Agência Nacional de Vigilância Sanitária

Regulatory Guide - Anvisa

Periodical Pharmacovigilance Report/ PPR

In accordance with RESOLUTION – RDC no. 4, dated 10/Feb/09 (DOU 11/Feb/09): Provides for pharmacovigilance norms for the holders of marketing authorization for medical drugs for human use.

Brasília, August 2009.

Guide - Periodical Pharmacovigilance Report /ANVISA

Regulatory Guide - Anvisa
Periodical Pharmacovigilance Report / PPR

PART I: GENERAL ASPECTS

1. Introduction

1.1 Objectives of the guide and the Periodical Pharmacovigilance Report

This guide is considered a regulatory document, and aims at providing practical guidance on the preparation of Periodical Pharmacovigilance Reports (PPR) by the marketing authorization holders (MAH), as described in RDC no. 4 dated 10 February 2009 (DOU 11/Feb/2009).

This document refers to the guideline E2C (R1) of the *INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH, 2005),* with adaptations, and aims at establishing a harmonious relation with the international periodical safety reports.

The PPR is a document which all human use drug marketing authorization holders are responsible for, and aims at periodically presenting to Anvisa an update of domestic and international safety data, with their respective benefit-risk profile assessment, in a standardized and consolidated way.

During the period covered by the report, the PPR addresses the analysis of adverse event reports, review of accumulated data, presentation of safety data from studies, and other safety related information, as well as updates of the risk minimization plan, when applicable.

The PPR data also include ineffectiveness reports, mainly for drugs used in the treatment of conditions with risk of death, or for other products, such as contraceptives and vaccines. Although this type of event should not necessarily be included in line listings, such findings should be discussed in the PPR (see section 2.8), when clinically relevant.

In addition, data on exposure or adverse events during pregnancy or lactation should be discussed in the PPR.

The PPR is also an important tool for the marketing authorization holders to carry out systematic analyses on a regular basis, with early identification of problems and intervention suggestions. Effective actions to control the safety and effectiveness of their products will guarantee the permanence of pharmaceutical products in the market, and will particularly contribute towards the population's health.

In previously defined periods (Chart 1), the marketing authorization holders in Brazil should elaborate the PPR with their product's safety information, as well as a critical assessment of the benefit-risk relation based on new information or alterations of known information. Such assessment should indicate if there is evidence related to changes in the safety profile of the drug, which might motivate alterations to registration or information leaflet.

1.2 Background

The PPRs are applied to all drugs under health surveillance. However, the new drugs (new synthetic, semi-synthetic molecule entities, new vaccines, and biotechnological drugs) are of special pharmacovigilance interest because, when a new medicinal product is submitted for marketing approval, the demonstration of its efficacy and the evaluation of its safety are based

on studies with a restrict number of patients. The limited number of research subjects included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a throughout evaluation of the safety profile.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization. Thus, a report including the safety information in the period pushes the periodical review of the benefit-risk profile of the drug, both by the marketing authorization holder and Anvisa, which makes it a shared responsibility.

In recent years, the adverse event notification from different sources, the development of new pharmacovigilance procedures, and the mutual exchange of safety data have contributed towards timely detection of drug related problems.

In cases of serious adverse events, the MAH should notify the Health Surveillance Brazilian System (SNVS) Health Surveillance Notification and Investigation System on an expedited basis, because all information cannot be evaluated with the same degree of priority, despite the fact that pharmacovigilance consolidated reports are periodically forwarded.

The PPR favors a global assessment of the drug because it presents the world-wide safety experience of a medicinal product at defined times post-authorization. Thus, it is used in order to:

- Submit to the regulatory authority all the relevant new safety information from appropriate sources;
- Relate these data to patient exposure;
- Summarize the market authorization status in different countries and any significant variations related to safety;
- Create periodically the opportunity for an overall safety reevaluation;
- Indicate whether changes should be made to product information in order to optimize the use of the product.

The renewals of drug registration, which usually happen every 5 years, also need safety reevaluation. Therefore, a cumulative report on the data of the period favors a global view of the benefit-risk profile of the drug in the user population. Thus, the PPR is a key document in this process.

1.3 Periodicity

As described in the legislation in force, the periodicity for new drug PPR elaboration is as follows (Chart 1):

I – every six months, in the first two years after the authorization is granted;
II – annually in the three years after the period mentioned in the previous item, until the first renewal;
III – whenever requested by Anvisa.

The PPR should be submitted to Anvisa, in compliance with the periodicity and the 60-day limit after the data lock point.

Considering the initiative by Anvisa related to the electronic petitioning in the drug registration area, the PPR may be forwarded in accordance with the pertinent guidance on the subject.

For the products registered before the date this resolution entered into force, the submission will be done at the moment of product renewal, or according to other legal provisions.

Out of the routine (Chart 1), PPRs for periods and deadlines different from the ones legally defined may also be requested from the MAH, if necessary.

Chart 1. Periodicity of elaboration and submission of the Periodical Pharmacovigilance Report for new medicinal products.

PPR Elaboration	PPR coverage period	Submission to Anvisa	Submission
1	6 months	6 months	Executive summary
2	6 months	12 months	Executive summary + PPR of the period
3	6 months	18 months	Executive summary
4	6 months	24 months	Executive summary + PPR of the period
5	12 months	36 months	Executive summary
6	12 months	48 months	Executive summary
7	5 years	5 years	PPR of the period or bridging report of the last 5 years
8, 9 etc	5 years	10 years on	Other renewals – PPR of the period or bridging report of the last 5 years
At any moment	When requested	When defined by Anvisa	Cumulative data of the period requested – addendum report

1.4 General Principles

1.4.1 One PPR for one active substance

One single report should cover all products with the same pharmacologically active substance of the same MAH.

If possible and relevant, the data for indication or population (e.g. children vs. adults), dosage forms, route of administration, or specific dosages should be reported in separate presentations in the report, and the safety points to be considered should be addressed adequately, but within the single PPR. However, a view on the combined data should be provided.

For combinations of substances also marketed individually, the MAH should present a PPR for the combination (RDC 136/03).

The drug and non-drug combinations should be elaborated as PPR when they exist as medicine product registration. If there is the need to send Anvisa separate reports for the drug (pharmacovigilance and drug areas) and non-drug (health product area), the same final data lock point should be established to facilitate the assessment.

1.4.2 General information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals, as well as data on serious, unlisted ADRs, which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information, and may generate safety signals. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended in this document.

Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g., population exposed, increase in duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PPRs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to Anvisa, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, these data should be included and discussed in the PPR, even if it is known that they are included in another company's PPR.

1.4.4 Drug Birth Date (DBD)

Each medicinal product should have a birth date (DBD) for the purposes of counting time for the elaboration of PPRs. This date will be the date of registration in Brazil granted to a single MAH. Each DBD is linked to a single registration number, equivalent to the nine first digits of the registration.

The start date of the period for PPR elaboration will be considered in two situations:

- For the products registered in Brazil only, the date of produt registration in Brazil will be considered the birth date;
- For products registered in Brazil that have previous marketing authorization in other countries, the PPR may be elaborated for the sum of the Periodical Safety Report of the last period available, based on the International Birth Date (IBD), added by an addendum report, in a single document. The latter will have as start date the date of first registration in Brazil, and will cover domestic and international safety data in the form of addendum to the international periodical safety report, in compliance with the periodicity established in the legislation in force. However, a view of the combined data should be provided in the joint report.

For new medicinal products registered, but still unavailable for consumption in the period covered by the PPR, if there are no pharmacovigilance data, the MAH should send a negative declaration by the PPR submission deadline.

Synchronization of PPR with PSUR

When the IBD does not coincide with the DBD, the following situations should be observed:

- When the additional period is shorter than three months for a PSUR presented every six months or annually; or when the additional period is shorter than six months for a long-

term PSUR (over one year), the last PSUR should be presented plus line listing or summary of tabulations covering the additional period, with comments on relevant data and new important risks, if identified.

- If the additional period is longer than three months for a six-month or anual PSUR, or if it is longer than six months for a long-term PSUR, the last PSUR should be presented plus an Addendum Report.

Data lock point

It is the date when the database is closed for analysis (see Chart 1), which started at the DBD.

The MAH should submit the PPR within the maximum period of 60 (sixty) consecutive days after the data lock point.

Bridging Report (BR)

The Bridging Report is a document that sums the information presented in two or more PPRs to cover a specific period when a single report is required by the regulatory agency (Chart 1).

The objective of the bridging report is to supply the regulatory authorities with a general view of the PPRs. A consolidated analysis of the previous PPRs should be done based on crossing of information.

The BR should provide a brief summary integrating two or more PPRs (e.g. two consecutive six-month reports for an annual report, or ten consecutive six-month reports to make a five-year report).

Usually, the BR should not include line listings, once the tabulation summary presented should provide enough safety information for the period.

Whenever a BR is elaborated, a new tabulation summary should be extracted from the database. Thus, the tabulation summary will reflect the most updated data available at the moment they are generated.

Case counting may differ from the individual tabulation summary previously presented in the PPRs mentioned in this BR, because they are generated from a dynamic database, which is continuously updated.

BR format should be identical to the usual PPR, but its content should consist of brief highlights and a general view of previous PPR data.

The BR may be requested at any moment by the regulatory authority.

A BR should have the following sections:

- Introduction (purpose);
- Authorization worldwide scenario (brief description of marketing scenario in several countries, if applicable);
- Regulatory Action Update (summary of the actions carried out in the period);

- Alterations in the MAH safety reference documents (health professional and patient information leaflet, or *Company Core Safety Information* – CCSI, whichever is applicable);
- Exposure data (estimates of the number of patients exposed in the period. The method should be clearly mentioned);
- Individual cases or line listing (if requested);
- Tabulation summary;
- Studies (summary of any efficacy and safety studies on the drug);
- Other information (only important safety information should be described, such as AE data obtained after the PPR data lock point);
- Safety Evaluation and Conclusions (reference solely to unsolved points and applicable measures to address the safety problem identified).

Addendum Report (AR)

Addendum Report is an update of the last PPR of a drug and covers a period outside the regular cycle of elaboration and submission of the PPR, that is, outside the period defined by the DBD.

This report may be used when there is the need to submit a PPR on a date different than the regular cycle, and the last PPR was elaborated over three months before, for a six-month or annual report, or over six months for a long interval (over one year) report. This period should be calculated from the time elapsed since the data lock point of the most recent PPR.

An addendum report may be requested at any moment by Anvisa.

The addendum report should present the safety data received between the data lock point of the most recent PPR and the data lock point requested by the regulatory authority. The addendum report is not expected to provide a detailed analysis of additional cases, because they may be included in the next PPR.

The proposed report should contain new information or alterations presented by the medicinal product since the last PPR.

Depending on the circumstances and on the volume of additional data since the last programmed report, the addendum report should follow the PPR format or may be presented in a simplified way, containing at least the following sections:

- Introduction (objective);
- Significant regulatory measures taken by the MAH for safety reasons;
- Alterations in the MAH safety reference documents (health professional and patient information leaflet, or *Company Core Safety Information* – CCSI, whichever is applicable; a copy of such documents should be included, if they are different from the ones presented in the last PPR);
- Exposure data (estimates of the number of patients exposed in the period. The method should be clearly mentioned);
- Line listing or tabulation summary;

- Conclusions (brief review of new cases included and a comment on whether they are in accordance with the known safety profile of the medicinal product).

New PPR submission necessities

For products in a long-term PPR cycle (5 years or longer), the return to 6-monthly or annual reporting could apply after important additions or changes in clinical use are first approved for this product. For example:

- A new, clinically dissimilar indication;
- New approved use in a special patient population, such as children, pregnant women or the elderly;

In the case of new safety signals, in specific organ systems, a specific report may be elaborated voluntarily by the MAH, or requested by Anvisa.

New PPR submission necessities aim at an analysis focusing the newly-indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations. In addition it can be used to give special attention to the safety profile, thus it is necessary to comply with the deadlines for new medicinal products (Table 1)

Additional time for submissions

In rare circumstances, an MAH can make a special request to the Regulatory Authority for 30 additional calendar days to submit a PPR, except for marketing authorization renewal. Necessarily, this request should be made before the data lock point. The RA will attempt to send response to MAH as rapidly as possible.

The basis of such a request should be justified and could include:

- A large number of case reports for the reporting period, provided that there is no new significant safety concern;
- Issues raised by Regulatory Authorities in the previous PPR for which the MAH is preparing additional or further analysis in the next PPR;
- Issues identified by the MAH for additional or further analysis.

The MAH should make such a request only for the single PSUR in question and not for subsequent PSURs. The Regulatory Authority will generally expect subsequent PSURs to be submitted on the appropriate date and to retain their original periodicity.

1.4.5 Reference safety information

One of the PPR objectives is to establish which information recorded during the monitoring period is in accordance with the previous safety knowledge on the medicinal product. This is important to indicate what regulatory alterations should be made. The information leaflet is an essential document in this process. However, it should not have much content and should not be mistaken for a drug monograph, due to its purpose of being a simple document for quick reference, as accessible and guiding information for health professionals and users.

Some MAHs have their own safety base documents in a format of safety technical sheet. This document presents drug consolidated safety data. In some countries, this document is denominated "*Company Core Safety Information*" (CCSI). This document may help to assess if

an adverse event is considered “listed” or “unlisted”, based on all information on domestic and international registration.

Thus, the terms “listed” or “unlisted” refer to the CCSI or the safety technical sheet, which are different from the terms “predictable/ expected/ described” or “unpredicted/ unexpected/ not described”, used to indicate if the safety data are or are not contained in the domestic information leaflet. They serve as base guidance to health professionals, because an AE not described in the information leaflet is thus considered unexpected, and should be notified, even if it is known as “listed”.

In the absence of a CCSI or a document of safety technical sheet type, there should be an indication of the Drug Safety Reference Document (DSRD) used to consider a “listed” or “unlisted” AE.

It is important to note that the terms listed in the current PPR should be mentioned with reference to a previous safety technical sheet or CCSI, without an immediate inclusion of the new findings in the period with the safety reference document. The same idea is applied to the new information on AE related to predictability and the leaflet information.

The changes made to the safety documents (information leaflet or safety technical sheet) should be explained in sections 2.4 Alterations to MAH safety reference documents or 2.9 Safety General Assessment.

1.4.6 Presentation of individual case histories

Sources of information

In general, the following sources of information on adverse event cases are available to MAHs and should be included in the PPR:

a) Direct reports to MAHs: spontaneous notifications from health care professionals; spontaneous notifications from non-health care professionals or consumers; MAH-sponsored clinical studies[1] or compassionate use.
b) Literature;
c) ADR reporting systems of regulatory authorities;
d) Other sources of data, including ADR reports exchanged between contractual partners;

Description of adverse events

Whenever possible, the event terms used in the PPR should be derived from the WHO Adverse Reactions Terminology (WHO-ART) or compatible dictionaries.

However, when the notifying reporter’s terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms.

Under such circumstances, the following should be borne in mind:

- in order to make it available on request, the “verbatim” information supplied by the notifying reporter should be present in the original document (source document) and should be kept on file in the original language and in the reported term;

[1] What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

- in the absence of a diagnosis by the reporting health-care professional during the notification, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data;
- if a MAH disagrees with a diagnosis that is provided by the notifying health care professional, it may indicate such disagreement within the line listing of cases (see below);
- MAH should try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter, but described in a given notification;
- Reports on free sample drugs.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH's medical interpretation (identified by asterisk or other means).

Line listings and summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting the MAH full case reports or by means of notifications as individual cases, carried out according to chapter 3 of RDC no. 4/2009 (in general, the greatest interest lies on the serious, non-described ones, issued in a maximum period of 7 to 15 days).

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (see 1.4.6a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible).

However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see 1.4.6d) might not be possible without standardization of data elements, or appropriate due to the paucity of information. Therefore, summary tabulations or even a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non-serious listed ADRs).

1.4.7 Periodical Pharmacovigilance Report and the Risk Management Process

The Pharmacovigilance Plan (PP) and the Risk Minimization Plan (RMP), when existing at the moment of registration, or in its subsequent updates, should be sent together with the PPRs, unless other requirements are established as a condition for marketing authorization. In general, safety issues should be identified in the initial phases of a new drug development, and these issues should be addressed in a PP/RMP. These documents may propose several actions to better address safety issues, such as: education (physicians, patients, sales representatives etc.), the use of safety databases, promotion of specific studies, among others.

PP and RMP will serve as guidance documents and there should be a general assessment summarized in the PPR. This section will serve to update the reviewer on plan development. If there are substantial changes in the PP and the RMP, a new version should be sent separately.

2. Contents of a Periodical Pharmacovigilance Report – PPR

Please find below information and explanations on the contents of a PPR. This section aims at facilitating the understanding on the report and promoting an adequate and harmonious elaboration of the PPR among MAHs.

2.1 Introduction

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances, despite individually reflecting a specific coverage period.

Reference should be made not only to product(s) covered by the report but also those excluded (that had the same active substance). Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PPR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see 1.4.6), the possibility of data duplication should be noted.

The PPRs contain restricted information. Therefore, its first page should contain an alert phrase on data confidentiality.

2.2 World-wide Market Authorization Status.

This section of the report provides cumulative information on the product, which should be presented as explicative summary and detailed in an appended table. Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorization, and subsequent renewal;
- any qualifications surrounding the authorization, such as limits on indications if relevant to safety;
- treatment indications and special populations covered by the market authorization, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of a license application submission if related to safety or efficacy;
- dates of launch when known;
- trade name(s).

Indications for use, populations treated (e.g., children vs. adults) and dosage forms may be the same in most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted.

Country entries should be listed in chronological order of regulatory authorizations.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organized. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 Update of Regulatory Authority or MAH Actions Taken for Safety Reasons.

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission, such as:

- marketing authorization suspension;
- marketing authorization cancellation;
- failure to obtain a marketing authorization renewal;
- restrictions on distribution;
- clinical trial suspension;
- dosage modification;
- changes in target population or indications;
- formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health professional (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 Changes to MAH Reference Safety Information

The version of the Drug Safety Reference Document (DSRD) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PPR and include the date of last revision.

Changes to the DSRD, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised DSRD should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials. During that period the amended reference document may contain more “listed” information than the existing product information in many countries.

When meaningful differences exist between the DSRD and the safety information in the official data sheets/ product information documents approved in other countries, a brief comment should be prepared by the company, describing the differences in Brazil and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PPR.

2.5 Patient exposure

Where possible, an estimation of accurate patient exposure should cover the same period of the report. While it is recognized that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate, e.g. patient-year. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions

or number of dosage units are considered appropriate; the method used should be explained. If the patient/time adjustment is not possible, it may be carried out by means of active substance/bulk sales.

The concept of a Defined Daily Dose (DDD) and Daily Dose (DD) may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs. adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PPR, a relevant denominator should be provided. For ongoing and blinded studies, an estimation of patient exposure may be made.

When exposure data are based on information from a period that does not fully cover the period of the PPR, the MAH can make extrapolations using the available data. When this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PPR period in question (e.g., stable sales over a long period of time, seasonality of use of the product).

The MAH should use a consistent method of calculation across PPRs for the same product. If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PPR introducing and highlighting the change.

If the exposure calculation includes the volume of free sample drug distribution, it should be informed.

In Summary Bridging Reports, patient exposure data should be presented based on the period covered by the report.

2.6 Presentation of Individual Case Histories

It is impractical to present all case reports for the reporting period in this section of the PPR. A brief description of the criteria used to select cases for presentation should be given.

This section should contain a description and analysis of selected cases. Fatalities should be presented separately. New and relevant safety information should also be presented and grouped by medically relevant headings or System Organ Classes (SOCs).

2.6.1 General Considerations

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PPR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PPR, and the correction or clarification noted relative to the earlier case description.

With regard to the literature, MAHs should monitor standard, recognized medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once in the PPRs. Also, no matter what “primary source” is given a case, if there is a publication, it should be noted and the literature citation given.

Medically unconfirmed spontaneous reports that originate with consumers or other non-health care professionals should be submitted as addenda summary tabulations. However, these reports are not usually discussed in the PPR itself, except for serious events that justify their inclusion, and they should be presented as line listings separately. When included in the safety data analysis (section 6 or 9), there should be a note on it.

2.6.2 Cases presented as line listings.

The following types of cases should be included in the line listings (Table 2).

- all serious reactions, and non-serious unlisted reactions, from spontaneous or requested[2] notifications;
- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
- all serious reactions, and non-serious unlisted reactions, from the literature;
- all serious reactions from regulatory authorities

In general, non-serious, listed ADRs occur in all countries where the product is commercialized. Therefore, a line listing of spontaneously reported non-serious listed reactions described should be submitted as addenda summary tabulation in the PPR.

The line listings should include each patient only once regardless of how many adverse event terms are reported for the case. If there is more than one adverse event, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions. Such experiences should be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number;
- Countries in which case occurred;
- Source (e.g., clinical trial, literature, spontaneous, requested, regulatory authority);
- Age and sex;
- Daily dose of suspected drug (and, when relevant, dosage form and route);
- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section);
- Dates of treatments. If not available, best estimate of treatment duration;
- Description of reaction as reported, and when necessary as interpreted by the MAH. See Section 1.4.6 for guidance.
- Patient outcome (at case level) (e.g., recovered, at recovery, not-recovered, recovered with sequel, fatal, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/ rechallenge results if available).

[2] Patient support or disease management programs, researches requesting patient demographic data, satisfaction researches, or any other situation created by the company where the patient may report an ADR.

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.3 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, listed, spontaneously reported reactions (see also 2.6.2)

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from other sources should normally be presented only as a summary tabulation, see Table 2. Tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description of existing cases rather than a formal table is considered suitable.

The data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in a table or as a narrative.

“Comments” field

The “Comments” field should be used only for information that helps to clarify individual cases.

2.6.4 MAH’s Analysis of Individual Case Histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on relevant findings (their nature, medical significance, mechanism, reporting frequency, etc.).

The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (Section 2.9).

2.7 Studies

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed. However, only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information, should be included with a discussion of any final or interim results. The MAH should not routinely catalogue or describe all the studies.

2.7.1 Newly analyzed company-sponsored studies.

All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2 New safety studies planned, initiated or continuing during the reporting period.

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PPR as described under 2.7.1.

2.7.3 Published safety studies

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarized and publication reference given.

2.8 Other Information

2.8.1 Efficacy-Related Information

For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2 Late-Breaking Information.

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 2.9).

2.8.3 Risk management

When there is a Pharmacovigilance Plan or a Risk Minimization Plan, they should be briefly described in this Section. The aim is to provide an overall view of what processes and methods will be used as tools for minimizing the risks identified, and how their impact would be measured. Likewise, when there are updates, these plans should also be submitted together with the current PPR.

2.8.4 Benefit-risk analysis report

When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this Section.

2.9 Overall Safety Evaluation

A concise analysis of the data presented, taking into account any late-breaking information (Section 2.8.2.), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- A change in characteristics of listed reactions, e.g. severity, outcome, target population;
- Serious unlisted reactions, placing into perspective the cumulative reports;
- Non-Serious unlisted reactions;
- An increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following:

- drug interactions;
- ADR from drug quality deviations;
- ADR from unapproved use of medicinal products;
- experience with overdose, deliberate or accidental, and its treatment;
- drug abuse or misuse;
- positive or negative experiences during pregnancy or lactation;
- experience in special patient groups (e.g., children, elderly, organ impaired);
- effects of long-term treatment.

The lack of significant new information on any item above should be justified in a safety analysis of a product.

Discussion and analysis for the Overall Safety Evaluation should be organized by SOC rather than by listedness or seriousness. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.

2.10 Conclusion

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the Drug Safety Reference Document (DSRD);
- specify and justify any action recommended or initiated;
- Alterations in the leaflet information text.

3. Appendix

1. Glossary of special terms

Company Core Data Sheet (CCDS): A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI): All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date): The date designated as the cut-off date for data to be included in a PPR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

Drug Safety Reference Document (DSRD): safety information document prepared by the MAH, preferably CCDS, CCSI and, in its absence, health professional information leaflet or technical report safety consolidated data.

International Birth Date (IBD): The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

Information leaflet (for health professionals and for patients): according to legislation in force.

Listed Adverse Drug Reaction: An ADR whose nature, severity, specificity, and outcome are consistent with the information in the DSRD.

Periodical Pharmacovigilance Report (PPR): document that should be presented periodically to regulatory authorities by all MAHs regulated by Anvisa, containing local and international safety data, with their respective benefit-risk analysis, in a standardized and consolidated way.

Periodic Safety Update Report (**PSUR):** document that aims at periodically updating regulatory authorities with post-commercialization safety information on a medicinal product.

Safety sign: reported information on possible causal relation between an ADR and a drug, this relation being unknown or having been previously documented incompletely. Usually, more than one report is necessary to generate a sign, depending on the seriousness of the event and the quality of information.

Spontaneous Report or Spontaneous Notification: An unsolicited communication to a company, regulatory authority or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

Unlisted Adverse Drug Reaction: An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the DSRD.

2. TABLES

- Table 1 –
Example of Presentation of World-Wide Market Authorization Status

Country	Action-Date	Launch Date	Trade Name(s)	Comments
Sweden	A – 7/90 RA – 10/95	12/90	Bacteroff	- -
Brazil	A – 10/91 A – 1/93	2/92 3/93	Bactoff Bactoff IV	- IV dosage form
United Kingdom	AQ – 3/92	6/92 7/94	Bacgone Bacgone-c (skin infs)	Elderly (> 65) excluded (PK) Topical cream
Japan	LA – 12/92	-	-	To be refiled
France	V – 9/92	-	-	Unrelated to safety
Nigeria	A – 5/93 A – 5/93	7/93 1/94	Bactoff Bactoff	- New indication
Etc.				

Abbreviations for Action: A = authorized; AQ = authorized with qualifications; LA: lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorization renewal.

- Table 2 –
Guidance for Presentation of Individual Case Histories or Summary Tabulation
(See 2.6.2, 2.6.3 and 2.6.4 for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH	S	-	+
- Spontaneous ADR reports*	NS U	-	+
	NS L**	+	-
- MAH sponsored studies	S A	-	+
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
- Regulatory Authorities	S	-	+
- Contractual partners	S	+	-
- Monitoring Program***	S	+	-

* Medically unconfirmed reports should be provided as a PPR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.

** Line listing should be provided as PPR addendum only on request by regulatory authorities.

S = serious; L = Listed; A = attributable to drug (by investigator or sponsor); NS = non-serious; U = Unlisted.

*** Record from specific programs or systems to follow-up patients during treatment with drugs.

- Table 3 –
(Example of Summary Tabulation)
Number of reports by term (signs, symptoms and diagnoses) from spontaneous (medically confirmed), clinical study and literature
Cases: all serious reactions

Número de notificações por termos (sinais, sintomas e diagnostico) das espontâneas (clinicamente confirmados), dos estudos clínicos e da literatura.
Casos: todas os eventos graves.

(An * indicates an unlisted term)

Body system/ ADR term	Spontaneous and Regulatory bodies	Clinical trials	Literature
Central Nervous System			
Encephalitis*	2	0	0
Etc.			
Etc.			
_____ Sub-total	_____	_____	_____
Cardiovascular System			
Ventricular tachycardia *			
Etc.			
_____ Sub-total	_____	_____	_____
Etc.			
Total			

Note: This table is only one example of different possible data presentations which are at the discretion of the MAH.

PART II: ELABORATION OF THE PERIODICAL PHARMACOVIGILANCE REPORT – PPR

Detailed instructions are described below for the elaboration of a PPR by the MAH.

The model serves as guidance to help filling the PPR, and it is a filling-up guidance only. The PPR should not be identically written.

Key:

1) ***Bold italic***: example and text suggestion;

2) Information in *Double underlined italic*: data that should be replaced according to the filling-up of each report;

3) Underlined*:* filling-up instruction or guidance

Cover Sheet

It will be the first sheet of the report and aims at providing the information to identify the company, the Pharmacovigilance area and responsible person, the medicinal product and the period covered by the report.

The following information should be included on the document Cover Sheet:

1. Drug name: *trade name and active substance;*

2. Company name and address: *corporate headquarters / main office;*

3. Contact for the local Pharmacovigilance: *according to RDC 04/09 Article 3*

- Name of the person responsible for the Pharmacovigilance

- Job

- Department

- Address: *address of the Pharmacovigilance department or other company responsible for the report preparation*

- Telephone

- E-mail

4. Period covered by the report: *starting date and data lock point;*

5. Report date: *date the report elaboration was completed;*

6. Date of authorization in Brazil and of the first international authorization (when applicable);

7. Report number: *sequential number used by the company for identification;*

8. Declaration of confidentiality: *text informing the report is restricted to regulatory authorities and MAHs, and the report use and reproduction is not allowed for other purposes.*

Example of Cover Sheet

Drug name: trade name and active substance

PERIODICAL PHARMACOVIGILANCE REPORT

Company name and address

Contact for local Pharmacovigilance:
- Name of the person responsible for the Pharmacovigilance
- Job
- Department
- Address
- Telephone
- E-mail

Period covered by the report

Date of report

Date of authorization in Brazil

Date of international authorization (when applicable)

Number of report

[Declaration of Confidentiality]

Name of Company	**Confidential**	*Name of Product*
PPR No		

Executive Summary

The PPR executive summary should provide a summary in Portuguese of the most relevant information in the report.

The executive summary introduction should contain a simple sentence informing the analysis period covered by the PPR. Information should be added on the number of countries where the medicinal product is commercialized, as well as on partner companies, where there are commercialization contracts, when applicable.

The text development should present a brief history of the medicinal product, therapeutic indication, presentations available in the market, sources of notifications, data on patient exposure according to the volume of product distributed during the reporting period, number of ADRs received by the company during the report review period, and a summary on the relevant safety findings.

Whenever applicable, the text should mention all safety measures taken by the regulatory authorities or the MAH, in any country where the product is commercialized, in the period covered by the Report. When applicable, a brief report on the safety clinical studies should be made, including published studies.

The executive summary should end with a conclusion on the drug safety profile, emerging safety issues, and signs. When applicable, it should inform the proposed adequacy measures, including changes in information leaflets.

Example of Executive Summary

This document is the third Periodical Pharmacovigilance Report of name of product (active substance) covering the period of dd mmm yyyy to dd mmm yyyy.

Reports and other data from the marketing partner company [name of company] are included. (When applicable)

In Brazil, the product is authorized for XX (describe indications), in the following presentations...

The product is currently authorized in XX [number] countries. No safety measures were taken by the regulatory authority or the MAH. The current information leaflet is dated dd mmm yyyy.

or

The product is currently authorized in XX [number] countries. The current information leaflet is dated dd mmm yyyy. During the review period, the section "Drug Interaction" was updated (note on the interaction with serotonin reuptake inhibitors), and convulsion was added to the section "ADR".

Approximately XX [number] patients were given [name of product] in clinical studies sponsored by name of company. Regarding sales data, patient exposure was estimated at approximately XX million patients-year.

XX [number] spontaneous reports were received as a whole, XX of which were serious (XX [number] unlisted), and XX [number] were not serious (XX [number] unlisted). In addition to those, there were XX [number] reports requested (XX [number] unlisted).

Interstitial nephritis, arrhythmia and anemia were identified in the previous PPR of [name of product] as relevant safety findings and should be closely followed-up.

A cumulative analysis of interstitial nephritis reports did not provide evidence of causal relation with [name of product]. The product will still be closely followed-up for additional interstitial nephritis reports.

The cumulative number of arrhythmia reports was not significant in relation to the great number of patients treated and the characteristics of the population of treated patients. Arrhythmia will no longer be considered a relevant safety finding, unless additional reports require a reevaluation of this issue.

Cumulative analyses disclosed other possible causes in approximately half the reports on anemia/ hemoglobin reduction...

Briefly inform on safety clinical studies, including published studies: mention only important safety clinical studies and/ or publications with new safety information (e. g. which result in changes in the information leaflet) or inform that no safety clinical studies were identified.

[Name of product]-associated anemia will have a special evaluation in all reports and its inclusion in the section "ADR" will be considered.

NOTE: Alternatives of conclusion

The product will still be closely followed-up regarding interstitial nephritis reports. The safety profile of [name of product] in relation to all other aspects remains consistent with the information provided in the leaflet.

or

Based on this PPR analysis, it is concluded there is no need of change in the DSRD.

or

The benefit-risk profile for [name of product] remains favorable.

or

Based on this PPR analysis, nephritis risk minimization actions will be adopted, which will be specified in the Risk Minimization Plan.

Analytical Table of Contents

(Add)

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1. Introduction

The introduction should contain a simple sentence informing the PPR number and period of analysis. When applicable, information should be added on the number of countries where the medicinal product is commercialized and on partner companies,

when there is a commercialization contract. Excluded presentations should also be informed, justifying the exclusion.

The text should present a brief history of the medicinal product, action mechanism, therapeutic indication, dosage, and the presentations available in the market.

The data in this section should be provided by the MAH Department of Registration/ Regulatory Matters. This information may be presented in a text or in table format.

Example of Introduction

This document is the third Periodical Pharmacovigilance Report (PPR 3) of Product® (active substance: XXXXXX) consolidated for regulatory authorities in the format established by RDC 04/09. It summarizes the safety data received and processed by Name of Company related to world-wide sources in the period of 01 Jul 2008 to 31 Dec 2008. The current report supplements the previous one, RPF 2, of the period of 01 Jan 2008 to 30 Jun 2008 . The next report on *Product®, RPF 4,* will cover the period of *01 Jan 2009 to 30 Jun 2009. The product is referred to as Name of Product or Active substance in the rest of the document.*

More details on the action mechanism, indications, dosage forms, and use instructions are presented in the DSRD – Drug Safety Reference *(Annex 1).*

2. Market Authorization Status

Information should be provided on marketing authorization for the medicinal product in Brazil or other countries, as follows:

- Date of market authorization;
- Any qualifications surrounding the authorization, such as limits on indications and other relevant information;
- Treatment indications and special populations covered by the market authorization;
- Lack of approval, including explanation, by regulatory authorities;
- Withdrawal by the company of a license application submission if related to safety or efficacy;
- Dates of launch when known;
- Trade name(s).

This information may be presented as text or table.

Example:

Product was first authorized in Brazil on 24 Oct 1969. It is currently authorized in XX [number] countries in the world. For a full view on the regulatory status, please refer to Annex 2. (When applicable)

Product is indicated for XX and ZZ, and should not be used by people under 12 year old and pregnant women.

For XX presentantion, the authorization was not approved on dd mmm yyyy, in name of country, for the following reasons. For a full view on the regulatory status, please refer to Annex 2. (When applicable)

The license application submission was withdrawn for the following reasons …

Or

There was no withdrawal of a license application submission related to safety or efficacy.

The product was launched on dd mmm yyyy, in the following countries...

The active substance is registered under the names Product® in the following countries...

3. Update of Regulatory Authority or MAH Actions Taken for Safety Reasons

(Section provided by the MAH Department of Registration/ Regulatory Matters)

This section should include details on actions relating to safety that were taken during the period covered by the report:

- Marketing authorization suspension;
- Marketing authorization cancellation;
- Failure to obtain a marketing authorization renewal;
- Restrictions on distribution;
- Clinical trial suspension;
- Dosage modification;
- Changes in target population or indications;
- Formulation changes.

The safety related reasons that led to these actions should be described and any supplementing documentation related to them should be appended to the report.

The safety related reasons that led to these actions should be described and documented in the appendix, when appropriate. Details on regulatory actions relating to safety that were taken during the period covered by this report should be included. Any communication with the health profession (e.g., Dear Doctor letters) as a result of such actions should also be described with copies appended.

4. Changes to MAH Reference Safety Information

*(*Section provided by the Department of Registration/ Regulatory Matters*)*

This item should be based on the Drug Safety Reference Document (DSRD) in force during the period covered by this report, and the document used to evaluate the listed ADR should be mentioned.

Changes to the aforementioned document, related to the drug safety, should be included.

When applicable, a comparison of the different versions of the Drug Safety Reference Document (DSRD) should be done and included in this report.

Documentation of the possible changes carried out should be appended to this report.

Eventual safety discussions that were not totally implemented should be mentioned as an item during the period covered in this PPR. The implementation actions should be included in the next PPR.

Example:

Prescription/ Leaflet Information dated 26 Jan 2000 (Annex 1) is in the Drug Safety Reference Document (DSRD) for the period covered by this report, and is used as reference for prescription information in all countries where the product is commercialized, such as*:*

Item XX was considered rare and now is deemed frequent.
or
The DSRD reference information were not altered during the reporting period.
or
There is no significant difference between the CDS and the health professional leaflet information.

5. Patient exposure

This section should provide the number of patients exposed to the medicinal product during the reporting period. A detailed explanation on the method used for the estimate should be presented.

It is essential that the MAH choose one of the following methods, described as standard, so their data history contains the same basis for comparison.

The following exposure estimate measures (denominator) may be used: patient-day, patient-month, patient-year, defined daily dose, daily dose, number of prescriptions, number of doses, or per dosage unit made available in the market, among others.

An estimate of the number of patients exposed during the review period should be provided, based on daily dose, estimates of treatments in the period and sales data. The method used for such estimates should be described.

The patient exposure calculation in clinical studies should be mentioned separately from the exposure data related to the medicinal product distribution in the period.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

Example 1:

The detailed data on the number of units distributed are in annex XX.

For the estimate number of exposed patients, we considered that a 15 ml flask hás enough volume for 30 days when used in the dosage recommended on the information leaflet. Therefore, for the 15 ml presentation, the number of units

distributed in the year corresponds to the number of patients-month, and the latter divided by 12 corresponds to the number of patients-year. For the 30 ml presentation, before estimating the number of units distributed, it should be multiplied by 2, because the presentation volume is enough for two months use

For example, the estimate for 2008:

- *Product1® 15 mL – 1,151,536 units distributed*
  - *1,151,536 = 1,151,536 patients month*
- *Product® 30 mL – 841,097 units distributed*
  - *841,097 x 2 = 1,682,194 patients month*

5.1.Product1®:

2002: 1,151,536 patients-month or 95,961 patients-year.
2003: 1,082,620 patients- month or 90,218 patients-year
2004: 1,244,062 patients- month or 103,671 patients-year
2005: 1,018,051 patients- month or 84,837 patients-year

5.2. Product1®:

2002: 1,682,194 patients- month or 140,182 patients-year.
2003: 1,933,456 patients- month or 161,120 patients-year
2004: 2,341,254 patients- month or 195,104 patients-year
2005: 2,205,076 patients-month or 183,756 patients-year

Example 2:

Detailed data on the number of units commercialized are in annex II.

Because the medicinal product is of continuous use and administered as a sole daily dose, we considered the monthly consumption is one kit per patient, regardless the presentation. The number of units sold per month to the number of patients-month, and the latter divided by twelve, corresponds to the number of patients exposed in a year.

5.1. Product2® (tablet – 20 mg):

2003: 159,006 patients-month or 159,006 patients-year
2004: 285,085 patients-month or 285,085 patients-year
2005: 306,519 patients-month or 306,519 patients-year
2006: 319,040 patients-month or 319,040 patients-year
2007: 277,955 patients-month or 277,955 patients-year*

5.2. Produto2® (tablet – 40 mg):

2003: 59,808 patients-month or 59,808 patients-year
2004: 115,565 patients-month or 115,565 patients-year
2005: 84,616 patients-month or 84,616 patients-year
2006: 64,361 patients-month or 64,361 patients-year
2007: 13,950 patients-month or 13,950 patients-year*

Therefore, the estimated number of patients exposed during the reporting period is 1,685,905 patients-year.

Example 3:

Patient year.

Patient year = quantity of the product sold in the period (in mg) ÷ DDDx365

Example 4:

Estimate based on the average treatment

Patients exposed = quantity of the product sold in the period (in mg) ÷ quantity in mg of an average treatment (treatment for the target population)

Note: DDD is the defined daily dose and may be obtained from the WHO website. There is one DDD for each active substance.

6. Presentation of individual case histories

6.1. General Considerations

In this PPR section, the data received by the MAH during the reporting period should be listed. All ADRs should be codified.

Example:

A total of XX [number] of health professional notifications describe XX ADRs received during the reporting period. Of these XX, XX serious ADRs were notified, including XX unlisted and XX listed ADRs. The sum of serious and non-serious reports tabled may exceed the total of cases notified due to data distribution in the database.
In addition, XX consumer reports describe XX ADRs received during the reporting period. This report includes XX unlisted ADRs, XX serious ADRs and XX non serious ADRs...

The table below presents the reports and the ADRs according to the report source.

Source	Number of Notifications	Number of ADRs
Spontaneous/ Regulatory Authority	XX	XX
Literature	XX	XX
Clinical studies	XX	XX
Consumer	XX	XX

6.2. Presentation of the line listing

In this topic the ADR cases classified as serious or unlisted from spontaneous or requested notification, literature identified reports, ADRs from compassionate use, drug-attributed ADRs by both the investigator and the sponsor, as well as regulatory authority notifications will be presented.

Describe the total notifications and identified events, with details on the distribution by body system.

The line listing should be organized by body system (standard organ system classification scheme), and contain the following information:

- Case identification (MAH case reference number)*;*

- Country or State in which case occurred (when applicable);
- Source (e.g., clinical trial, literature, spontaneous, regulatory authority);
- Age and sex;
- Daily dose;
- Date of onset of the reaction;
- Dates of treatment;
- Description of ADR;
- Patient outcome;
- Comments, if relevant;
- Causality.

Example

During this reporting period, we received XX [number] medically confirmed ADR notifications related to product XX.

Reference no.	Country	Source	Age and Sex	Dosage	Starting Date	Duration of treatment	ADR Description	Outcome	Comment
10005329 Hematological and lymphatic system disorders									
Report code	Brazil	Spontaneous	29, male	--	--	~15 days	Leucopenia Reticulocytosis*	Unknown	Causality: improbable. Despite the loss of DAJ DHFAHFHFJALLFJALJFLA
Number of cases in this group: 1									
10007541 Cardiac disorders									
Report code	France	Literature	34, female	1.2 mg	--	Sole dosage	Cardiac arrest Pulmonary edema Bradycardia Hypertension Hypotension Sedation Mydriasis Complication of procedure	Recovered	Causality: related. As anesthesia, the patient was given BLABJAB ALJBALJBALSJLBJALB
Number of cases in this group: 1									

References in literature:

Report code	Reference of article.
Report code	Reference of article.

Note: the asterisk (*) indicates unlisted reaction.

6.3. Summary tabulations

Elaborate separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions. Other breakdowns might also be appropriate (e.g., by source of report, by body system, by type of report).

Example:

Table 6.3-1 general view of cases per notifier

	Serious		Non serious		Total
Type of report	**Unlisted**	**Listed**	**Unlisted**	**Listed**	
Spontaneous					
Post-commercialization safety studies					
Bioequivalence studies					
Clinical trials					
Total					

Table 6.3-2 Distribution of ADR by Body System for the primary event

Body system	Total	Serious spontaneous reports				Serious and suspected requested reports				Non serious reports			
		Unlisted		Listed		Unlisted		Listed		Unlisted		Listed	
		HCP	Non- HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP
Blood and lymphatic system events	*78*	***21***	***3***	***15***	***0***	***0***	***0***	***2***	***2***	***8***	***1***	***24***	***2***
Cardiac events	*38*	***13***	***5***	***12***	***0***	***0***	***0***	***0***	***0***	***5***	***2***	***1***	***0***
Congenital, family, and genetic events	*11*	***5***	***1***	***2***	***1***	***0***	***0***	***0***	***1***	***1***	***0***	***0***	***0***
Ear and labyrinth events	*14*	***0***	***0***	***0***	***0***	***1***	***0***	***0***	***0***	***6***	***3***	***2***	***2***
Endocrine events	*20*	***14***	***2***	***1***	***0***	***0***	***0***	***0***	***0***	***3***	***0***	***0***	***0***
Eye events	*60*	***11***	***5***	***2***	***2***	***0***	***0***	***0***	***0***	***14***	***6***	***14***	***6***
Gastrointestinal events	*159*	***12***	***6***	***5***	***0***	***0***	***0***	***1***	***0***	***37***	***31***	***39***	***28***
General conditions and conditions related to the administration location	*184*	***16***	***7***	***3***	***1***	***0***	***0***	***1***	***1***	***35***	***56***	***27***	***37***
Hepatobiliary events	*26*	***10***	***2***	***10***	***0***	***0***	***0***	***2***	***0***	***0***	***1***	***0***	***1***
Immunologic system events	*58*	***5***	***0***	***26***	***4***	***0***	***0***	***3***	***1***	***2***	***3***	***11***	***3***
Infections and infestations	*50*	***15***	***6***	***1***	***0***	***1***	***0***	***0***	***1***	***13***	***13***	***0***	***0***
Injuries and complications related to procedures	*133*	***3***	***3***	***5***	***1***	***2***	***0***	***0***	***1***	***15***	***15***	***66***	***22***
Investigations	*189*	***26***	***9***	***35***	***3***	***0***	***0***	***0***	***1***	***42***	***29***	***29***	***15***
Metabolic and nutritional events	*245*	***21***	***6***	***142***	***5***	***1***	***0***	***11***	***0***	***10***	***6***	***42***	***1***
Musculoskeletal and connective tissue events	*71*	***13***	***2***	***11***	***2***	***0***	***0***	***0***	***0***	***22***	***14***	***4***	***3***
Benign, malign, and unspecified neoplasms	*7*	***7***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***
Nervous system events	*545*	***62***	***20***	***79***	***25***	***1***	***0***	***4***	***13***	***39***	***66***	***104***	***132***
Pregnancies, puerperium, and prenatal conditions	*13*	***10***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***3***	***0***
Psychiatric events	*196*	***44***	***21***	***13***	***13***	***1***	***0***	***0***	***2***	***38***	***46***	***9***	***9***
Kidney and urinary events	*27*	***7***	***4***	***0***	***0***	***0***	***0***	***0***	***0***	***8***	***8***	***0***	***0***
Reproductive system and mammary events	*53*	***3***	***1***	***0***	***0***	***1***	***0***	***0***	***0***	***28***	***20***	***0***	***0***
Respiratory, thoracic, and mediastinum events	*43*	***9***	***1***	***3***	***2***	***0***	***0***	***0***	***0***	***13***	***15***	***0***	***0***
Skin, subcutaneous, and tissue events	*412*	***18***	***1***	***82***	***7***	***2***	***1***	***6***	***1***	***37***	***20***	***170***	***67***
Social circumstances	*1*	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***1***	***0***	***0***
Surgical and medical procedures	*19*	***12***	***7***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***
Vascular events	*24*	***5***	***5***	***0***	***0***	***0***	***0***	***0***	***1***	***8***	***5***	***0***	***0***
Total	*2676*	*362*	*117*	*447*	*66*	*10*	*1*	*30*	*25*	*384*	*361*	*545*	*328*

*__HCP__ = Health care professional
__Non-HCP__ = Non health care professional

6.4. MAH's Analysis of Individual Case Histories

This section may be an essential part of the report or attached to it, and provides a narration of unlisted individual cases (serious and non-serious).

In addition to those, all fatal cases should be included. This section may also be applied for special interest cases.

Cases reported by health care professionals or medically confirmed cases from other sources should be described, including all relevant information, such as:

- Source and patient's demographic data;
- Medical and product history;
- Suspected medical product, dates of use and of reaction;
- Event progress and outcome;
- Laboratory evidence;
- If fatal, relevant details;
- Reexposure information, if applicable;
- Notifier evaluation;
- Medical evaluation and MAH comments on the case;
- Causality evaluation.

Example:

During this reporting period, three cardiac event fatal cases were notified (cases X, Y and Z – see line listing table). However, a causal relation with the product was not considered, because two patients presented previous history of coronary syndrome and diabetes mellitus, and the third one used a concomitant medication.
If a small quantity of reports does not justify the inclusion of a table, these may be described in this section.

7. Studies

Data from studies are available, in some companies, in the area responsible for Medical-Scientific or Clinical Research information.

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information during the reporting period should be included in a summarized text.

7.1. Newly analyzed company-sponsored studies

All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations.

Example:

In YYYY (year), a random Double blind study was conducted to evaluate the product safety and efficacy, and there was no evidence of safety finding. (Otherwise, findings should be detailed).

Or

Table 1 Concluded studies describing important safety information

Number of study	Short title	Number of patients	Safety findings
XX0000TT	**Open study in patients with kidney impairment**	**200**	**No dosage ajustment needed**

7.2. Targeted new safety studies planned, initiated or continuing during the reporting period

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies should be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PPR as described under 10.1.

Example:

Due to the great number of anemia cases identified in the previous PPR, a study to evaluate the product safety is in progress (Study ABC123). Up to the moment, 200 patients were included and there is no risk evidence associated to the product. (If there are no planned, initiated or ongoing studies, it should be informed)

Or

Table 7.2 New safety studies

Number of study	Short title	Number of patients	Safety findings	Number of study
ABC123	**Open study in cardiopathic patients**	**200**	**Under evaluation**	**-**

7.3. Published safety studies

Reports in the scientific and medical literature, e.g. *MEDLINE, EMBASE, LILACS, Cochrane*, containing important safety findings within the reporting period should be summarized and publication reference(s) given. For the purpose of inclusion in this item, the notifications should contain the same active substance and dosage form of the medical product commercialized by the MAH.

The medical-scientific publications containing safety information on the medicinal product at issue, which were published during the reporting period, should be included in this item.

Regarding the literature, the MAHs should monitor the standard medical and scientific periodicals, acknowledged as providing safety information on their medicinal products, and/ or use one or more literature search/ summary services to this end.

According to the quantity of studies, these may be described or listed as a table, following ABNT (Brazilian Association of Technical Standards) or Vancouver citation rules.

Example:

In accordance with X, Y e Z (names of authors), a relation between the use of medicinal product XX and the incidence of anemia was found in the population XXX. (If there are no publication with relevant findings, please inform..). (give reference)

8. Other information

8.1. Efficacy-Related Information

For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

Example:

Of all notifications, XX reports of suspected therapeutic ineffectiveness were identified, but there was no evidence...
or
After investigation carried out by the quality guarantee team, there was evidence that the batch had altered levels of the active substance...

8.2. Late-Breaking Information

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 12).

Example:

After this report data base was frozen, a notification was received on a serious ADR related to the product. (Inform preliminary details of the case and the initial causality evaluation).

8.3. Risk management

Summarize the Pharmacovigilance Plan or a Risk Minimization Plan, when applicable. The aim is to relate processes and methods that will be used as tools to minimize the identified risks and to measure their impact. Similarly, when there are updates, these plans should also be submitted concomitantly with the current PPR.

8.4. Benefit-risk analysis report

When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this Section.

Example:

The analysis carried out confirms that the Product® remains an effective and safe medicinal product to treat the indicated diseases, when administered as recommended. For this reason, no benefit-risk analysis was planned.
or
During the review period, cases of nephritis in diabetic patients were reported. Those patients took the medication used for the indication XXX, which may represent a risk for the population treated, indicating an unbalance in the benefit-risk relation. Thus, the following measures are in progress: (describe)

9. Overall Safety Evaluation

Describe how the most important cases were chosen to be discussed in previous sections.

Add an analysis and a conclusion regarding fatal cases, life-threatening cases, and other unlisted serious cases, as well as unlisted and listed serious cases; the occurrence or not of change in its frequency, nature, severity or any other characteristic of the safety profile.

Subdivisions may be created for areas of interest, such as System Organ Classes (SOC), sub-populations, dosage, and indications.

Concise analysis of the data collected during the reporting period, including late-breaking information.

Such data should contain any new information, addressing the following issues:

- Drug interactions;
- ADR from drug quality deviations;
- ADR from unapproved use of medicinal products;
- Drug intoxication, deliberate or accidental, and its treatment;
- Drug abuse or misuse;
- Positive or negative experiences during pregnancy or lactation;
- Experience in special patient groups (e.g., children, elderly, chronic);
- Effects of long-term treatment.

The significant lack of new information should be mentioned for each item previously described.

This section should present the MAH proposed measures to keep or reestablish the positive benefit-risk profile, including alterations on the information leaflet (this does not exempt the MAH from meeting other requirements).

Example:

Arrhythmias, interstitial nephritis and anemia were identified in the previous PPR for [name of product] as relevant safety findings requiring control.

Arrhythmia

Arrhythmias were reported during the review period of this report, in a total of 7 cases, 4 of them with an alternative explanation for the reported events. The cumulated number of arrhythmia reports (27, including 11 serious ones) is not worth of mention, considering the number of treated patients and the characteristics of the population in treatment...

Interstitial nephritis

XXXXXXXXX

Anemia

XXXXXXXXX

10. Conclusion

The relation between the findings in the studied population and the events observed in this period should be included in this item.

If the findings are listed or not, compared to the safety documents, it should be mentioned in this section, as well as the possible actions that were or will be taken, justifying them.

Indicate when the results of corrective actions will be observed in practice.

Example:

Three safety findings were identified in the previous PPR, as follows: interstitial nephritis, arrhythmia and anemia. Based on the data received during the reporting period, [name of product] keeps being monitored for future cases of interstitial nephritis. Arrhythmias are no longer considered a relevant finding, unless future reports require a reevaluation for this item. Anemia is subjected to special evaluation for all cases reported, and will be considered for inclusion in the DSRD.

No other safety finding was identified. The safety data are still in accordance with the accumulated previous experience and with the safety information presented in the DSRD.

According to the total number of ADR notifications received and the exposed patient estimate, this product is considered safe.

11. Reference

Include all references used to elaborate this report.

12. Appendix

The documents contained herein will be only those expected for this guide, which need additional clarification, guidance, or in order to improve the reading of this document, beyond the central sections. In order to facilitate the use of this appendix, section and paragraph numbers should correspond exactly to the number in the sections of the guide.

Example:

Annex 1 Core Data Sheet

Append to the last version of DSRD.

Annex 2 World-wide market authorization status

A table should be elaborated to present the accumulated information, as described in item 2. Details per country should be described in chronological order per regulatory submission.

Anexo 3 Line listings

Separate the line listings, which should be presented per source of report, as described in item 6.1.

Anexo 4 Summary tabulations (accumulated data)

Summary tabulations (accumulated data) should preferrably present terms in accordance with medical dictionaries for all notifications. Such data should be separated according to their source, i.e. clinical trials, spontaneous, requested, and literature, which were included in the database up to the lock point.

Example:

XX [number] unlisted serious spontaneous reports and XX [number] unlisted serious reports from clinical trials were received.

PART III: REFERENCES

1. Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs E2C(R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2005, 29 p. (acessado em 17/05/2009 em http://www.ich.org/LOB/media/MEDIA477.pdf)

2. EMEA – Volume 9A of The Rules governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Set, 2008

3. Good Pharmacovigilance Practice Guide. London: Pharmaceutical Press, 2009. 211 p.

3. Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. 2001.

4. PHARMACOVIGILANCE, 2 ed. Editores **RONALD D. MANN e ELIZABETH B. ANDREWS.** John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, 2007. 688 p.