The Periodic Safety Update Report

Periodic Benefit-Risk Evaluation Report (PBRER)
ICH E2C (R2)

What is a Periodic Safety Update Report (PSUR)

- Pharmacovigilance documents providing safety update information and an evaluation of the risk-benefit balance of a vaccine.
- They shall be submitted by Marketing Authorisation Holders at defined time points during the post authorization phase.
- They are required according to the defined schedule whether they are being marketed or not.
- The schedule may be defined as part of conditions of registration or according to EU reference dates for listed products.
- The format of PSUR submissions is as defined in ICH E2C (R2).

What is the main objective of a PSUR?

- To present a comprehensive and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information in a cumulative risk benefit analysis.
- This should be undertaken the context of ongoing pharmacovigilance and risk management plan.

PSUR vs PBRER

- European Union (EU) – Guideline on good pharmacovigilance practices (GVP) Module VII - Periodic Safety Update Reports (Revision 1)
  - Defines scope, objectives, format and content of the PSUR
  - Format and content are based on ICH-E2C(R2) Guideline on Periodic Benefit Risk Evaluation Reports (PBRER)
Some important definitions

- **International Birth Date (IBD)**
  - The date of the first marketing approval of a medicinal product anywhere in the world (not always known)

- **Data Lock Point (DLP)**
  - Is the cut off date for data to be included in a PSUR

When are PSURs required?

- Once a product is registered PSURs are required at defined periods (even if the product is not on the market)

- One PSUR may cover global markets, all dosage forms and formulations for the same active substance

- For combination of substances which are also registered individually a PSUR may be prepared separately for the combination or as a separate report for the single substance depending on circumstances.

Frequency of PSURs is country specific

Typical PSUR requirements are:

- Immediately upon request
- Every 6m after Marketing Authorisation
- Every 6m for the first 2 years on the market
- Annually for subsequent 2 years
- Thereafter at 3 yearly intervals
- OR AS DEFINED BY EU LIST
List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

<table>
<thead>
<tr>
<th>Active substances and combinations of active substances</th>
<th>European Union reference date (EUR)</th>
<th>PSUR Submission Frequency</th>
<th>SLP Submission date (According to the timelines defined in CHMP/361/2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine (H1N1): split, intr., recombinant</td>
<td>28/02/2009</td>
<td>1 year</td>
<td>29/02/2015</td>
</tr>
<tr>
<td>Influenza vaccine (H1N1): whole, intr., inactivated</td>
<td>4/03/2009</td>
<td>1 year</td>
<td>29/03/2016</td>
</tr>
<tr>
<td>Influenza vaccine (H1N1): whole, intr., inactivated, grown in egg, label-injured</td>
<td>29/01/2011</td>
<td>6 months</td>
<td>24/02/2015</td>
</tr>
<tr>
<td>Influenza vaccine (H1N1): whole, live (inactivated)</td>
<td>24/01/2014</td>
<td>6 months</td>
<td>18/03/2015</td>
</tr>
<tr>
<td>Human papillomavirus 3-valent vaccine (recombinant)</td>
<td>28/08/2007</td>
<td>1 year</td>
<td>17/11/2014</td>
</tr>
<tr>
<td>Human papillomavirus 4-valent vaccine (recombinant)</td>
<td>28/08/2009</td>
<td>1 year</td>
<td>21/11/2014</td>
</tr>
</tbody>
</table>

The relationship with the Risk Management Plan

- When both a PSUR and RMP are required they should be updated and submitted together.
- The Marketing Authorization Holder needs to consider if identified risk in the PSUR requires that the RMP be updated...

An example of an updated the Global Risk Management Plan

- CSL committed to conducting or supporting prospective observational studies following 2010 febrile reactions in children
- To accurately capture the season data in a timely manner, the following data lock points were implemented:
  - August to 31 January (covering the majority of the NH season)
  - February to 30 April (covering early SH season)
  - February to 31 July (covering the majority of the SH season)
  - August to 31 October (covering early NH season)

Sources of information for the PSUR

- Direct Reports to the MAH
  - Spontaneous notifications from health-case professionals
  - Spontaneous notifications from consumers/patient
- Literature-all sources
- AEFI reporting Systems of Regulatory Authorities
  - Spontaneous and non-spontaneous
- Other Sources of data
  - National Immunization Programs including data from other companies
  - Post marketing studies conducted by Health Authorities
  - Data in special registries
Periodic Benefit-Risk Evaluation Report (PBRER) …

- The three ICH regions have adopted the ICHE2C(R2) Guideline Periodic Benefit Risk Evaluation Report (PBRER Guideline)
- Australia has adopted this guideline
- Preparation of PSURs follow the structure set out in the PBRER Guideline
- Is a useful guideline broadly applicable to other countries
- Links PSURs with Risk Assessments and simplifies reporting requirements
  - Line listings for AEFI no longer required

A PSUR submission should consist of

- Covering Letter
  - Summary of the submission being made covering Product License Number, Product name and PSUR reporting period
- Application form
  - Product license number  Period of PSUR, Contact person
- PSUR. Should be in Adobe pdf format and no more than 20MB

Executive Summary

- Reporting interval
- Product-mode of action/therapeutic class/indication/ doses/routes of administration
- Estimated subject exposure from clinical trials and post approval
- Countries where the product is approved
- Summary of overall Risk/Benefit
- Actions taken for safety reasons

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1. Introduction
2. Worldwide Marketing Approval Status
3. Actions taken in the Reporting Interval for Safety reasons
4. Changes to Reference Safety information
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8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-Clinical Data
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10. Literature
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12. Late Breaking information
13. Overview of signals, New, Ongoing, Closed
14. Signal and Risk Evaluation
15. Benefit evaluation
16. Integrated Benefit-Risk Analysis for Authorized Indications
17. Conclusions
18. Appendices to PSUR

PSUR timelines are country specific

- China:
  - Annually for first 5 years
- India:
  - Every 6 months for the first 2 years then annually...
  - Applicable to new drugs until 4 years after launch
- Singapore: every 6 months for first 2 years
- Malaysia:
  - 6 monthly for 2 years then yearly for next 3 years.
  - Thereafter as required by authority
- Indonesia:
  - Currently no requirement.***

Snap Quiz

Which statements are true and which are false?

A Periodic Safety Update Report

- captures all data on AEs, is submitted to the regulator and is approved by General Manager
- is prepared by the department responsible for Pharmacovigilance/Safety and approved by that department
- is a comprehensive summary of serious adverse events, investigations completed and actions taken
- is independent of prescribing information and labelling
- is the sole means of communicating adverse events to regulatory authorities