Salud
Secretaría de Salud

COFEPRIS
COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

PHARMACOVIGILANCE GUIDE FOR THE PREPARATION OF PERIODIC REPORT OF SECURITY

This document defines, in accordance with the provisions of section 8.2.1 of the Mexican Official Standard NOM-220-SSA1-2016, Installation and Operation of Pharmacovigilance and its amendments, published in the Official Gazette of the Federation on September 30, 2020, the information that the Periodic Safety Report for medicines or vaccines must contain.

March-2025

Change control: update to current institutional stationery

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1. DEFINITIONS

Benefit/risk balance : the result of the evaluation of the positive therapeutic effects of the drug or vaccine in relation to the risks.

National Pharmacovigilance Center (CNFV): to the area of the Evidence and Risk Management Commission , attached to COFEPRIS, which is responsible according to the applicable regulations, to issue the policies and guidelines for the operation of the Pharmacovigilance in the national territory.

Distinctive name : the name that the laboratory or manufacturer assigns as a trademark to its pharmaceutical specialties in order to distinguish it from other similar ones, subject to approval by the health authority and registration before the competent authorities.

Generic name or generic name: the name of the medicine or vaccine, determined through a pre-established method, which identifies the drug or active substance, internationally recognized and accepted by the health authority.

Medication error : any preventable event that may cause harm to the patient or result in the inappropriate use of medications and vaccines, when these are under the control of health professionals or the patient or consumer. These incidents may be related to the practice professional, with products, with procedures or with systems, including failures in prescription, communication, labeling, packaging, name (distinctive or generic), preparation, dispensing, distribution, administration, education, monitoring and utilization.

Clinical **study :** any research carried out on human beings that aims to discover or verify the clinical and pharmacological effects and/or other pharmacodynamic effects of an investigational product and/or identify any adverse reaction and/or study the absorption, distribution, metabolism and excretion in order to evaluate the efficacy and safety of a drug under investigation.

For the purposes of this Standard, they are divided into two types: a) intervention studies (also known as clinical trials) and b) non-intervention studies (observational studies). These include phase I, II, III, and IV studies referred to in Article 66 of the Regulations of the General Health Law on Health Research.

Completed clinical study: This is a clinical study that has already been completed and for which the final report is available.

Pharmacovigilance study (safety-related): Any clinical study related to an authorized drug or vaccine that seeks to identify, characterize, or quantify a safety risk. This allows for confirming the drug or vaccine's safety profile, proposing effective measures, and measuring their effectiveness in minimizing risks. These studies may have an interventional or non-interventional study design.

Adverse event (AE): Any undesirable medical occurrence that may occur in a research subject during the clinical research phase of a drug or vaccine but that does not necessarily have a causal relationship with it.

Event supposedly attributable to vaccination or immunization (ESAVI): Clinical manifestation(s) or medical event(s) that occur after vaccination and are supposedly attributed to vaccination or immunization. The timing will depend on the vaccine.

Lack of efficacy (therapeutic failure, therapeutic ineffectiveness): the absence, decrease or changes in the therapeutic effect that appear unexpectedly with the use of medicines and vaccines for the authorized indication.

Pharmacovigilance: Activities related to the detection, evaluation, understanding, and prevention of adverse events, suspected adverse reactions, adverse reactions, events supposedly attributable to vaccination or immunization, or any other safety issues related to the use of medicines and vaccines.

Reference Safety Information: All relevant safety information contained in the authorized product information (e.g., IPPA) prepared by the Sanitary Registration Holder or its Legal Representative in Mexico.

Medication: Any substance or mixture of substances of natural or synthetic origin that has a therapeutic, preventative, or rehabilitative effect, presented in pharmaceutical form and identified as such by its pharmacological activity and physical, chemical, and biological characteristics. When a product contains nutrients, it will be considered a medication, provided that it is a preparation that individually or in combination contains vitamins, minerals, electrolytes, amino acids, or fatty acids in concentrations higher than those of natural foods, and is also presented in a defined pharmaceutical form and the indication for use contemplates therapeutic, preventative, or rehabilitative effects. As established in Article 221, Section I, of the General Health Law.

Safety profile: the result of the evaluation of the benefit/risk balance of the drug or vaccine, which is reflected in a document.

Safety concern or safety issue: an identified significant risk, significant potential risk, or missing information for a medicine or
vaccine.

Information Cut-Off Point (ICP): The date on which the periodic safety report period ends, from which information must be collected for the next periodic safety report to be submitted and which determines the maximum time for its submission.

Adverse drug reaction (ADR): an unwanted response to a drug, in which the causal relationship with the drug is at least reasonably attributable.

Unexpected adverse reaction: an adverse reaction whose nature or severity is not described in the product's prescribing information or in the documentation submitted for its Sanitary Registration.

Periodic Safety Report (PSR): the document that provides an evaluation of the benefit/risk balance of a medicine/vaccine and that is submitted by the holder of the

Sanitary Registry or its legal representative in Mexico to the CNFV in defined periods after the authorization of the Sanitary Registry or commercialization of the product.

Pharmacovigilance Officer: A healthcare professional trained in pharmacovigilance, responsible for coordinating and implementing pharmacovigilance activities, who will be the sole valid point of contact with the National Commission for the Protection of the Rights of Persons with Disabilities (CNFV).

Identified risk: an unwanted medical event for which there is sufficient evidence of an association with the drug or vaccine of interest.

Significant risk: An identified or potential risk that may negatively impact the product's benefit/risk balance or have implications for public health. What constitutes a significant risk will depend on several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health.

Potential risk: an undesirable medical event for which there are grounds for assuming an association with the medication or vaccine of interest, but said association has not been confirmed.

Signal: Information arising from one or more documentary sources, including observations and experiments, which suggests a potentially new causal association or a new aspect of a previously known association between an intervention and an event or set of related events, whether adverse or beneficial, and which is considered sufficient to justify action to verify the information.

New signal: one that has been identified during the benefit/risk assessment of the periodic safety report. A new signal is also considered when clinical information from a previously closed signal becomes available during the periodic safety report assessment interval.

Signal in progress: one that remains under evaluation at the information cut-off point during the benefit/risk assessment of the periodic safety report.

Closed signal: one whose assessment has been completed during the benefit/risk assessment of the periodic safety report.

Suspected adverse drug reaction (SDR): any undesirable clinical or laboratory manifestation that occurs after the administration of one or more medications.

Sanitary Registration Holder or their Legal Representative in Mexico: the natural or legal person who holds the Sanitary Registration granted by COFEPRIS for a medicine/vaccine, which complies with Article 168 of the Health Supplies Regulations.

Pharmacovigilance Unit (UFV): the entity dedicated to the implementation and development of Pharmacovigilance activities.

Vaccine: a biological preparation intended to generate immunity against a disease by producing antibodies, to eliminate, prevent or control pathological conditions.

2. INTRODUCTION

Periodic Safety Reports (PSRs) provide information related to the benefits and risks of a medicine or vaccine in everyday medical practice and long-term use in the post-licensure or post-marketing phase. This can extend to safety assessments in special populations and situations that could not be investigated in pre-licensure clinical studies.

If a new medicine or vaccine is approved by the Regulatory Authority for marketing, it means that its safety and efficacy have been proven and that the adverse events presented during pre-marketing clinical studies were clinically and statistically acceptable in a controlled group of patients and during a short follow-up period, although this does not mean that the benefit/risk ratio is definitive.

The benefit/risk ratio should be monitored over time through the RPS provided to the Regulatory Authority, with concise information, whether new or emerging, that allows for a thorough and critical analysis of said ratio.

This guide is based on NOM-220-SSA1-2016, Installation and Operation of Pharmacovigilance, and its amendments. This guide describes the requirements for the preparation, time periods, and deadlines required for periodic safety reports to be submitted to the Regulatory Authority.

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3. OBJECTIVES

3.1. GENERAL OBJECTIVE

Describe the necessary requirements to guide the holder of the health registration, the legal representative in Mexico, or the holder of the orphan drug recognition document in the preparation, the periods to be covered, and the delivery times of periodic safety reports on medicines and vaccines according to NOM-220-SSA1-2016, installation and operation of pharmacovigilance and its modifications.

3.2. SPECIFIC OBJECTIVES

- Describe the information required in each of the sections that make up the structure of the RPS.
- Report the times and periods established in NOM-220-SSA1-2016 installation and operation of pharmacovigilance and its modifications for the submission of the RPS to the CNFV.
- Report what types of medications they must prepare and submit their RPS to the CNFV.
- Inform what type of medicines their RPS should prepare and integrate them into the file in order to be available to the authority when required.

4. GENERALITIES

This guide is based on the provisions of NOM-220-SSA1-2016, installation and operation of pharmacovigilance, and its amendments, as well as international regulations. Therefore, none of the points in the established structure for preparing the RPS should be omitted.

4.1 If there is no information for any of the sections that make up the RPS, it is necessary to write the corresponding justification for the omission of said information within the same point.

4.2 The RPS must be submitted in electronic format (CD/USB), so you should not enter the information on paper.

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This guide is based on the provisions of NOM-220-SSA1-2016, installation and operation of pharmacovigilance, and its amendments, as well as international regulations. Therefore, none of the points in the established structure for preparing the RPS should be omitted.

4.1 If there is no information for any of the sections that make up the RPS, it is necessary to write the corresponding justification for the omission of said information within the same point.

4.2 The RPS must be submitted in electronic format (CD/USB), so you should not enter the information on paper.

4.3 The RPS must be signed by the person responsible for the unit. Pharmacovigilance, who must be duly accredited by the CNFV.

4.4 The RPS must be in Spanish in the sections that are requested as such. For more information see Annex 1. RPS compliance table.

5. SUBMISSION LETTER

To submit the RPS, a free written document must be submitted through the Center Comprehensive Services (CIS) directed to the Executive Directorate of Pharmacopoeia and Pharmacovigilance, which must contain the following essential technical information:

- Generic name of the medicine or vaccine.
- Distinctive name of the medicine or vaccine.
- Pharmaceutical form of the medicine or vaccine.
- Health Registration Number with the fraction or recognition number in orphan drug case.
- Corresponding RPS number.
- Corresponding revision number (when applicable).
- Period covered by the RPS (dd/mm/yyyy).
- Please inform us if you have a non-marketing form prior to submitting this RPS. If so, please indicate the non-marketing period.
- Electronic format in which the procedure is submitted (CD/USB).

Note: Please verify that the information is available and correct. If sending in CD format, please do not place labels on it.

- Complete details of the unit and the person responsible for pharmacovigilance (updated and valid with the CNFV) that include:

- Name and autograph signature of the person responsible for the Unit of Pharmacovigilance
- Address.
- Telephone number and extension, if applicable.
- Email.

6. STRUCTURE

The holder of the health registration, the legal representative, or the holder of the orphan drug recognition certificate in Mexico, through the head of the pharmacovigilance unit, must submit the RPS in electronic format, in Spanish (in the applicable fields), and contain the following information:

6.1 Cover.

6.2 Executive summary.
6.3 Table of contents.

6.4 Introduction.

6.5 Status of the authorization in the national and international market.

6.6 Update on actions taken by regulatory authorities for safety reasons.

6.7 Changes to product safety reference information.

6.8 Estimation of exposed patients.

6.9 Summary table of individual cases of SRAM, ADR, AE, ESAVI or any other safety problem related to the use of medicines and vaccines, accumulated.

6.10 Summary of facts presented during the clinical studies within the reported period.

6.11 Findings in studies whose primary objective is safety.
6.12 Information from other clinical studies.

6.13 Preclinical/non-clinical information.
6.14 Scientific literature.

6.15 Other periodic reports.
6.16 Lack of efficacy in clinical studies.

6.17 Updated information

6.18 Signal generation: new, in progress and closed.

6.19 Signals and risk assessment.

6.20 Summary of security problems in Mexico.
6.21 Benefit evaluation.

6.22 Risk/benefit balance analysis.

6.23 Conclusions and actions.
6.24 Annexes.

6.25 List of information sources.

6.26 List of annexes.
6.27 List of abbreviations.

Note: International companies may do the following:

- Reference some sections of the national RPS to the international one.
- Translate information partially from the international RPS, as long as it complies with the requirements of this guide.

For further reference on this point, please review ANNEX I “RPS compliance table”:

6.1. COVER

The RPS cover page must be submitted on letterhead by the holder of the Health Registry, including the following:

- Generic name of the medicine or vaccine.
- Distinctive name of the medicine or vaccine.
- Pharmaceutical form and presentation(s) of the medicine or vaccine.
- Health Registration Number with fraction (for orphan drugs)
  You must enter the recognition number.
- Time period covered by the RPS (dd/mm/yyyy).
- Marketing start date in Mexico.
- Number of patients exposed during the period.
- Number of notifications sent to the CNFV in the period of the RPS that is submitting.

6.2. EXECUTIVE SUMMARY

The purpose of this section is to provide a summary in Spanish of the most important information from each section of the RPS, a maximum of two pages long. Therefore, if you have an international RPS, it must be translated and included in this section, provided it complies with the requirements stated above.

6.3. TABLE OF CONTENTS

In this section, a paginated index will be created, linking to the section to which it refers, which must include all the sections that comprise the national RPS.

A paginated index of the information available in the international RPS should not be created. Information referenced in the international RPS should be included in each section of the national RPS.

6.4. INTRODUCTION

Within this section, a brief description of the therapeutic indication(s) and the target population authorized in Mexico must be included.

- Therapeutic indication(s)
- Authorized target population in Mexico.
- Therapeutic group.
- Mechanism(s) of action.
- Route of administration.
- Pharmaceutical form.
- Dosage by age group (dose including units, frequency of administration) administration and administration period).

Note: Companies that attach an international report must translate this section into Spanish, provided that the international RPS complies with the requirements stated here. Otherwise, they will need to prepare an introduction for Mexico.

6.5. STATUS OF THE AUTHORIZATION IN THE NATIONAL MARKET AND INTERNATIONAL

You must describe the authorization status of each country where the medicine or vaccine has a Sanitary Registration for marketing, which must include at least the points indicated in Table I.

Table I. Worldwide authorization status of medicines or vaccines that have Health Registration for marketing

COUNTRY	DENOMINATION DISTINCTIVE	SHAPE PHARMACEUTICAL	POSOLOGY*	INDICATION(S) THERAPY AUTHORIZED	DATE OF OBTAINING REGISTRATION SANITARY	START DATE OF MARKETING

The company that has an international report must fill out table I only with information referring to Mexico and specify within this section: the page number(s) where it is located the corresponding information in the international report on the status of authorization at the level international.

Note: for Table I , only information from the countries where you are the holder of the health registration or legal representative of the medicine or vaccine should be filled out . question.

6.6. UPDATE OF ACTIONS TAKEN BY REGULATORY AUTHORITIES FOR SAFETY REASONS.

This section should describe the actions requested or taken by national and international regulatory authorities, during the research stages and during commercialization.

6.6.1. Actions related to investigational drugs or vaccines

Indicate whether the approved and marketed drug or vaccine is undergoing any studies for approval of a new indication(s), as well as for use in another population or changes to the conditions of use already approved. This indicates that any of the following actions have been taken by regulatory authorities:

- Denial of authorization of a clinical study for ethical or legal reasons security.
- Partial or complete suspension of a clinical study or early termination of an ongoing clinical study due to safety findings or lack of efficacy.
- Withdrawal of the drug or vaccine during the investigational stage.

- Denial of marketing authorization for a new indication under investigation, including the voluntary cancellation of a marketing authorization application.

- Changes in risk management activities, including:
- Modification(s) to the protocol for safety or efficacy reasons (e.g., dose change, changes in study inclusion/ exclusion criteria, intensification of subject monitoring, limitation on study duration).

- Restriction(s) on the study population or indications.
- Changes in the informed consent document in relation to the security issues.
- Changes in formulation.
- Special security information requirements requested by Agencies Regulators.
- Issuance of a communication to researchers or health professionals.
- New protocols to address security issues.

6.6.2. Actions related to marketed medicines or vaccines:

- Denial of marketing authorization, whether general or for a specific indication, including voluntary withdrawal of the application by the holder.

- Denial of extension or renewal of the Sanitary Registry by the Regulatory Authority.

- Suspension of marketing authorization or withdrawal from the market.
- Actions taken due to product quality issues.
- Suspension of the supply of the medicine or vaccine by the holder of the Registry Sanitary.
- Changes in risk management activities, including:
- Significant restrictions on the distribution or introduction of any risk minimization measures.

- Changes related to product safety (including changes in labeling, therapeutic indication(s), or intended populations).

- Communication(s) to health professionals for safety reasons product.

• New requirement(s) in additional Pharmacovigilance activities requested by the regulatory agency, such as in post-marketing programs or studies.

Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in their international report must be translated.

6.7. CHANGES TO PRODUCT SAFETY REFERENCE INFORMATION

This section must specify any changes to the content of the IPPA authorized in Mexico that occurred during the period covered by the RPS. Some examples could include, among others, the following: modifications to information related to contraindications, warnings, precautions, adverse reactions, interactions, findings from ongoing or completed clinical studies, and nonclinical findings. These changes must be specified as shown in Table II.

Table II. Modifications to the authorized IPPA submitted to the Regulatory Authority

SECTION OF THE IPP	INFORMATION PREVIEW	CHANGES MADE	DATE OF MODIFICATION AND REQUESTING AUTHORITY OF THE MODIFICATION

The company that has an international report must complete Table II in Spanish.
Only with information referring to Mexico and specify within this section: page(s) and section(s) where the corresponding information is found in the international report on changes to the international product safety reference information.

6.8. ESTIMATION OF EXPOSED PATIENTS

This section must be submitted in Spanish and only tables III, IV, V and VI (as applicable) must be filled out with information related to Mexico.

Consistent methods should be used to estimate subject/patient exposure where possible, and their limitations should be described and justified in detail.

6.8.1. Cumulative exposure of patients in clinical studies

Information regarding cumulative patient exposure in clinical studies aimed at the approval of new indication(s), as well as use in another population, or changes to previously approved conditions of use, among others, must include clinical studies conducted in Mexico. This information must also be presented as indicated in Tables III and IV.

The cumulative number of patients exposed in ongoing or completed clinical studies should be considered from the start of the study.

Table III. Cumulative estimate of patients exposed in studies clinicians

TREATMENT	RANGODE AGE	NUMBER OF PATIENTS EXPOSED BY GENDER			NUMBER TOTAL OF PATIENTS EXPOSED
		FEMALE	MALE	A STRANGER	
Medicine in research (it is the product of this RPS):					
Medication of reference (it is the product against which the clinical study is compared) when it exists, necessary to add more lines:					
Placebo (when (apply):					
				Total of patients exposed:	

Table IV. Cumulative estimate of exposed patients in populations special during clinical studies

Special populations	Number of patients exposed
Pediatric population	
Geriatric population	
Pregnant women	
Breastfeeding women	
Patients with liver failure, cardiac or renal	
Patients with relevant comorbidities	
Populations with genetic polymorphisms relevant	
Pregnant women with HIV	
Other special populations	

Additional information should include descriptions of differences between clinical studies, such as doses, routes of administration, and differences in exposure time of patients randomly assigned to the investigational or reference drug (when applicable).

- Companies that have an international report and do not have a research center in Mexico must include the title of this section and specify the page number(s) where the corresponding information is located in the international report.

- The company that has an international report and has a research center in Mexico must include the title of this section, translate and include in tables III and IV the information referring to Mexico, and must also specify: the page number(s) where the corresponding information is found in the international report.

6.8.2. Post-marketing exposure by patient interval

Information must be submitted for the period covered by the RPS as indicated below for the following categories:

TO) Post-marketing exposure

Table V. Estimated number of patients exposed during post-marketing in the RPS period

COUNTRY OR REGION	RANGE OF AGE	NUMBER OF PATIENTS EXPOSED TO MEDICINE OR VACCINE BY GENDER			TOTAL OF PATIENTS EXPOSED TO MEDICINE OR VACCINE	SHAPE PHARMACEUTICAL	WAY(S) OF ADMINISTRATION
		FEMALE	MALE	UNKNOWN			

Note 6.8.2.1: When there is evidence in the reports that indicates a sign of safety, exposure data within relevant subgroups should be be presented in detail if possible. It is important to provide as much information in the table.

B) Post-authorization use in special populations

When a drug or vaccine has been used in special populations, available information on the number of patients exposed and the method for calculating it must be provided. Some of the special populations to be considered are presented, by way of example but not limited to, Table VI.

C) Other uses after authorization

If the holder of the health registration, the legal representative, or the holder of the orphan drug recognition document is aware of patterns that are considered relevant to the interpretation of the safety data, they must provide a brief description of them. Some examples may include, but are not limited to: overdose, abuse, misuse, and uses not established in the IPPA authorized for Mexico.

If possible, the holder of the health registration, the legal representative or the holder of the orphan drug recognition document must briefly describe whether there are other uses that are not established in the IPPA authorized for Mexico.

and that can be linked to clinical guidelines, evidence from clinical studies or the absence of authorized alternative treatments.

Table VI. Estimate of patients exposed during post- marketing exposure in populations specials

Special populations	Number of patients exposed
Pediatric population	
Geriatric population	
Pregnant women	
Breastfeeding women	
Patients with liver failure, cardiac or renal	
Patients with relevant comorbidities	
Populations with genetic polymorphisms relevant	
Pregnant women with HIV	
Other special populations	

The company that has an international report must complete tables V and VI only with information referring to Mexico and specify within this section: page(s) and section(s) where the corresponding information is found in the international report on the estimate of patients exposed internationally.

6.8.3 Calculation of exposed patients

National and international companies must submit information in Spanish, specifying and detailing the method used to calculate the number of patients exposed in Mexico for each of the marketed presentations, as well as justifying its use.

The user must post each of their presentations, informing them of their marketing status.

If you do not market any presentation of your medication, you must report this in this section.

6.9. SUMMARY TABLE OF INDIVIDUAL CASES OF SRAM, RAM, EA, ESAVI OR ANY OTHER SAFETY PROBLEM RELATED TO THE USE OF MEDICINES AND VACCINES, ACCUMULATED

6.9.1. Summary tabular presentation of the sum of serious adverse events from clinical studies

This subsection must present the total number of serious adverse events from clinical studies aimed at the approval of a new indication(s), as well as the use in another population or changes in the conditions of use already approved, among others; using the format shown in Table VII. The health registration holder must explain any omissions in the data (for example, clinical study data may not be available for products marketed for several years). The following must be taken into account:

- When using the Medical Dictionary for Regulatory Activities (MedDRA) for coding adverse events, the System Organ Class (SOC) and Preferred Term (PT) levels must be specified for both the investigational drug or vaccine, as well as for the reference drug and placebo.

- Tabulations should include information from blinded clinical studies (when applicable) and not blind.

Table VII. Sum of serious adverse events in clinical studies

SOC / PT	MEDICINE IN INVESTIGATION (SPECIFY)	STUDY CLINICALBLIND	MEDICINE FOR REFERENCE OR COMPARATOR(S) (SPECIFY)	PLACEBO
SOC 1				
PT				
PT				
SOC 2				
PT				
PT				
PT				

6.9.2 Summary tabular presentation of the sum and interval of serious and non-serious SRAMs, ADRs or AEFIs after the marketing of medicinal products or vaccines

The following serious and non-serious SRAMs, ADRs, and AEFIs from the international date of first marketing to the RPS cutoff point being submitted should be provided, based on Table VIII: These include reports from healthcare professionals, patients/consumers, health registration holders or ex officio holders of orphan drug recognition, and scientific literature, as well as serious adverse events from non-interventional studies. The information should include cumulative and interval data from the RPS organized by System Organ Class (SOC) and Preferred Term (PT) levels. Additional tables of adverse reactions may be presented by indication, route of administration, or other variables.

Table VIII. Post-market **serious and non-serious SRAM, RAM or ESAVI and Serious AEs in non-intervention studies**

SOC / PT	SPONTANEOUS, INCLUDING THOSE FROM HEALTH PROFESSIONALS, PATIENTS/CONSUMERS, RECORD HOLDERS AND SCIENTIFIC LITERATURE.					SERIOUS ADVERSE EVENTS STUDIES OF NO INTERVENTION	
	GRAVES		NOT SERIOUS		TOTAL ACCUMULATED***	GRAVES	
	INTERVAL*	CUMULATIVE**	INTERVAL*	CUMULATIVE**		INTERVAL*	CUMULATIVE**
SOC 1							
PT							
PT							
PT							
SOC 2							
PT							
PT							

* The interval covers the period covered by the corresponding RPS.
** The cumulative total includes the period from the start of marketing to the RPS information cut-off point.
presented.
*** The accumulated total is the sum of the accumulated number of serious and non-serious spontaneous notifications.

Companies that attach an international report must specify in Spanish the title of this section and include the page(s) of the attached document where the information requested in this section is included (tables VII and VIII).

6.10. SUMMARY OF FACTS PRESENTED DURING CLINICAL STUDIES WITHIN THE REPORTED PERIOD

Relevant information can be categorized by gender and age (particularly pediatric versus adult populations), indication, dose, and country.

Information on completed or ongoing clinical studies must be included in the post-marketing stage, designed to identify, characterize or quantify a safety problem or confirm the safety profile of the drug or vaccine, which must contain the information shown in Table IX.

Table IX. Summary of completed or ongoing clinical studies

Title of the study: *(Write the full title of the clinical study)*					
ID from the study:	**Type of study:**	**Population studied:**	**Date of beginning of the study:**	**Date of ending:**	**State:**
(Protocol number or other identifier)	*(Example: Study clinical randomized, study of cohorts, study of cases and controls, etc*	*(Include country and other descriptors) population relevant, example, population pediatric or patients with insufficiency renal)*	*(As defined by the holder of* Record Sanitary)	*(As defined by the holder of* Record Sanitary)	*(Example: In course or finished)*

The information to be considered in this section may be derived from any of the following points:

- Completed clinical studies. You must provide a brief summary of the clinically important emerging efficacy and safety findings from clinical studies conducted during the reporting period.

• Ongoing clinical studies. If the registrant is aware of clinically important information arising from ongoing clinical studies, they must describe it here.

• Long-term follow-up. This section should provide information on the long-term follow-up of patients included in clinical trials of the investigational medicinal product or vaccine, where applicable. This includes biotechnological and biological medicinal products (e.g., gene therapy, cell therapy products, and tissue-engineered products).

• Other therapeutic uses of the medicinal products or vaccines. This section of the RPS should include clinically important safety information from other programs conducted by the marketing authorization holder that follow a specific protocol for systematic data collection.

You must include in this section the information from patient monitoring programs in indications approved in the authorized IPPA.

• New safety data related to fixed-dose therapies. If the medicinal product or vaccine is a fixed-dose combination product, important safety information derived from the combination, whether authorized or in development, should be summarized at this point.

• Companies that have an international report and do not have a research center in Mexico must include the title of this section and specify the page(s) where the corresponding information is located in the international report.

• The company that has an international report and has a research center in Mexico must include the title of this section, translate and include in table IX the information referring to Mexico, and must also specify: page(s) where the corresponding information is found in the international report.

6.11. FINDINGS IN STUDIES WHOSE PRINCIPAL OBJECTIVE IS SAFETY

• Both national and international companies must submit the following: information in Spanish.

• This section should present information on global findings in studies whose main objective is safety, coming, for example, and not

limiting, non-intervention studies, epidemiological studies, registries, active surveillance programs and drug utilization studies.

Such information must be listed whether it has been carried out or is in progress during the period covered by the RPS, as requested in Table X.

Table X. List of studies whose main objective is safety

COUNTRY WHERE IT WAS HELD THE STUDY	NUMBER OF IDENTIFICATION OF THE STUDY	TITLE OF THE STUDY	NUMBER OF NOTIFICATIONS TOTALS TO THE CONCLUSION OF THE STUDY

6.12. INFORMATION FROM OTHER CLINICAL STUDIES

6.12.1. Other clinical studies

Information related to the benefit/risk assessment of the drug or vaccine from any other source of studies, including the results of pooled analyses or meta-analyses of randomized clinical trials, should be summarized.

6.12.2. Medication errors

Important information should be provided on patterns of medication errors and potential medication errors, even when unrelated to SRAM, ADR, and ESAVI.

Such information may be relevant for the interpretation of safety data or the international evaluation of the benefit/ risk profile of the medicinal product or vaccine.

- The company that attaches an international report must include the title and specify within this section: page(s) of the attached document where the information requested in this section is included.

6.13. PRECLINICAL/NON-CLINICAL INFORMATION

- This section should include the main safety findings arising from nonclinical in vivo and in vitro studies underway or completed during the RPS period, where applicable (for example, carcinogenicity, teratogenicity, toxicity, reproduction, or immunogenicity studies) of the already approved and marketed drug or vaccine; when a study is being conducted for the approval of a new indication(s), as well as use in another population or changes to the conditions of use already approved.

- The company that attaches an international report must include the title and specify within this section: page(s) of the attached document where the information requested in this section is being referenced.

6.14. SCIENTIFIC LITERATURE

This section should include a summary of safety findings, published in the peer-reviewed scientific literature or made available as unpublished manuscripts, that the Registration Holder, legal representative, or the holder of the official document recognizing the medicinal product as an orphan medicinal product became aware of during the RPS period, when relevant to the medicinal product.

Literature searches for RPS should be broader than those for individual adverse reaction cases, as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active ingredient.

Special types of security information that should be included, but which cannot be found by a search specifically constructed to identify individual cases, include:

- o Pregnancy outcomes (including termination) without adverse outcomes.
- o Use in pediatric populations.
- o Compassionate use and patient access programs.
- o Lack of effectiveness.

- o Asymptomatic overdose, abuse or misuse.
- o Medication error in which no adverse reactions occurred.
- o Important nonclinical safety results.

If relevant and applicable, information on other medicinal products or vaccines containing the same active ingredient should be considered.

The publication reference must be provided in Vancouver style.

The company that has an international report must include the title of this section and specify the page(s) where the corresponding information is referenced in the international report.

6.15. OTHER PERIODIC REPORTS

- When the holder of the health registration, the legal representative or the holder of the orphan drug recognition document prepares multiple RPS for a single active ingredient (for example, covering different therapeutic indications or pharmaceutical forms) and does not attach an international report, significant findings from other RPS must be summarized in this section.

- The company that has an international report must include the title of this section and specify the page(s) where the corresponding information is referenced in the international report.

6.16. LACK OF EFFICACY IN CLINICAL STUDIES

- This section should include information on clinical studies that indicate a lack of efficacy of medications or vaccines and that may reflect a significant risk to the treated population.

- The company that has an international report must include the title of this section and specify the page(s) where the corresponding information is referenced in the international report.

6.17. UPDATED INFORMATION

- This section should include any relevant, late-emerging information regarding safety, efficacy, and potential effectiveness that was submitted after the data cutoff date and before the RPS submission. For example, contraindications, warnings, precautions, or new adverse reactions resulting from an alert.

- Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in their international report must be translated.

6.18. SIGNAL GENERATION: NEW, IN PROGRESS, AND CLOSED

This section should provide information on international safety signals that have been closed during the RPS period, as well as those currently in progress, for which the health registration holder, the legal representative in Mexico, or the holder of the orphan drug recognition document has already undertaken a review or evaluation process.

It should be noted that a signal may be derived from qualitative processes (e.g., individual case reports and case series) or quantitative processes (e.g., findings from clinical trials or epidemiological studies). New clinically significant information derived from an already closed signal during the RPS submission period will also constitute a new signal. Other examples include:

- Clinically significant changes in risk severity.
- Increase in the frequency of the identified risk.
- Potential risk that, if confirmed, could justify a new warning, precaution, or restriction in the indication, in the population, or other risk minimization activities.

This information must be presented as requested in Table XI.

Table XI. Presentation of new, ongoing and closed signals

DESCRIPTION OF THE SIGNAL	DATE OF DETECTION	STATE (NEW, IN PROGRESS, CLOSED)	DATE OF CLOSING (YEAH APPLY)	FOUNTAIN OF THE SIGN	REASON FOR THE EVALUATION AND SUMMARY OF THE INFORMATION IMPORTANT OF THE SIGNAL	METHOD OF ASSESSMENT OF THE SIGNAL	ACTIONS TAKEN OR PLANNED

When a competent authority has requested that a specific topic (not considered a signal) be monitored and reported in the RPS, the health registration holder, legal representative, or orphan drug recognition office holder must summarize the outcome of the analysis in this section if it is negative. If the specific topic becomes a signal, it must be included in the tabulation of signals and discussed in the "Signal Assessment" section of the RPS (section 7.19.2 of this guideline).

Companies submitting an international report must provide the information requested in Table XI in Spanish. Therefore, the information available in their international report must be translated.

6.19. SIGNS AND RISK ASSESSMENT

In this section, the holder of the health registration, the legal representative, or the holder of the orphan drug recognition document in Mexico must provide the following:

6.19.1. Summary of security concerns

Within this subsection, important safety concerns during the interval covered by the RPS should be presented:

- Significant risks identified.
- Significant potential risks.
- Missing information that is considered important.

The following factors should be considered when determining the significance of each risk:

- Medical severity of the risk (including the impact on individual patients).
- Frequency, predictability and reversibility.
- Potential impact on public health (frequency; population size) treated).
- Potential to avoid the use of medicinal products with a preventive benefit due to disproportionate public perception of risk (e.g., vaccines).

For products without existing safety specifications, this section provides information on identified and potential important hazards, and missing information associated with the use of the product, based on pre- and post-marketing experience.

Significant identified and potential risks may include, for example:

- Significant adverse reactions.
- Interactions with other medicinal products.
- Interactions with food and other substances.
- Medication errors.
- Effects of occupational exposure.
- Effects of the pharmacological class.

6.19.2. Signal evaluation

Within this subsection, you must report the results of the assessments for all safety signals (whether or not they have been classified as important) that were closed during the RPS interval. A safety signal may be closed because it is refuted or because it is determined to be a potential or identified risk following the assessment.

The two categories to be included in this section are:

1. Those signals that after evaluation have been refuted as “False” signals based on medical judgment and scientific evaluation of currently available information.

Those signals that after evaluation have been categorized as 2. potential or identified risks, including lack of effectiveness.

For both categories of closed signals, a concise description of the evaluation of each signal must be included in order to clearly describe the basis on which the signal was refuted or considered a potential risk or identified by the health registration holder, legal representative, or the holder of the orphan drug recognition office in Mexico.

It is recommended that the level of detail provided in the description of the signal assessment reflect the medical significance of the signal (e.g., severe, irreversible, leading to increased morbidity or mortality) and the potential public health importance (e.g., widespread use, frequency, use outside the recommendations in the product information) and the extent of the available evidence. If multiple assessments are included in both closed signal categories, they may be presented in the following order:

- Closed and refuted signals.
- Closed signals that were important potentials. categorized as risks

- Closed signals that were categorized as identified risks important.
- Closed signals that are potential risks not categorized as important.
- Closed signals that are identified risks not categorized as important.

When applying the evaluation of closed signals it can be presented by indication or population.

The description of the signal evaluation shall include the following information, as appropriate:

- Source or trigger of the signal.
- Relevant background for the evaluation.
- Assessment methods, including information sources, search criteria [where applicable, specific MedDRA terms (e.g., PT, HLT, and SOC, among others), or standardized MedDRA questions (SMQs) that were reviewed] and analytical approaches.

- Results, including a summary and critical analysis of the data considered in the signals assessment; when integral to the assessment, this may include a description of a case series or an individual case (e.g., an index case of well-documented agranulocytosis or Stevens-Johnson syndrome).
- Discussion.
- Conclusion.

The evaluations and conclusions of the health registration holder, the legal representative, or the holder of the orphan drug recognition certificate in Mexico must be supported by information and clearly presented.

6.19.3. Risk assessment and new information

Within this subsection, they must provide a critical assessment of new information relevant to previously recognized risks that is not included in the “signal assessment” section (point 7.19.2 of this guide).

In the tabulation of signals (see Table XI) and evaluated in the section “Signal evaluation” (point 7.19.2 of this guide), new information that constitutes a signal with respect to a previously recognized risk or a previously refuted signal is also closed during the RPS reporting interval.

Updated information on a previously recognized risk that does not constitute a signal should be included in this section. Examples include information confirming a potential risk as an identified risk, or information that allows for any additional characterization of a previously recognized risk.

The new information can be organized as follows:

1. Significant potential risks.

2. Significant risks identified.
3. other potential risks not classified as important.
4. other identified risks not classified as significant.
5. Updating missing information.

The assessment focuses on new information that has emerged during the time period covered by the RPS. It should be concise and explain the impact, if any, on the understanding and characterization of the risk. Where applicable, the assessment may form the basis for an updated characterization of a significant potential risk and risk identified in the "Risk Characterization" section (section 7.19.4 of this guide).

It is recommended that the level of detail of the assessment included in this section be proportional to the available evidence on the risk and its medical significance and relevance to public health.

Assessment(s) of new information and updates to missing information may be included in this section of the RPS. Each assessment should include the following information, as appropriate:

- Source of the new information.
- Relevant background for the evaluation.
- Evaluation method(s), including data sources, search criteria and analytical approaches.
- Results: summary and critical analysis of the data considered in the evaluation of risks.
- Discussion.
- Conclusion, including whether or not the evaluation supports an update of the characterization of any potential risks and risks identified in the “Risk Characterization” section (point 7.19.4 of this guide).

6.19.4. Risk characterization

Within this subsection, you should characterize the identified and potential significant risks based on accumulated information (e.g., not restricted to the reporting interval), and describe the missing information.

Depending on the nature of the information source, the risk characterization should include (where applicable):

- Frequency.
- Number of cases (numerator) and precision of the estimate, taking into account the source of the data.
- Extent of use (denominator) expressed as number of patients, patient-time, etc., and precision of the estimate.
- Estimation of relative risk and precision of the estimate.
- Estimation of absolute risk and accuracy of the estimate.
- Impact on the individual patient (effect on symptoms, quality or quantity of life).
- Impact on public health.
- Patient characteristics relevant to risk, for example: patient factors (age, pregnancy/breastfeeding, liver/ kidney impairment, relevant comorbidities, disease severity, genetic polymorphism).
- Dose, route of administration.
- Duration of treatment, risk period.
- Risk prevention, example: predictability, ability to monitor a "sentinel" adverse reaction or laboratory marker.
- Reversibility.
- Potential mechanism.
- Strength of the evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information may constitute a significant risk, it should be included as a safety concern. Limitations of the safety database (in terms of the number of patients studied, cumulative exposure, or long-term use, etc.) should be discussed.

For RPS of medicines with several indications, formulations or routes of administration, where there may be significant differences in risks

Identified and potential risks, it may be appropriate to present the risks by indication, formulation, or route of administration. Headings that could be considered include:

- Risks related to the active substance.
- Risks related to a specific formulation or route of administration (including occupational exposure).
- Risks related to a specific population.
- Risks associated with non-prescription use (for compounds that are available in both prescription and non-prescription formats).

6.19.5. Effectiveness of risk minimization (if applicable)

Within this subsection, the following must be submitted, where applicable:

Risk minimization activities intended to prevent the occurrence of one or more adverse reactions related to exposure to a medication or to reduce their severity if they occur. The objective of a risk minimization activity is to reduce the likelihood or severity of an adverse reaction to a medication.
Risk minimization activities may consist of routine risk minimization activities (e.g., product labeling) or additional risk minimization activities (e.g., direct communication with Healthcare Professionals / educational materials).

The RPS shall contain the results of evaluations of the effectiveness of risk minimization activities relevant to the benefit-risk assessment.

Relevant information on the effectiveness and/or limitations of specific risk minimization activities for identified significant risks that have become available during the RPS interval should be summarized in this sub-section of the RPS.

Of particular interest is the knowledge of the effectiveness of risk minimization activities in any country or region where they may be useful in other countries or regions. Information can be summarized by region, if applicable and relevant.

NOTE: Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in your international report must be translated.

6.20. SUMMARY OF SECURITY PROBLEMS IN MEXICO

Within this section, you must describe the SRAMs, ADRs, AEs, ESAVIs, and drug and vaccine safety problems that occurred in Mexico during the RPS period, as requested below.

Table XII. Summary of SRAM, RAM, EA, ESAVI and problems
Drug and vaccine safety in Mexico

CODIFICATION OF THE NOTIFICATION	DATE OF SHIPPING TO CNFV	SRAM, RAM O ESAVI (PT)	SEVERITY/GRAVITY	CAUSALITY	SRAM, RAM OR ESAVI UNEXPECTED OR EXPECTED
IQF/XXXXX/00025/2020	dd/mm/yyyy	Vomit	Mild	Possible	Expected
		Myalgia	Moderate	Probable	Unexpected
		Heart attack myocardium	Serious	Probable	Unexpected
IQF/XXXXX/00037/2019/S6	dd/mm/yyyy	Vomiting	Mild	Possible	Expected
		Diarrhea	Mild	Possible	Expected
Codification issued by the corresponding system (NotiReporta, e-reporting, etc.)	dd/mm/yyyy	Headache	Moderate	Unexpected	Doubtful

NUMBER OF NOTIFICATIONS GRAVES	NUMBER OF NOTIFICATIONS NO GRAVES	TOTAL NUMBER OF NOTIFICATIONS
1	2	3

SRAM, RAM OR ESAVI CLASSIFIED BY PT	TOTAL NUMBER OF SRAM, RAM OR ESAVI CLASSIFIED BY PT
Vomit	2
Myalgia	1
Myocardial infarction	1
Diarrhea	1
Headache	1

The company that has an international report must fill out table XII only.
with information about Mexico in Spanish.

6.21. BENEFIT EVALUATION

Within this section, they must specify the underlying information and any new information identified regarding the benefits of a drug or vaccine that supports the benefit/risk assessment.

6.21.1. Important information

Within this subsection, information on the efficacy and effectiveness of the drug or vaccine known during the RPS period, on which the benefit assessment is based, must be presented.

This information must be related to the therapeutic indication authorized in Mexico for the drug or vaccine. If these have multiple indications, populations, or routes of administration, the information must be individually characterized by these factors, where relevant.

6.21.2. New information identified on efficacy/effectiveness

Within this subsection, they must include new information on the efficacy and effectiveness of the authorized indications that become available during the RPS period.

6.21.3. Characterization of the benefits

Within this subsection, you should provide a description of the baseline information on the benefits of the medicine or vaccine and any relevant new information available during the RPS period, for the approved indications. A critical assessment of both the strengths and limitations of the efficacy and effectiveness references should be made, and may consider the following points: a brief description of the evidence of benefit (including comparator, effect size, statistical rigor, weaknesses and strengths of the methodology and

consistency of results across studies), new information that questions the validity of a surrogate endpoint (if applicable), clinical significance of the effect size, generalizability of treatment response across patient populations, adequacy of dose-response characterization, duration of effect, comparative efficacy, and determination of the extent to which efficacy results from clinical trials are generalizable to patient populations treated in clinical practice.

Note: Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in their international report must be translated.

6.22. ANALYSIS OF THE BENEFIT/RISK BALANCE

Within this section, they must include a general assessment of the benefit/risk ratio of the drug or vaccine, as used in clinical practice.

6.22.1. Benefit/risk context – medical need and important alternatives

Within this subsection, they must provide a brief description of the medical necessity of the drug or vaccine in the authorized indications, including a summary of the alternatives to treatment (medical, surgical, other, or no treatment).

6.22.2. Evaluation of the benefit/risk analysis

Within this subsection, they must provide an assessment of the benefit/risk balance specific to each indication and population. Therefore, for medicinal products or vaccines with more than one therapeutic indication authorized in Mexico, the benefit/risk balances must be evaluated and presented individually for each indication. If there are significant differences in the benefit/risk balance between populations within an indication, the benefit/risk assessment must be presented by population, if possible.

The benefit/risk assessment should be presented and discussed in a manner that facilitates the comparison of benefits and risks, for which the following points should be considered:

1. Relevant information about risks and benefits.
2. The context of use of the drug or vaccine (condition to be treated, prevented) or diagnosed; its intensity and severity as well as the population to be treated).
3. With respect to benefit, consideration should be given to its nature, clinical importance, duration, and degree of generalization, as well as evidence of efficacy in patients who do not respond to other therapies or alternative treatments.
4. Regarding risk, consider its clinical significance, for example: nature of toxicity, severity, frequency, degree to which it can be prevented, reversibility, impact on patients, uses outside the approved indications, new use or misuse.
5. The strengths, weaknesses, and uncertainty of the evidence should be considered in the benefit/risk assessment, so the impact of uncertainty on the benefit and risk assessment will be described.
6. A clear explanation of the methodology and the reasoning used to develop the benefit/risk assessment:

6.1. The assumptions, considerations, and judgment or weighting that support the conclusions of the benefit-risk assessment must be clear.

6.2. If a formal quantitative or semi-quantitative benefit-risk assessment is provided, a summary of the methods shall be included. of the

When significant new information is requested or a specific RPS has been requested by the health authority, a detailed benefit-risk analysis based on cumulative data should be presented. Conversely, when little new information is available during the reporting interval, the primary focus of the benefit-risk assessment may be an evaluation of updated safety data during the reporting intervals.

Note: Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in their international report must be translated.

6.23. CONCLUSIONS AND ACTIONS

Within this section, they should conclude with the implications of any information arising during the relevant period in terms of the overall assessment of the benefit/risk balance for each authorized indication, as well as for the relevant subgroups (if applicable).

Note: Companies submitting an international report must provide the requested information in Spanish. Therefore, the information available in their international report must be translated.

6.24. ANNEXES

The following documents must be attached to the RPS, within the same electronic device in editable PDF format, as separate files (one PDF file per annex):

Annex I Comprehensive Prescribing Information (IPPA) authorized for the drug or vaccine in Mexico.

Annex II Simple copy of the Health Registry.
Annex III When PSUR or PBRER apply that cover the RPS period.
Annex IV Others (when applicable).

6.25. LIST OF INFORMATION SOURCES

A list must be made that includes all the bibliographic references used for the preparation of the RPS, which must be provided in the Vancouver style.

6.26. LIST OF TABLES

All tables used in the RPS, along with their respective names, must be listed in Roman numerals, as well as the page where they are located.

6.27. LIST OF ABBREVIATIONS

An alphabetical list of all abbreviations used in the RPS, along with their meanings, must be made.

7. PERIODICITY AND TIMES OF SUBMISSION TO THE NATIONAL CENTER OF Pharmacovigilance

7.1 NEW MOLECULES

7.1.1 For medicines considered as molecules with recent authorization of the sanitary registration, they must submit RPS to the national center of pharmacovigilance complying with the periods and times established in point 8.2.4 of the NOM-220-
SSA1-2016, Installation and operation of pharmacovigilance and its modifications, based on the registration date in Mexico as mentioned below:

- 4 semiannual RPS during the first 2 years.
- Subsequently, deliver annual RPS for the following 3 years.

7.1.2. Starting with their third annual report, the health registration holder or their legal representative may opt for rescheduling to align with their international calendar. To this end, they may submit a bridge RPS, which may not exceed three years of information.

7.1.3 Starting with the third annual RPS or the bridge RPS (if rescheduling applies), the health registration holder or their legal representative must prepare only triennial RPSs and include them in their file. RPSs should not be submitted to the CNFV unless requested by the authority.

7.2 INNOVATIVE MEDICINES AND VACCINES

7.2.1 For medicines considered as innovative molecules with authorized health registration after January 1, 2015 and that were being marketed before the entry into force of NOM-220-SSA1-2016, Installation and operation of pharmacovigilance and its modifications, they must continue with the last RPS accepted by the CNFV respecting the information cut-off points until complying with their 4 semi-annual reports and their 3 annual reports.

7.2.2. Starting with their third annual report, the health registration holder or their legal representative may opt for rescheduling to comply with their international calendar. To this end, they may submit a bridge RPS, which may not exceed three years of information.

7.2.3 Starting with the third annual RPS or the bridge RPS (if rescheduling applies), the health registration holder or their legal representative must prepare only triennial RPSs and include them in their file. They should NOT submit the RPS to the CNFV unless requested by the authority.

7.3 OF NEW ORPHAN DRUGS

7.3.1 For medicines that have been recognized as orphan drugs for the first time in Mexico, they must submit the corresponding RPS to the National Pharmacovigilance Center, complying with the periods and times established in point 8.2.7 of NOM-220-SSA1-2016, Installation and Operation of Pharmacovigilance and its modifications, based on the first date of recognition as an orphan drug in Mexico, as mentioned below:

- Semiannual for the first 2 years.
- Annual during subsequent years.

7.3.2. Starting with their third annual report, the holder of the orphan drug recognition document may opt for rescheduling in order to align with their international calendar. To this end, they may submit a bridge RPS, which may not exceed one year of information.

7.3.3 From the third annual RPS or the bridge RPS (in case its rescheduling applies) the holder of the orphan drug recognition certificate must continue with the preparation of the annual RPS and include them in his/her file.
They should NOT submit RPS to the CNFV unless requested by the authority.

7.4 ORPHAN MEDICINES WITH RECOGNITION DATE OF FIRST TIME AUTHORIZED AFTER JANUARY 1, 2015

7.4.1 For medicines considered as orphan drugs with official authorization for orphan drug recognition for the first time in Mexico after January 1, 2015 and that were being marketed before the entry into force of NOM-220-SSA1-2016, Installation and operation of pharmacovigilance and its modifications, they must continue with the last RPS accepted by the CNFV respecting the information cut-off points until they comply with their 4 semi-annual reports and their 3 annual reports.

7.4.2. Starting with their third annual report, the holder of the orphan drug recognition document may opt for rescheduling in order to align with their international calendar. To this end, they may submit a bridge RPS, which may not exceed one year of information.

7.4.3. Starting with the third annual RPS or the bridge RPS (if rescheduling applies), the holder of the orphan drug recognition certificate must continue preparing the annual RPS and include them in their file.

They should NOT submit RPS to the CNFV unless requested by the authority.

7.5 FOR NEW GENERIC MEDICINES

7.5.1 RPS shall not be submitted to the CNFV unless requested by the authority.

7.5.2 They must prepare RPS based on their health registration date in Mexico, respecting the cut-off periods established in section 8.2.4 of NOM-220- SSA1-
2016, installation and operation of pharmacovigilance and its modifications as mentioned below:

- Every 6 months for the first 2 years.
- Annual for the next 3 years.
- Subsequently every 3 years.

7.5.3 RPSs must include them in their corresponding file in order to have them available when requested by the authority.

7.6 FOR MEDICINES THAT HAVE SANITARY REGISTRATION WITH AN AUTHORIZATION DATE PRIOR TO JANUARY 1, 2015

7.6.1 RPS shall not be submitted to the CNFV unless requested by the authority.

7.6.2 Starting with their third annual report, the holder of the health registration or their legal representative may opt for rescheduling in order to adjust to their international calendar. To this end, they may submit a bridge RPS, which may not exceed 3 years of information.

7.6.3 From the third annual RPS or the bridge RPS (in case its rescheduling applies) the holder of the health registration or his legal representative must
continue with the preparation of the Triennial RPS and include them in your file.

They should NOT submit RPS to the CNFV unless requested by the authority.

7.7 ORPHAN DRUGS THAT HAVE RECOGNITION FOR THE FIRST TIME IN MEXICO PRIOR TO JANUARY 1, 2015

7.7.1 RPS shall not be submitted to the CNFV unless requested by the authority.

7.7.2 They must prepare annual RPS based on their last RPS accepted by the CNFV, respecting the cut-off periods established in sections 8.2.7 of NOM-220-
SSA1-2016, Installation and operation of pharmacovigilance and its modifications and include them in your file in order to have them available when the authority requests them.

7.8 TIMES OF SUBMISSION OF THE RPS TO THE CNFV

The RPS of medicines and vaccines according to numeral 8.2.4 and 8.2.7 of NOM-220-
SSA1-2016, Installation and operation of pharmacovigilance and its modifications must be entered (when applicable) into the CNFV, after the Information Cut-Off Point (PCI), as shown in the following table:

Table A. RPS submission times of medications and vaccines for CNFV after PCI

PERIOD	DELIVERY TIMES FROM RPS TO CNFV POST- PCI
Biannual	70 calendar days
Annual	90 calendar days
Triennials	They must be prepared and integrated into your files and be available to the authority when these are required. Delivery times to the CNFV will be indicated in the letter corresponding.

Table B. RPS submission times of orphan drugs to the CNFV after PCI

PERIOD	DELIVERY TIMES FROM RPS TO CNFV POST- PCI
Biannual	70 calendar days
Annual	90 calendar days
Annual	After the submission of the third annual report must be prepared and integrate them into their files and be available to the authority when these are required. The times delivery to the CNFV will be indicated in the letter corresponding.

8. NON-MARKETED MEDICINES

8.1 NEW MOLECULES AND ORPHAN DRUGS WITH RECENT RECOGNITION OFFICE IN MEXICO

8.1.1 For medicines and vaccines considered new molecules that have a health registration or orphan drugs that have a recognition letter for the first time in Mexico and have not been marketed, they must submit to the CNFV the non-marketing form by attaching in PDF format the copy of the health registration (updated and valid) or orphan drug recognition letter.

8.1.2 The holder of the health registration, legal representative, or holder of the orphan drug recognition certificate in Mexico must wait until the first six-month period has elapsed before submitting the non-marketing form to the CNFV.

8.1.3 The non-marketing form will cover the entire period during which the product is not marketed, so you will not need to periodically update this document.

8.1.4 Once marketing resumes, the CNFV must be notified of the start of the same within the corresponding RPS, so it will not be necessary to inform the CNFV in a separate procedure.

8.1.5 The cut-off date for starting the RPS will be the date of granting of the health registration in Mexico or the orphan drug recognition document.

EXAMPLE						
1st Biannual	**2nd Semester**	**3rd Semester**	**4th Semester**	**1st Annual**	**2nd Annual**	**3rd Annual**
Not Marketed (One letter for the entire period of non-marketing)					*Marketed* *Once started, marketing resume he submission of the RPS based on the date of health registration.*	*Marketed*

Note : In the case of RPS that are subject to the CNFV after a period of non- marketing, the holder of the Sanitary registration, the legal representative in Mexico or
The holder of the official document recognizing orphan drugs must indicate

clearly in the submission document, the period (dd/mm/yyyy) that the medicine was not marketed.

8.2 INNOVATIVE MEDICINES OR ORPHAN MEDICINES WITH SANITARY REGISTRATION OR RECOGNITION DATE AUTHORIZED AFTER JANUARY 1, 2015 THAT WERE ALREADY MARKETED AND DISCONTINUED MARKETING.

8.2.1 They must submit a non-marketing form as long as the non-marketing period is equal to or greater than the submission period established in NOM-220-SSA1-2016, installation and operation of pharmacovigilance and its modifications, indicated for that product, and must also mention the reasons for it.

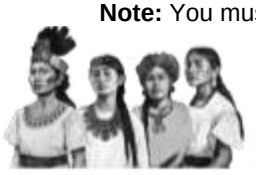
8.2.2 In the event that the non-marketing period is less than the period covered by the RPS as established in NOM-220-SSA1-2016, Installation and operation of pharmacovigilance and its modifications, you should NOT submit the non-marketing form, you will have to submit the RPS as established, clearly indicating the non-marketing period(s) within the submission document.

the 8.2.3 In the event that the non-marketing period is equal to or greater than the period covered by RPS as established in NOM-220-SSA1-2016, installation and operation of pharmacovigilance and its modifications, a non-marketing form must be submitted which will validate the time of the entire non-marketing, once marketing has started again, the preparation of the RPS must continue, respecting the reporting times based on the date of health registration or official recognition of orphan drug for the first time in Mexico.

EXAMPLE

1st Biannual	2nd Biannual	3rd Biannual	4th Biannual	1st Annual	2nd Annual	3rd Annual
Marketed	*Not Marketed*		*Marketed No*	*Marketed*	*Marketed*	*Marketed*

Note: You must respect the submission times based on the date of



registration and not restart with semi-annual reports after a non-marketing
or schedule the following RPS based on the start of marketing.

8.3 FOR NEW GENERIC MEDICINES AND MEDICINES THAT HAVE SANITARY REGISTRATION OR RECOGNITION OFFICE FOR THE FIRST TIME IN MEXICO WITH AN AUTHORIZATION DATE PRIOR TO 01

JANUARY 2015

8.3.1 They shall not submit non-marketing orders to the CNFV unless the authority requests it.

8.3.2 They must prepare the non-marketing documents and include them in their
file in order to have them available when the authority requests it.

8.3.3 Once the non-commercialization has concluded, they must continue with the preparation of the corresponding RPS based on the last RPS accepted by the
CNFV or date of granting of health registration (new generic molecules) and include them in your file so that they are available when the authority requests them.

8.4 REQUEST FOR RPS TO HEALTH REGISTRY HOLDERS, LEGAL REPRESENTATIVES OR EX OFFICE HOLDERS FOR ORPHAN DRUG RECOGNITION BY THE CNFV.

For RPS that are requested by the health authority, the 8.4.1 holder of the health registry, legal representative, or official holder of orphan drug recognition in Mexico will be requested by institutional email Modnom220fv@cofepris.gob.mx and in writing via local and foreign courier as appropriate, the RPS must be entered through the CIS. The delivery time and the period of the RPS will be informed in writing, it is important to mention that the period of the requested RPS will be the most recent according to its calendar, complying with the times established in NOM-220-SSA1-

2016.

9. NON-MARKETING FORMAT

9.1 Holders of health registration, legal representatives or holders of the office of recognition of orphan drug status in Mexico, they must inform the CNFV (when applicable) of the non-commercialization of their products by means of a free written document through the Comprehensive Service Center (CIS) addressed to the Director of the Executive Directorate of Pharmacopoeia and Pharmacovigilance, which must contain the following information:

- Distinctive name of the medicine, vaccine or orphan drug.
- Generic name or generic name of the medicine, vaccine or orphan drug.
- Pharmaceutical form of the medicine, vaccine or orphan drug.
- Authorized presentation(s).
- Health Registration Number with fraction or Recognition Letter
- Period of non-commercialization (year/month/day).
- Detailed justification for the reason for non-marketing.
- Data of the unit and the person responsible for pharmacovigilance

Annex: simple copy of the Health Registry in PDF format

10. AMENDMENTS

10.1 If there is a change in the health registration number or distinctive name, you must report this situation on the cover page of the RPS, and you must also add both copies of the health registration to the "Annexes" folder.

10.2 When there is a transfer of ownership of the Health Registry between individuals, you must attach to the RPS a copy of the response letter from the CNFV specifying the session in your favor.

10.3 The non-marketing format is by health registration, not by presentation, so if only some presentations are not marketed, the health registration holder, the legal representative or holder of the orphan drug recognition document in Mexico must submit the corresponding RPS in which they report the presentations that were not marketed during the corresponding period.

10.4 The data of the unit and the person responsible for Pharmacovigilance must be current and up-to-date.

10.5 All RPS must be submitted electronically (do not submit on paper).

10.6 If information is missing in any section of the RPS, its absence must be justified.

10.7 All re-submissions must be submitted to the CNFV within the first 2 months after receiving the response issued by the CNFV, unless otherwise stated.

10.8 For medicines and vaccines with a registration date after January 1, 2015, for which an RPS was rejected before the entry into force of NOM-220-
SSA1-2016 and its amendments will no longer be required to submit the RPS to the CNFV. They must make the corresponding correction, include it in their file, and keep it available to the authority. RPSs should not be submitted to the CNFV unless requested by the authority.

10.9 The rescheduling (bridge RPS) used to align with your international calendar must be equal to or less than 3 years for medicines and vaccines and 1 year for orphan medicines.

10.10 All RPS, including the bridge RPS (recalendarization), must continue the last RPS accepted by the CNFV.

10.11 Only those registries that have at least four semi-annual reports and three annual reports accepted by the CNFV may submit RPS (bridge) that allow matching with their international calendar.

10.12 Request the holder of the health registration, the legal representative or the holder of the orphan drug recognition document in Mexico to clarify any doubt or present the additional information that is required, in accordance with the provisions of section 7.4.2.5 of the Mexican Official Standard NOM-220-SSA1-2016, Installation and

operation of Pharmacovigilance and its modifications.

10.13 All documents submitted by the holder of the health registration, the legal representative, or the holder of the orphan drug recognition certificate in Mexico will be integrated into the corresponding file for information analysis purposes and will be available to the CNFV when required to guarantee the product's safety profile.

11. CONSIDERATIONS FOR THE APPLICATION OR REQUEST OF THE THIRD PARTY TRANSIENT

THIRD.- "The procedures entered into prior to the entry into force of this modification may be resolved in their terms upon simple request to the email farmacovigilancia@cofepris.gob.mx", as stipulated in NOM-220-
SSA1-2016, Installation and operation of Pharmacovigilance and its modifications.

In light of the above, it is important to mention that in order to have a specific email address for this request, the CNFV makes available the email Modnom220fv@cofepris.gob.mx, intended exclusively to address requests arising from the provisions of the third transitory provision of NOM-220-SSA1-2016, Installation and operation of Pharmacovigilance and its modifications.

To carry out the application for the THIRD transitory application you must do the following:

- Send the request to Modnom220fv@cofepris.gob.mx, addressed to the CNFV. The request must be sent by the Head of the Pharmacovigilance Unit, who is registered and up-to-date with the CNFV. The email must include complete information about the person in charge and the Pharmacovigilance Unit.
- List the procedures that request the application of the third transitory provision.

No. CIS	DATE OF ENTRANCE	TYPE OF PROCEDURE	DENOMINATION GENERIC	DENOMINATION DISTINCTIVE

It is requested to verify that the procedures listed do apply to them under the third transitory provision of

according to NOM-220-SSA1-2016 and its amendments. After submitting your application to the CNFV, you will receive a response within 7 days.

Note: If the CNFV has already resolved certain procedures on the requested list, the Third Transitory Provision will only apply to those procedures that have not been resolved by the date of the request.

12. REFERENCES

Official Journal of the Federation. Mexican Official Standard MODIFICATION NOM-1.
220-SSA1-2016, Installation and operation of pharmacovigilance. Available from: https://
www.dof.gob.mx/nota_detalle.php?codigo=5601541&fecha=30/09/2020

2. Official Gazette of the Federation. Mexican Official Standard NOM-220-SSA1-2016,
Installation and Pharmacovigilance Available from: http://www.dof.gob.mx/
nota_detalle.php?codigo=5490830&fecha=19/07/2017 [Accessed July 19, 2017].

European Medicines Agency. Guideline on good pharmacovigilance practices 3.
(GVP): Module VII – Periodic safety update report (Rev 1).

4. Available from:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline
/2013/04/WC500142468.pdf [Accessed July 11, 2017].

Annex 1 RPS compliance table

All titles must be in Spanish and none must be omitted.			
	QUALIFICATION	NATIONAL	INTERNATIONAL
1	Front page	☑	In Spanish
2	Executive Summary	☑	In Spanish
3	Table of Contents	☑	In Spanish
4	Introduction	☑	In Spanish
5	Authorization status in the national market and international	☑	Information from Mexico only. In Spanish.
6	Update of the actions taken by regulatory authorities for safety reasons	☑	Translate global RPS information
7	Changes to the information of product safety reference	☑	Include in Spanish only the information of Mexico, the rest of the information can be referenced globally
8	Estimate of Exposed patients 8.1 Patient Calculation	☑	Include in Spanish only the information of Mexico, the other information can be referenced to the global report
9	Summary table of individual cases of SRAM, RAM, AE, ESAVI or any other safety problem related to the use of accumulated medications and vaccines	☑	The report may be referenced to the global report.
10	Summary of facts presented during clinical studies within the reported period	☑	Include only information from Mexico in Spanish, the rest of the information can be referenced globally (In case of having a research center in Mexico)

11	Findings in the studies whose objective main points security	☑	Translate global RPS information
12	Information from others clinical studies	☑	The report may be referenced to the global report.
13	Preclinical/non-clinical information clinic	☑	The report may be referenced to the global report.
14	Scientific literature	☑	The report may be referenced to the global report.
15	Other periodic reports	☑	The report may be referenced to the global report.
16	Lack of effectiveness in clinical studies	☑	The report may be referenced to the global report.
17	Updated information	☑	Translate global RPS information
18	Signal generation : new, in progress and closed	☑	Translate global RPS information
19	Signs and evaluation of risk	☑	Translate global RPS information
20	Summary of problems security in Mexico	☑	In Spanish
21	Benefit assessment	☑	Translate global RPS information
22	Balance sheet analysis benefit/risk	☑	Translate global RPS information
23	Conclusions and actions	☑	Translate global RPS information
24	Annexes	IPPa RS	IPPa RS Global RPS (PBRER)