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.

  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133157.pdf
- 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)

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)**

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

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 European Union reference dates and frequency of submission of periodic safety update reports (PSURs)

Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the	PSUR Submission Frequency	DLP	Submission date (According to the timelines defined in GVP Module VII, Section A)
BCG vaccine (freeze-dried)	Not Available*	5 years	2/03/2018	31/05/2018
cholera vaccine (inactivated, oral)	28/04/2004	3 years	28/04/2017	27/07/2017
diphtheria / tetanus / pertussis (acellular, component) / haemophilus type b conjugate vaccine (adsorbed)	16/10/1996	5 years	15/10/2017	13/01/2018
diphtheria / tetanus / pertussis (acellular, component) / hepatitis B (rDNA) / poliomyelitis (inactivated) / haemophilus type b conjugate vaccine (adsorbed)	15/02/2016	6 months	15/08/2016	24/10/2016
diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) / haemophilus type b conjugate vaccine (adsorbed)	14/11/1997	3 years	13/11/2017	11/02/2018

List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the consultation phas	PSUR Submission Frequency	DLP	Submission date (According to the timelines defined in GVP Module VII, Section A)
influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted)	20/05/2008	1 year	29/09/2015	8/12/2015
influenza vaccine (H1N1)v (whole virion, inactivated, prepared in cell culture)	4/03/2009	1 year	31/10/2016	9/01/2017
influenza vaccine (intranasal, live attenuated)	27/01/2011	6 months	16/12/2015	24/02/2016
human papillomavirus 9-valent vaccine (recombinant, adsorbed)	10/12/2014	6 months	10/12/2015	18/02/2016
human papillomavirus vaccine (rDNA) - 2-valent	20/09/2007	1 year	17/11/2015	26/01/2016
human papillomavirus vaccine (rDNA) - 4-valent	20/09/2006	1 year	31/05/2016	9/08/2016

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 professsionals
  - MAH sponsoroed clinIcal studies or named patient use
  - 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 simpifies reporting requirements
  - Line listings fo AEFI no longert 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 traisl and post approval
- Countries where the product is approved
- Summary of overall Risk/Benefit
- Actions taken for safety reasons

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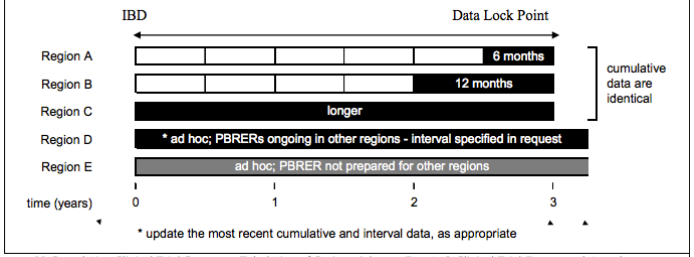
PSUR timelines are country specific

Figure 1: Submission of PBRERs Based on the Same Data Lock Point, with Various Reporting Periods.

Shading indicates period of interval data.
For all reports, the cumulative data reflect all data from the IBD/DIBD**.



** Cumulative Clinical Trial Summary Tabulation of Serious Adverse Events & Clinical Trial Exposure data only

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