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Retrospective Overview of the Requirements for Aggregate Reports in Pharmacovigilance

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Abstract

This article is an overview of the process of aggregate reporting in pharmacovigilance where the main characteristics of PSUR are presented. 2012 is a crucial moment of the safety reporting when some changes were made and which reflect the main point of the evaluation of the reports – from detailed line-listings of the adverse drug reactions to the cumulative summaries of the serious adverse events, mainly in clinical trials, and the main approach, which is the evaluation of the risk/benefit balance. This leads to discovering new indications of the drugs and a proposal for changes in Summary of Product Characteristics of the observed medications.

Key words: PSUR, PBRER, pharmacovigilance, risk/benefit evaluation

1. Introduction

1.1. Essentials

Periodic safety update reports (**PSURs**) are pharmacovigilance documents intended to **provide an evaluation of the risk-benefit balance** of a medicinal product for submission by marketing authorization holders (MAHs) in the light of **new or changing information at defined time points during the post-authorization phase**. The required format and content of

PSURs in the EU are based on those for the **Periodic Benefit Risk Evaluation Report (PBRER)** described in the ICH-E2C (R2) guideline. The PBRER replaces the PSUR format previously described in the ICH-E2C (R1). In the EU, the report shall be described and named as PSUR [IR Art 34 and 35].

1.2. Time

They are submitted regularly with periodicity established in Regulation (EC) No 726/2004 and Directive 2001/83/EC. Once marketed, 6-monthly PSUR submissions should be continued following initial placing on the market in the EU and until two full years of marketing experience in the EU has been gained. Then, PSURs should be submitted once a year for the following two years and thereafter at 3-yearly intervals (fig.1).

1.3 Where

They should be submitted to the **Competent Authorities** of all Member States (EU) and to **the Agency** if products are authorised through centralised procedure, or only to the **Competent Authorities** if they are authorised nationally.

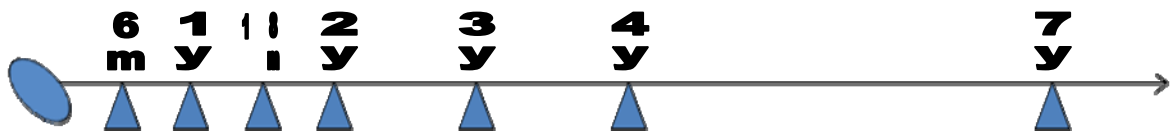


Figure 1. 6-monthly reports are no more required

2. Format and contents of the PSUR

The PSUR shall be **based on all available data** and shall **focus on new information** which has **emerged since the data lock point (DLP) of the last PSUR** (now amended). Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment.

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:

- non-clinical studies;
- spontaneous reports;
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilization information;
- clinical trials, including research in unauthorized indications or populations;
- observational studies, including registries;
- patient support programs;
- systematic reviews and meta-analysis;
- marketing authorization holders sponsored websites, including social media;

- published scientific literature or abstracts, including information presented at scientific meetings;
- unpublished manuscripts made available to the marketing authorization holder;
- licensing partners, other sponsors or academic institutions and research networks;
- competent authorities (worldwide) websites.

The above list is not intended to be all inclusive, and additional data sources may be used by the MAH in evaluation of the benefit-risk profile, as appropriate to the product and its known and emerging important benefits and risks.

When preparing the PSUR, the ICH-E2C (R2) guideline on PBRER should also be applied. When no relevant information is available for any of the sections, this should be stated.

Main sections include the sections shown in Tab.1.

Part I: Title page including signature	7. Summaries of significant findings from clinical trials during the reporting interval
Part II: Executive Summary	
Part III: Table of Contents	
1. Introduction	7.1. Completed clinical trials
2. Worldwide marketing authorization status	7.2. Ongoing clinical trials
3. Actions taken in the reporting interval for safety reasons	7.3. Long-term follow-up
4. Changes to reference safety information	7.4. Other therapeutic use of medicinal product
5. Estimated exposure and use patterns	7.5. New safety data related to fixed combination therapies
5.1. Cumulative subject exposure in clinical trials	8. Findings from non-interventional studies
5.2. Cumulative and interval patient exposure from marketing experience	9. Information from other clinical trials and sources
6. Data in summary tabulations	10. Non-clinical Data
6.1. Reference information	11. Literature
6.2. Cumulative summary tabulations of serious adverse events from clinical trials	12. Other periodic reports
6.3. Cumulative and interval summary tabulations from post-marketing data sources	13. Lack of efficacy in controlled clinical trials
	14. Late-breaking information
	15. Overview of signals: new, ongoing or closed
	16. Signal and risk evaluation

- 16.1. Summaries of safety concerns
- 16.2. Signal evaluation
- 16.3. Evaluation of risks and new information
- 16.4. Characterisation of risks
- 16.5. Effectiveness of risk minimization (if applicable)
- 17. Benefit evaluation
 - 17.1. Important baseline efficacy and effectiveness information

- 17.2. Newly identified information on efficacy and effectiveness
- 17.3. Characterisation of benefits
- 18. Integrated benefit-risk analysis for authorized indications
 - 18.1. Benefit-risk context – Medical need and important alternatives
 - 18.2. Benefit-risk analysis evaluation
- 19. Conclusions and actions
- 20. Appendices to the PSUR

Table 1.

3. Template for cover page for PSUR submission

PERIODIC SAFETY UPDATE REPORT			
for <div style="border: 1px solid red; border-radius: 50%; padding: 2px; display: inline-block;">ACTIVE SUBSTANCE(S): <INN> ATC CODE(S): <Code(s)></div>			
MEDICINAL PRODUCTS COVERED:			
Invented Name of the Medicinal Product(s)	Marketing Authorisation Number(s)	Date(s) of Authorisation <i>(Underline (Harmonised) EU Birth Date)</i>	Marketing Authorisation Holder
<>	<>	<>	<>
<>	<>	<>	<>
AUTHORISATION PROCEDURE in the EU: <Centralised/Mutual Recognition/Decentralised/Purely National> INTERNATIONAL BIRTH DATE (IBD): <Date> EUROPEAN UNION REFERENCE DATE (EURD): <Date>			
INTERVAL COVERED BY THIS REPORT: from <Date> to <Date (i.e. data lock point)> DATE OF THIS REPORT: <Date>			
OTHER INFORMATION: <Other identifying or clarifying information if necessary>			
MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS: <Name> <Address> <E-mail address> (contact person for the PSUR procedure)			
NAME AND CONTACT DETAILS OF THE QPPV: <Name> <Address> <Telephone number> <Fax number> <E-mail address>			
SIGNATURE (QPPV or designated person): <Signature>			
DISTRIBUTION LIST²¹			
<Competent Authority in the EU>		<Number of copies>	

Title and product

Products hold by MAH with the same INN

Type of authorisation procedure

Dates

Covered Interval

MAH

Qualified Person responsible for Pharmacovigilance

Figure 2. Cover page

4. General principles

❖ General scope – presentation, analysis and evaluation of new or changing safety data received during period covered by the PSUR. For this purpose, analysis of adverse reaction reports, an overview of cumulative data, safety data from studies and other relevant safety information, as well as follow-up of any Risk Management Plan should be adequately addressed in the PSUR.

❖ One PSUR – One MAH – All elements of the data for the product should be presented in **separate sections** and included in a **single PSUR**. It is recommended that information on all indications, dosage forms, routes of administration and regimens for a given active substance for medicinal products authorized to one Marketing Authorization Holder should be included in a single PSUR, with a single DLP common for all aspects of product use to facilitate a consistent, broad-based examination of the safety information for the active substance(s) in a single document. All elements of the data for the product should be presented in separate sections.

❖ Products authorized to more than one MAH – Where a product is authorized to more than one MAH, in the case of multiple applications, **submission of common PSURs is acceptable** provided that the products remain identical in all respects apart from their invented names and that the PSURs are submitted separately by each MAH. Each MAH remains responsible for the appropriate submission of PSURs for their products. The DLP should be based on the birth date used for the first authorized product. The submission cover letter should confirm that the data in these PSURs are identical.

❖ Frequency of Review and Reporting -

➤ Regular and Ad Hoc Submission of PSURs –

- Before initial placing on the EU Market:
 - Immediately upon request from a Competent Authority or the Agency;
 - At least every 6 months after authorisation (old).
- After initial placing on the EU Market:
 - 6-monthly PSUR submissions should be continued until 2 full years of marketing experience in the EU has been gained (old);
 - yearly PSURs for the following two years; and
 - thereafter PSURs should be submitted at 3-yearly intervals (amended);
 - in addition, PSURs should be submitted immediately upon request from a Competent Authority or, for centrally authorized products, from the Agency
 - the date of initial placing on the EU market is the date of launch, for the first time, in any Member State
 - Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP
 - When yearly or 3-yearly PSURs are due for submission, multiple 6-monthly or yearly PSURs are acceptable, provided that the MAH submits a PSUR Summary Bridging Report. It should be noted that in such cases, the MAH should not send 6-monthly or yearly PSURs 60 days after the DLPs of these 6-monthly or yearly PSURs, but should send them only at the required due date (yearly or 3-yearly) (amended).

- If a time gap occurs between the DLP of a regular PSUR and a request from a Competent Authority (e.g. renewal, Risk-Benefit Review, ad hoc PSUR request), a PSUR Addendum Report should also be submitted. For a PSUR that spans longer time intervals, e.g. 3 years, an Addendum Report would only be considered appropriate if the time since preparation of the 3-year PSUR and the locally required report is greater than 6 months (amended).

❖ Submission of Periodic Safety Update Reports for Renewal of Marketing Authorizations

– The MAH should **submit safety data** with the renewal application at least **6 months before the expiry date** of the marketing authorization in the EU and **lock the data** no more than **60 days before** submitting the PSUR. The DLP for submission of safety information should be at **4 years and 4 months** following the marketing authorization date. The MAH should submit the **PSUR**, or the PSUR plus PSUR Addendum Report and a **PSUR Summary Bridging Report**, bridging all PSURs covering the period of 4 years and 4 months. If the Competent Authority or the Agency concludes that an additional renewal is needed (**second** one), this conclusion may include a requirement for an **additional 6 months or 1 year** report. The second renewal application should discuss PSURs data covering a **5-year** period since the DLP of the PSUR(s) submitted with the first renewal application.

❖ Circumstances Where the Periodicity May Be Amended – Where an amendment is proposed, the **MAH** or Applicant should **submit**, as part of the application for a marketing authorization, a **reasoned request for the amendment**, which, if granted, **becomes part of the conditions of authorization**. Such application follows the procedures for a type II variation.

• Circumstances where less frequent submission of PSURs may be appropriate include:

- Products authorized through line-extensions to existing medicinal products;
- Newly authorized generic medicinal products.
- However, submission of PSURs at a lower frequency less than once every 3 year is not possible.

• Circumstances where more frequent PSUR submission may be required include:

- variations introducing new indications, populations, dosage forms and routes of administrations;
 - an active substance which is a different salt/ester or derivative (with the same therapeutic moiety);
 - the presence of an excipient without an established safety profile;
- and
- a Risk Management Plan (RMP) in place for a corresponding originator product requiring specific monitoring of a safety concern.

❖ Preparation of Periodic Safety Update Report according to the International Birth Dates –

- Medicinal products, which are also authorized **outside the EU**, will have an **International Birth Date (IBD)**.
- The IBD is the date of **first marketing authorization** of a medicinal product granted to the MAH **anywhere in the world**.
- For practical reasons, the IBD may be defined as the **last day of the month in which this first authorization date falls**.

- In order to harmonize PSUR submissions internationally, the MAH may use the **IBD to determine** the dates of the **DLPs** for the **PSUR submission schedule**, provided that the **first DLP falls within the 6 months following the EBD (European birth date)**.
- The **IBD and EBD can be harmonized (EU HBD)**. It is difficult but feasible process where the **MAH and Competent Authorities** may liaise and **designate an EU HBD** which may be the IBD.

❖ Reference Safety Information – an objective to a PSUR is to establish **whether information recorded during the reporting period is in accordance with previous knowledge of the medicinal product safety, and to indicate whether changes should be made to the Product Information or the Risk Management Plan**. Reference information is needed to carry out this comparison. It is common practice for MAHs to prepare their own Company Core Data Sheet (CCDS), which includes material relating to **safety, indications, dosing, pharmacology** and other information concerning the product. The safety information contained within the CCDS is referred to as Company Core Safety Information (CCSI).

❖ Presentation of Data on Individual Cases

(See fig. 3.)

Sources of Information

Generally, adverse reaction data from the following sources are potentially available to MAH and should be included in the PSUR: Adverse reaction reports notified directly to the Marketing Authorization Holder (or through schemes under its control):

- Spontaneous reports from Healthcare Professionals;
- Reports from MAH – sponsored studies or named-patient/compassionate use;
- Reports from Patients and other Consumers (not medically confirmed).
- Literature;
- Adverse reaction reports received from regulatory authorities worldwide:
- Spontaneous and non-spontaneous reports from Healthcare Professionals;
- Reports from Patients and other Consumers (not medically confirmed);
- Other sources of data including:
 - Exchange of reports on adverse reactions in the framework of contractual arrangements (e.g. licensors-licensees agreements)
 - Data from special registries;
 - Reports from poison control centres;
 - Epidemiological databases.

Description of the Adverse Reaction

The reaction terms used in the PSUR should be in accordance with the MedDRA terminology.

Line listings and/or Summary Tabulations

Depending on their type or source, available adverse reaction cases should be presented as line-listings and/or as summary tabulations. The transition from line-listings to cumulative summary is the most important change as it is mentioned further.

Presentation of individual case histories in the PSUR:

Source	Type of Case	Only Summary Tabulation	Line-Listing and Summary Tabulation
1. Direct Reports to MAH <ul style="list-style-type: none"> ▪ Spontaneous reporting* ▪ Post-authorisation safety studies and other studies ▪ Compassionate use programmes 	serious		yes
	non-serious unlisted		yes
	non-serious listed		yes**
	serious / attributable to drug by investigator or sponsor		yes
	serious		yes
2. Literature	serious		yes
	non-serious unlisted		yes
3. Other sources <ul style="list-style-type: none"> ▪ Regulatory authorities ▪ Contractual partners*** ▪ Registries ▪ Poison control centres ▪ Epidemiological databases 	serious		yes
	serious	yes	
	serious	yes	
	serious	yes	
	serious	yes	

*Medically unconfirmed reports should be provided as an annex to the PSUR as a line-listing
 **Line-listing should be provided as an annex to the PSUR
 ***For the purpose of this Table, the term contractual partners does not refer to persons and organisations to whom the MAH has transferred pharmacovigilance tasks and functions. Such persons and organisations are included in "Direct Reports to MAH"

Figure - 3

5. Model for a periodic safety updated report

➤ **PSUR section “Executive Summary”** – a brief overview of the PSUR which includes 1) MAH worldwide status; 2) information related to the covered period; 3) exposure data; 4) number of new cases reported and cumulative numbers; 5) other issues and safety concerns; 6) overall findings of the PSUR, and 7) conclusions.

➤ **PSUR section “Introduction”** – brief introduction of the product.

➤ **PSUR section “Worldwide Marketing Authorization Status”** – provides cumulative information. The following information should be provided, as a table, for all countries. 1) dates for marketing authorization and subsequent renewal; 2) any qualifications surrounding the authorization; 3) treatment indications and special populations covered by the authorization; 4) lack of approval, including explanation by the authorities; 5) dates of launch; 6) dates for withdrawal, revocation or suspension of the authorization; 7) invented name(s). If there are important differences for the same product in different countries, which would reflect different types of patient exposure, such information should be noted.

➤ **PSUR section “Update of Regulatory Authority or Marketing Authorization Holder Actions taken for Safety Reasons”** – actions relating to safety that were taken during the period covered by the PSUR and between DLP and PSUR submission: 1) marketing authorisation withdrawal, revocation or suspension; 2) failure to obtain a marketing authorisation renewal; 3) restrictions on distribution; 4) clinical trial suspension; 5) dosage modification; 6) changes in target population or indications; 7) formulation changes; 8) urgent safety restrictions.

➤ **PSUR section “Changes to Reference Safety Information”** – version of the CCDS with its CCSI. When meaningful differences exist between the CCSI and the EU/Member State’s Summary of Product Characteristics (SmPC), a brief comment should be prepared from the MAH to describe the local differences and their consequences on the overall safety evaluation.

➤ **PSUR section “Patient Exposure”** – Estimating patient exposure data for marketed medicinal products often relies on gross approximations of in-house or purchased sales data or volume to determine patient exposure. When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH may extrapolate using the available data.

➤ **PSUR section “Presentation of Individual Case Histories”** - This section should contain a description and analysis of selected cases containing new or relevant safety information and grouped preferably by medically relevant headings/MedDRA System Organ Classes (SOCs). If it is obtained subsequent information such a follow-up data for the individual cases, it should be submitted with the next PSUR.

- A) **“Cases Presented as Line-Listings”** –
 - All serious adverse reactions and non-serious unlisted adverse reactions from spontaneous reporting;
 - All serious adverse reactions (attributable to the medicinal product by either investigator or sponsor) available from post-authorization safety studies (PASS) and other studies (including those which are part of the Risk Management Plan) or named-patient/compassionate use;
 - All serious adverse reactions, and non-serious unlisted adverse reactions from the literature;
 - All serious adverse reactions transmitted to the MAH by worldwide regulatory authorities.
- ...in the form of an annex to the PSUR:
 - All non-serious listed adverse reactions from spontaneous reporting;
 - All serious and non-serious (listed and unlisted) adverse reactions reported by Patients/Consumers and other non-healthcare professionals (not medically confirmed).

- The following headings are also included in this section:
 - MAH case reference number
 - Country in which the case occurred
 - Source
 - Age and sex of the patient etc.

B) **“Cases Presented as Summary Tabulations”** – for each of the line-listings

C) **“Marketing Authorization Holder’s Analysis of Individual Case Histories”** – brief comments on the data concerning individual cases

➤ **PSUR section “Studies”** – all studies (non-clinical, clinical and epidemiological) yielding safety information (this includes lack of efficacy data) with a potential impact on product information, studies specifically planned, in progress and those published that addresses safety concerns should be included with a discussion of any interim or final results.

- A) **“Newly Analysed Studies”** – containing important safety information and newly analysed

- B) **“Targeted New Safety Studies”** – new studies specifically planned or conducted to examine a safety concern

- C) **“Published Studies”** – reports in the scientific and medical literature

- D) **“Other Studies”** – any relevant information from the data collected by pregnancy exposure registries and a discussion of the positive and negative experience

➤ **PSUR section “Other information”**

- A) **“Efficacy-related Information”** – products used in prevention or in treatment of serious or life-threatening diseases or products used in healthy Consumers medically relevant lack of efficacy reports, which may represent a significant hazard, should be described and explained

- B) **“Late-breaking Information”** – any important, new information received after the database was frozen for review and report preparation may be presented in here

- C) **“Risk Management Plan”**

- D) **“Risk-Benefit Analysis Report”**

➤ **PSUR section “Overall Safety Evaluation”** – MAH provides a concise analysis of the presented data

➤ **PSUR section “Conclusion”** – addresses the overall risk-benefit balance

Bridging and Addendum Reports are included in the Appendices

6. The essential changed of the new format PBRER

Historically, the aggregated reporting started in 1992 with CIOMS II guideline, then in 1996 followed Step 4 ICH E2C Guideline; in 2003 Step 4 Addendum to ICH E2C (R1) was published and the good pharmacovigilance practice (GPvP) guidelines came into effect in July 2012. The guidelines bring together a set of measures drawn up to facilitate the performance of Pharmacovigilance (PV) in the European Union (EU). The GPvP guidelines are divided into 16 modules, each covering a major process in PV. Module VII discusses changes to the format and

content of the PSUR.

A key aim of the PV legislation is to change the emphasis of the PSUR from a detailed presentation of individual case reports, to an evaluation of the risk benefit balance of a product. The major changes to the content of the PSUR are:

- **Risk evaluation:** signals (new, ongoing or closed), evaluation of risks and new information, and effectiveness of risk minimization activities.
- **Benefit evaluation:** important baseline efficacy/effectiveness, evaluation of efficacy/effectiveness and new information.
- **Integrated risk-benefit analysis**
- Measures that should help streamline the writing of safety documents

The detailed adverse drug reaction (ADR) line listings will be replaced by more concise cumulative summary tabulation of serious adverse events from clinical trials and cumulative and interval summary tabulations of ADRs, however they may be requested during the assessment. Case narratives will be provided where relevant to the scientific analysis of a signal or safety concern. Multiple six monthly, Bridging and Addendum reports will not be accepted.

There is no longer a requirement for detailed analyses of cases for special populations (e.g. pregnant/lactating women; organ-impaired patients; pediatric/elderly patients) unless being assessed as a potential risk.

PSUR GVP module (section B) is broadly aligned.

No PSURs for generic, well established, homeopathic and herbal products, Unless if a risk is identified or if there is a lack of information

EMA has generated a list of EU reference dates and frequency of submission, including products and substances for which PSURs are required. This list is displayed on the EMA web-portal and is updated monthly. Each MAH has the responsibility to check the web-portal for any updates.

The PSUR now has a modular format, which is intended to maximize efficiencies between different document types, since the same modules can be used in different documents. This is link to the gap and improvement analysis for E2E and E2F

- PSUR vs. Development Safety Update Report (E2F): These documents share a number of common sections – synchronization of submission schedules for these documents should facilitate the use of common text.
- PSUR vs. Risk Management Plan (RMP) (E2E): It is envisaged that certain PSUR and RMP sections will be used interchangeably across reports.
- ICH E2C R2 step 2 draft guideline has been drafted so that the content of some sections of the PSUR/PBRER could be identical to the corresponding sections of other documents. Thus, it is technically a new ICH guideline [ICH E2C (R2)] which ensures that the reports have the role of being periodic benefit risk evaluation reports.
- Allows sections or modules to be submitted at different times to multiple authorities across separate documents i.e. PSUR, DSUR and RMP.

- Maximizes utility and minimizes duplication

Time frames included:

- PBRER starts in Jan 2013 and the submission timelines have been amended
- PSURs up to 1 year – within 70 calendar days.
- PSUR longer than 1 year and ad hoc PSURs - within 90 calendar days.

7. Objectives of the new legislation – relevance to PSURs

Promote and protect public health by reducing burden of ADRs and optimizing the use of medicines. Other objectives are the clear roles and responsibilities; better evidence, more science based; better link between assessments and regulatory action; risk based/proportionate; reduced duplication/redundancy; integrate benefit and risk where appropriate; ensure robust and rapid EU decision-making; engage patients and healthcare professionals; increase transparency and accountability; provide better information on medicines; increased pro-activity/planning; proposal for changes in SmPC can be proposed in annexes, proposed product information; proposed additional PV and risk minimization activities; summary of ongoing safety concerns; reporting of results from post-authorization safety studies in PSURs; and effectiveness of risk minimization

8. Summary of the changes

PSURs shall contain:

- Summaries of ALL data relevant to benefits and risks, including results of all studies
- Scientific evaluation of the risk-benefit balance based on all available data, including data from clinical trials in unauthorized indications and populations
 - Estimation of population exposure based on all data of sales/prescriptions volume
 - No more line listings
 - But may be requested during assessment.
 - Summary tabulation still included (serious and non serious)
 - Case narratives to be provided where relevant to the scientific analysis of a signal or safety concern

Section 15 amendments - Overview of signals: new, ongoing, or closed

- significant difference in severity or frequency
- higher frequency or severity newly found in an indicated subpopulation
- an ongoing signal refers to a signal that was still under evaluation at the DLP
- Signal tabulation – brief description, date when MAH became aware, status at the end of the reporting interval (close or ongoing), date when the signal was closed, if applicable, source of the signal, brief summary of key data, plans for further evaluation and actions taken or

planned.

Section 16 - Signals and Risk evaluation. Details of assessment. Summary of safety concerns

- Important identified risks
- Important potential risks
- Missing information
- Evaluation of risks and new information
- Updated table – Update RMP (Risk management plan). New Important identified risks, new important potential risks, new non-important identified risks, new non-important potential risks and new missing information
 - Characterization of risks : same table in cumulative
 - Effectiveness of risk minimization (if applicable)
 - Summary of the effectiveness of risk minimization activities – Monitoring of RMP.

Flow chart of the mapping of signals & risks. Missing information could be an important risk

Section 17 – Benefit evaluation sections

- Baseline Efficacy and Effectiveness
- Newly Identified information on Efficacy and Effectiveness
- Characterization of Benefits
- Enough detailed

Section 18 – Benefit / Risk evaluation

Integrated Benefit/Risk Analysis for approved indications

- Only key risk and benefits
- Discuss strengths/weaknesses of evidence
- Used methodology: quantitative, qualitative
- Benefit-risk Context - Medical Need and Important Alternatives
- Benefit-risk Analysis Evaluation

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Authors Column



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