studied?
Comorbidities?
Risk factors?
What events can we expect in this population?

DISEASE
Natural history
Epidemiology
What events occur as part of disease?
Treatment options

Important identified/potential risks
Missing information
= Safety concerns

should evolve over time +/−

Safety concerns

Identify and characterize

Pharmacovigilance Plan

ROUTINE ACTIVITIES
Collection of AEFI/AESI
Signal detection
Targeted follow-up questionnaires
PSUR
Literature review

ADDITIONAL ACTIVITIES
Clinical trials
Vaccine safety studies
Vaccine effectiveness studies

Safety concerns

Prevent or minimise

Risk minimization measures

ROUTINE RISK MINIMISATION
Legal status
Pack size
SmPC
Package leaflet
Labelling

ADDITIONAL RISK MINIMISATION
Educational program (for healthcare professionals or patients)
Prescribing checklist
Controlled access program
Other (e.g. Direct Healthcare Professional Communication, Pregnancy Prevention Program…)

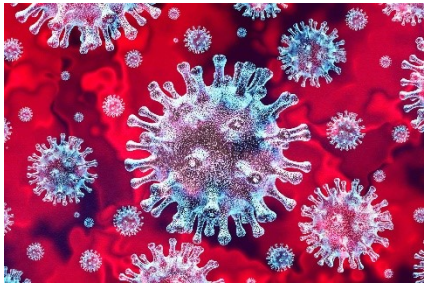
Key elements of the core EU-RMP[1]

Part I	Product(s) overview
Part II	Safety specification
Module SI	Epidemiology of the indication(s) and target population(s)
Module SII	Non-clinical part of the safety specification
Module SIII	Clinical trial exposure
Module SIV	Populations not studied in clinical trials
Module SV	Post-authorisation experience
Module SVI	Additional EU requirements for the safety specification
Module SVII	Identified and potential risks
Module SVIII	Summary of the safety concerns
Part III	Pharmacovigilance plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI	Summary of the risk management plan
Part VII	Annexes

Vaccine specificities[2] And COVID-19 specificities[3]

[1]Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev 2) - 28 March 2017 EMA/838713/2011 Rev 2
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp
[2]Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf
[3]Consideration on core requirements for RMPs of COVID19 vaccines
https://www.ema.europa.eu/en/documents/other/consideration-core-requirements-rmps-covid-19-vaccines_en.pdf

RMP requirements for COVID-19 vaccines



- EMA developed a guidance on RMP requirements for COVID-19 vaccines
  - Section-by-section guidance and requirements for drafting RMPs of COVID-19 vaccines

- WHO published COVID-19 vaccines: Safety Surveillance Manual

Consideration on core requirements for RMPs of COVID19 vaccines
https://www.ema.europa.eu/en/documents/other/consideration-core-requirements-rmps-covid-19-vaccines_en.pdf
COVID-19 vaccines: safety surveillance manual
https://apps.who.int/iris/bitstream/handle/10665/338400/9789240018280-eng.pdf?sequence=1&isAllowed=y

Key elements of the core RMP (COVID vaccines)
Safety specifications – important identified/ potential risks

- Include a **well justified list of important potential risks for which evidence exists**, and not a comprehensive list of all theoretical risks for vaccines in general.
- 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;
  - 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 including considerations for ADE).**
- When the clinical results do not raise particular safety concerns, it may be acceptable that no important identified risks are included in the RMP

Key elements of the core RMP (COVID vaccines) Safety specifications – missing information

- **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

RMP examples

- A European public assessment report (EPAR) is published for every human medicine application that has been granted or refused a marketing authorisation[1]

- **All RMPs for COVID-19 vaccines are published on the EMA's website**
  - Full body of the RMP and Annex 4 – specific adverse reactions follow-up forms) as part of EMA's exceptional measures to maximise the transparency of its regulatory activities on medicines for treatment and prevention of COVID-19.

[1] https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine

COVID-19 RMP examples
Safety specifications

Safety concerns	Pfizer	Moderna	Astra Zeneca
Important identified risks			
Anaphylaxis	x	x	None
Important potential risks			
Anaphylaxis			x
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	x	x	x
Nervous system disorders including immune-mediated neurological conditions			x

COVID-19 RMP examples
Safety specifications

Safety concerns	Pfizer	Moderna	AstraZeneca
Missing information			
Use in Pregnancy and while breastfeeding	x	x	x
Use in immunocompromised individuals	x	x	x
Use in individuals with autoimmune or inflammatory disorders	x	x	x
Use in frail individuals with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	x	x	x
Interaction with other vaccines	x	x	x
Long term safety	x	x	x

Key elements of the core RMP (COVID vaccines) Pharmacovigilance plan

- **Routine** pharmacovigilance activities to be implemented by the **MAH**
  - ICSR reporting
  - Signal detection
  - Specific follow-up questionnaire(s)
  - During the pandemic the MAHs are expected to submit **Summary Monthly Safety Reports**;
  - Enhanced passive surveillance
  - Traceability

Routine pharmacovigilance activities for Comirnaty® (1/5)

- Receipt and review of **individual AE reports**
- Data Capture Aids (**Targeted Follow up questionnaires** for VAED/vaccine lack of effect and anaphylaxis)

Targeted Follow-Up Questionnaires (TFUQs)

- To obtain additional structured information for reports of safety concerns and AESIs
- 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

Pfizer-BioNTech COVID-19 Vaccine Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced, particularly in relation to potential cases of vaccine lack of effect or vaccine associated enhanced disease (VAED).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

AE onset date (dd-Mmm-yyyy): _____

Patient Age (e.g., 65 years): _____

Patient Gender: ☐ Male ☐ Female ☐ Not Stated

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Don't Know

Ethnic Group: ☐ Hispanic/LatinX ☐ Non-Hispanic/Non-LatinX

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below)*:		
Phone Number:	Fax Number:	Email Address:

1. **Product information (Pfizer-BioNTech COVID-19 Vaccine)**

Dose	Date (dd-Mmm-yyyy)	Site of injection	Route	Batch/Lot number
1st dose				
2nd dose				

Follow-up Questions

Please provide additional details on a separate page if needed and reference the question number.

1. Does the patient have a positive test for SARS-CoV2?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (and indicate if this is a new infection or a recurrence)*

Details: (Please specify date of test and type of test – e.g., nasal swab reverse transcription–polymerase chain reaction (RT-PCR) test or nucleic acid amplification–based test (NAAT) or antigen test)

2. Does the patient have SARS-CoV2 antibodies at diagnosis?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)

3. Was/Is the patient hospitalized?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*

Details:

4. Was/Is the patient admitted to an Intensive Care Unit?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*

Details:

5. Is the patient still hospitalized?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*

Details:

6. If discharged, did the patient have SARS-CoV2 antibodies at hospital discharge?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details: (Please specify date of test, whether IgM /IgG or both and the titer if available)

7. Did the patient display clinical signs at rest indicative of severe systemic illness?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., Fever, RR ≥30 breaths per minute, HR ≥125 beats per minute, use of vasopressors to maintain BP, SpO2 ≤93% on room air, PaO2/FiO2 <300 mm Hg)?)*

Details:

8. Did the patient require supplemental oxygen (including high flow or ECMO) or receive mechanical ventilation?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., oxygen requirements, pulse oximetry results)*

Details:

9. Please provide information on any new or worsened symptoms/signs during the COVID-19 illness experienced (including date of onset/worsening)

Multiorgan failure ☐ Unknown ☐ No ☐ Yes → *If Yes, please indicate which organ systems were affected and provide information on the applicable systems below*

☐ Respiratory ☐ Cardiovascular ☐ Gastrointestinal/Hepatic ☐ Vascular ☐ Renal ☐ Neurological ☐ Hematological ☐ Dermatological ☐ Other

moderna

Anaphylaxis Reporting Form

INFORMATION ABOUT PERSON COMPLETING THIS FORM	INFORMATION ABOUT FACILITY WHERE VACCINE WAS GIVEN
Form completed by (name):_____ Country:_____ Address:_____ City_____State/Province_____Postal Code_____ Phone:_____ Email:_____ **Relation to Patient:** ☐Self ☐Family Member ☐ Other_____ ☐Healthcare Professional (select below): ☐Physician ☐Nurse ☐Office staff ☐ Other:_____	**Type of Facility:** ☐ Doctor's office, urgent care, or hospital ☐ Pharmacy ☐ Workplace Clinic ☐ Public health clinic ☐ School or student health clinic ☐ Nursing home or senior living facility ☐ Other: **Facility/Clinic Name:**_____ Country:_____ Address:_____ City:_____State/Province:_____Postal Code_____ Phone:_____Fax:_____
Best doctor/healthcare professional to contact about the adverse event:_____ Phone:_____ Fax:_____ Email:_____	

MODERNA VACCINE INFORMATION

Vaccine (type/brand)	Manufacturer	Lot number / Batch number	Route	Needle length / gauge	Dose Volume (mL)	Body site	Dose number in series	Date/Time Given
COVID-19 / mRNA-1273	Moderna					☐ Left ☐ Right	Dose 1	____/____/____ ____:____ ☐ am ☐ pm
COVID-19 / mRNA-1273	Moderna					☐ Left ☐ Right	Dose 2	____/____/____ ____:____ ☐ am ☐ pm

PATIENT INFORMATION

Initials: **Gender:** ☐ Male ☐ Female ☐ Unknown	Race (check all that apply):☐White ☐Black ☐Middle Eastern ☐N American Indian/Inuit/Métis ☐South Asian ☐East/Southeast Asian ☐Native Hawaiian/Pac Islander ☐Unknown ☐Other:_____
If female, pregnant? ☐ No ☐ Yes ☐ Unknown	
Age at vaccination or Date of birth:	Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown
Height: _____☐ inches ☐ centimeters Weight: _____☐ pounds ☐ kilograms	Allergies to medications, food, and other products:

MEDICAL HISTORY

Acute illnesses at the time of vaccination and up to one month before: ☐ None ☐Unknown	Start date (DD/MMM/YYYY)	Ongoing?	Stop date (DD/MMM/YYYY)
	____/____/____	☐ Yes ☐ No	____/____/____
	____/____/____	☐ Yes ☐ No	____/____/____

Previous allergic reaction history:

Does the patient have a history of allergic or hypersensitivity reactions?
☐ No ☐ Yes ☐ Unknown
Date ___/_____/_____ DD/ MMM / YYYY

If yes, please indicate if these are observed in relation to previous vaccines/immunisation
☐ No ☐ Yes ☐ Unknown
Date ___/_____/_____ DD/ MMM / YYYY

Please identify if patient has a history of any of the following medical conditions?
Anaphylaxis ☐ No ☐ Yes ☐ Unknown
Hypersensitivity reactions ☐ No ☐ Yes ☐ Unknown
Asthma ☐ No ☐ Yes ☐ Unknown
Hay fever ☐ No ☐ Yes ☐ Unknown
Urticaria/hives ☐ No ☐ Yes ☐ Unknown

Concurrent signs and symptoms and chronic or long-standing	Start date (DD/MMM/YYYY)	Recent change in status of chronic condition (i.e. significant worsening or improvement; treatment changes, etc)? If yes, please describe.

Routine pharmacovigilance activities for Comirnaty® (2/5)

- **Signal detection**
  - individual AE assessment at case receipt
  - regular aggregate review of cases for trends
  - statistically disproportionately reported product-AE pairs
  - weekly SD activities (incl. literature review)
  - Observed *versus* Expected (O/E) analyses as appropriate
- **Monitoring of regulatory authority safety alerts**

Routine pharmacovigilance activities for Comirnaty® (3/5)

- At the **country level**, the Pfizer Drug Safety Units perform routine pharmacovigilance activities including the **collection of AEs from various sources** and the reporting of AEs to the regulatory authority as per local regulatory guidelines.
- **Monthly Summary Safety Reports** to EMA (in addition to 6-monthly PSURs)

Summary Monthly Safety Reports must be sent to Regulatory Authorities*

Minimum content for EU:

- 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
- Risk/benefit considerations

** Need and periodicity of such reports will be re-evaluated based on the available evidence from post-marketing for each vaccine*

EU: European Union, HLT:High Level Terms (, SOC: System Class Organ, AESI: Adverse Events od Special Interest, O/E: observed-to-Expected analysis

Vaccine safety update - example

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2021

COVID-19 vaccine safety update

COMIRNATY

BioNTech Manufacturing GmbH

The latest safety data for this vaccine are in line with the known side effect profile, and the related reviews are presented in this update.
Reports of suspected severe allergic reaction have not identified new aspects regarding the nature of this known side effect.
No specific safety concern has been identified for vaccine use in frail elderly individuals.
The benefits of Comirnaty in preventing COVID-19 continue to outweigh any risks, and there are no recommended changes regarding the use the vaccine.

Safety updates provide the outcomes of the assessment of emerging data since marketing authorisation for COVID-19 vaccines. The assessments are carried out by EMA's safety committee (Pharmacovigilance Risk Assessment Committee (PRAC)). The safety updates are published regularly at Post-authorisation: Safety updates.

All published safety updates for Comirnaty are available at Comirnaty: safety updates.

Content:

https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf

Routine pharmacovigilance activities for Comirnaty® (4/5)

Potential Medication Errors: strategy

- Prevention of potential medication errors (reconstitution, administration, vaccination scheme, storage, multi-vial error, confusion with other COVID-19 vaccines) through:
  - **SmPC** (instructions for reconstitution and administration, vaccination scheme, and storage conditions of the vaccine)
  - **poster** with step-by-step instructions (vaccine storage, dose planning and preparation, and administration)
  - **brochures** (safe handling of thevaccine) and **dry ice**
  - **medical information call centers**

Routine pharmacovigilance activities for Comirnaty® (5/5)

Traceability: strategy by Comirnaty®

- **SmPC** (instructions to clearly record the name and batch number)
- Instructions to **report any suspected adverse reactions**
- Electronic devices (see next slide)
- **2-D barcode** (batch/lot and expiry date)
- **'Traceability and vaccination reminder card'**
  - pre-printed manufacturer name and vaccine brand
  - placeholder (due date, actual date of first and second doses, batch/lot numbers)
  - placeholder (name of vaccinee)
  - reminder to retain the card and bring to vaccinations
  - QR code that links to additional information
  - Adverse event reporting information
- **Stickers on vaccine dose** (batch/lot number)

Routine pharmacovigilance activities for Comirnaty® (6/5)

Cold chain handling and storage: strategy

- **Electronic device** on vaccine shipping containers (**real-time monitoring of geographic location and temperature, batch/lot tracing**)
  - Data may be used for the assessment of a safety signal

- **Joint adverse event and product complaint trending reviews** (including available batch/lot information) occur routinely with Global Product Quality

- **Educational materials** for vaccinators about proper handling of shipment container and vaccine

Key elements of the core RMP (COVID vaccines) Pharmacovigilance plan

- **Additional** pharmacovigilance activities
  - Continuation of **safety surveillance from ongoing clinical trials** should be a **priority** and included as additional PV activities
  - Safety studies including PASS
  - Effectiveness studies
  - Pregnancy registry

- Safety studies can be **conditions of the marketing authorisation**

RMP examples

Comparison of interventional studies

Pfizer	Moderna
- Trial in pregnant women	
- Immunogenicity of COVID-19 mRNA vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses - Phase II study of BNT162b2 in adults Receiving immunomodulators for rheumatoid arthritis (RA) - Phase II study in high-risk adults (frail elderly, immunocompromised, autoimmune and other high-risk individuals)	- Study of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Immunocompromised Adults
- Co-administration trial with seasonal influenza vaccine	

RMP examples

Comparison of non-interventional studies

Pfizer RMP	Moderna RMP
1. Safety Surveillance of the Pfizer COVID-19 Vaccine in the U.S. Department of Defense Population Following Emergency Use Authorization 2. Post-Emergency Use Authorization Active Surveillance of Adverse Events of Special Interest among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech COVID-19 Vaccine 3. A Post-Approval Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the Pfizer-BioNTech COVID-19 vaccine in the EU	1. Post-Authorization Safety of SARSCoV-2 mRNA-1273 Vaccine in the US 2. Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU
4. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of the Pfizer-BioNTech COVID-19 vaccine in the EU	
5. Test-negative design to evaluate the effectiveness of BNT162b2 against acute respiratory illness due to SARSCoV-2 infection among adults ≥18 years of age (US, EU)	3. Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S.
	4. Moderna mRNA-1273 Observational pregnancy outcome study (EU, CA, US)

RECOMMENDATION FOR AN EMERGENCY USE LISTING OF COVID-19 mRNA VACCINE (NUCLEOSIDE MODIFIED) SUBMITTED BY Pfizer Europe MA EEIG

Abstract

Novel COVID-19 mRNA vaccine (Nucleoside Modified) - Comirnaty® was submitted [illegible] Organization (WHO) for evaluation under the [illegible] EEIG

In support of EUL:

- Non-interventional studies (for primary data collection in healthcare workers) on AESI-based safety events should be proposed in some of the countries outside of EU and US (that is Rest of the World (RoW) countries), preferably, in a few countries spread across the WHO Regions with priority consideration for the countries that participated in the studies. The WHO-protocol (to be available mid-January) or an equivalent should be considered for these studies. The study design should be shared with WHO/PQ.

[illegible] the product evaluation group (PEG) and discussed by the technical advisory group for EUL (TAG-EUL).

https://extranet.who.int/pqweb/sites/default/files/documents/TAG-EUL_PublicReport_Pfizer_31DEC20.pdf

Key elements of the core RMP (COVID-19 vaccines) Risk Minimisation Measures

- Routine RMM
  - 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**.
- Additional RMM
  - "key messages that may be used for inclusion in national educational material" to facilitate national efforts for communication and risk management.

Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf
Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum I – Educational materials
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-addendum-i-educational-materials_en.pdf

Pfizer COVID-19 vaccine

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

Safety Concern	Routine risk minimisation activities
Important Identified Risk	
Anaphylaxis	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk	
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Use in pregnancy and while breast feeding	Routine risk communication: SmPC section 4.6 Fertility, pregnancy and lactation PL section 2. What you need to know before you receive Comirnaty Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Additional minimisation measures

- No additional minimisation measures for COVID-19 vaccines so far

- Examples of additional risk minimization measures
  - Educational tools
    - Educational tools targeting healthcare professionals/ patients
  - Controlled access programme (e.g., specific testing and/or examination of the patient)
  - Controlled distribution system
    - distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product
  - Pregnancy prevention programme
  - Direct health care professional communication (DHPC)

Educational materials for Dengvaxia® (dengue vaccine)

- Educational materials for Dengvaxia are in the public domain (Singapore and Brazil)

Physician Educational Material Dengvaxia™

This Physician Educational Material provides practical guidance on the use of Dengvaxia in Singapore. For full details, please refer to the Singapore package insert.

- **Approved Indication**

  Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 12 through 45 years of age living in endemic areas.

- **Posology and method of administration**

  The primary vaccination schedule consists of 3 injections of one reconstituted dose (0.5 mL) to be administered at 6-month intervals.

  Dengvaxia should not be administered to individuals less than 12 years of age.

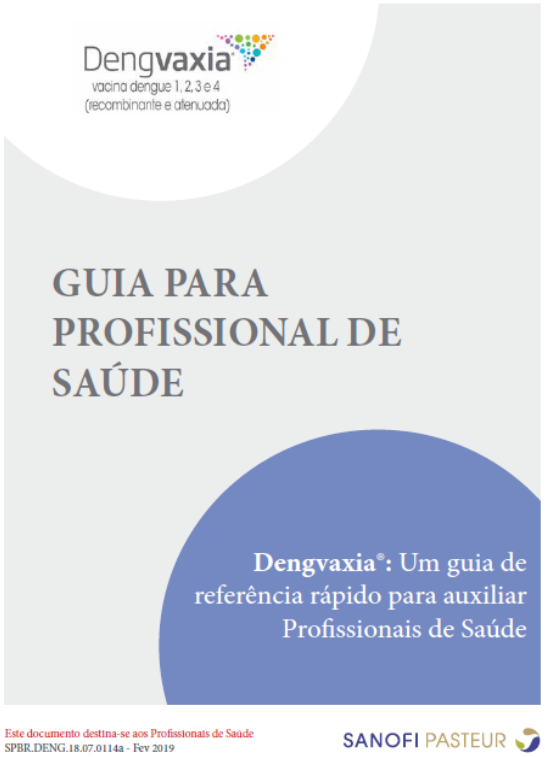
  Vaccination is not recommended for individuals who have not been previously infected by dengue virus.

  For individuals with unknown history of prior dengue exposure, previous infection can be substantiated through serotesting.

- **Considerations for the Singaporean population:**

  Clinical efficacy studies conducted in the 12 to 16 years-old population in endemic countries showed that the vaccine efficacy against symptomatic virologically confirmed dengue (VCD) cases due to any serotype is 69.2% and 60.4%, 53.2%, 76.2% and 88% for serotypes 1, 2, 3 and 4 respectively.

  The vaccine efficacy against severe VCD cases and against hospitalized VCD cases (i.e., hospital admission due to dengue, whatever the severity) is 95.5% (64.8; 99.4) and 81.3% (63.8; 90.4) respectively.



https://www.hsa.gov.sg/docs/default-source/hprg-vcb/pem-pmg-pac/dengvaxia-pem-v2_30082018.pdf
https://www.sbmt.org.br/portal/material-informativo-dengvaxia/?lang=en

EU-RMP assessment – guidance/ template

[insert only for PRAC endorsed reports; insert also EMA header and footer]

<insert full date>
<insert Doc.Ref.>
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC <Rapporteur> Risk Management Plan (RMP) Assessment Report

[Please delete the guidance text in green as well as the optional sentences that do not apply when circulating the report]

<Invented name>

<(Active substance)>

EMEA/H/C/<xxx>

Applicant:

https://www.ema.europa.eu/en/documents/other/scope-training-practical-guide-risk-management-plan-assessment_en.pdf
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/templates-assessors#risk-management-plan-assessment-report-templates-section

Take home messages

- An RMP should be submitted at initial marketing authorisation application
- RMP should contain
  - Safety specifications
  - Pharmacovigilance activities
  - Risk minimisation measures and evaluation
- RMP is living document – will be updated throughout the life cycle of the product.
- Specific considerations for RMPs of COVID-19 vaccines (EMA, WHO)
- MAH are encouraged to adopt existing formats, such as the EU-RMP format + regional Annexes, if necessary
- NRA should provide clear guidance on PV requirements
- Training to be provided to the smaller vaccine manufacturers


QUESTIONS

Back up slides

Interesting sites to learn more about RMPs

- https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plan-rmp-questions-answers
- https://www.pharmaceuticalonline.com/doc/ema-s-revised-format-for-risk-management-plans-what-you-need-to-know-0001
- https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans#risk-management-plans-for-covid-19-vaccines-section

Lessons learnt from novel vaccine introduction during pandemic and epidemic emergencies

- The 2009 H1N1 influenza pandemic demonstrated that few countries had a pandemic preparedness plan that comprehensively addressed vaccine deployment and monitoring of adverse events [1,2]
- Ebola epidemic (2014-2016) affected three countries in West Africa and led to an accelerated development of vaccines and therapeutics.
  - Collaboration between different partners
- The introduction of the first licensed dengue vaccine, (not in the context of an international public health emergency): vaccine-associated enhanced disease (VAED) was observed
  - Essential to prepare to manage VAED, which could be potentially induced by some of the COVID-19 vaccine candidates being developed.
- A common theme in these examples is the public concerns about the safety of the novel vaccines and rumours or adverse events that can arise during current and future pandemics

1 WHO. Main operational lessons learnt from the WHO pandemic influenza A(H1N1) vaccine deployment initiative. Available from: https://apps.who.int/iris/handle/10665/44711
2 European Medicines Agency. Pandemic report and lessons learned: outcome of the European Medicines Agency's activities during the 2009 (H1N1) flu pandemic. Available from: https://www.ema.europa.eu/documents/report/pandemic-reportlessons-learned-outcome-european-medicines-agencys-activities-during-2009-h1n1-flu_en.pdf.