

CLINICAL AND NON-CLINICAL SAFETY UPDATED DATA MANAGEMENT FOR MEDICINAL AND BIOLOGICAL PRODUCTS

A Case Study By B.Dinesh, India

(PG Diploma in Rehabilitation, M.Sc in Clinical Research Student of Texila American University)

Email:- dr.dineshmha@yahoo.com

INTRODUCTION

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a VMP to Competent Authorities at defined time points post-authorisation. At these times, MAHs are expected to provide succinct summary information on all adverse events together with a critical evaluation of the benefit-risk balance of the VMP in the light of any new or changing pharmacovigilance information.

This evaluation is necessary to ascertain whether further investigations need to be carried out and/or whether changes should be made to the SPC or other product information.

For VMPs:

- purely nationally authorized;
- authorized within the scope of Directive 87/22/EEC (ex-concentration procedure);
- that have benefited from the MRP or the DCP in accordance with Directive 2001/82/EC;
- that have been subject to referrals considered under Articles 36, 37 and 38 of Directive 2001/82/EC,

PSURs should be submitted to DGV in accordance with point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October.

The requirement for the submission of a PSUR applies irrespective of whether the VMP is marketed or not.

KEYWORDS

PSUR, Investigation, Report, Safety Signal, Events, DGV

ARTICLE SUMMARY

A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorization. At these times, marketing authorization (MA) holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information.

This evaluation should ascertain whether further investigations need to be carried out and whether changing information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorization and product information. PSURs must be submitted for all registered products regardless of marketing status. A single report may cover all products containing the same active substance(s) licensed by one MA holder.

The report will usually include all dosage forms and formulations, as well as all indications, associated with such an active. Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided. For combinations of substances which are also registered individually, safety information for the fixed combination may be reported either in a separate PSUR or be included as a separate presentation in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is essential

ARTICLE STRUCTURE

The periodic safety update report for marketed drugs (PSUR) was designed to be a stand-alone document that allows a periodic but comprehensive assessment of the worldwide safety data of a marketed drug or biological product. The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit-risk profile, an effective means of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism monitoring the effectiveness of such initiatives. For these reasons, the PSUR can be an important pharmacovigilance tool.

Numerous steps are involved in the PSUR process including: intake of adverse drug reaction information, case processing, data retrieval, data analysis, and medical review and risk assessment. These processes are heavily reliant on the availability of adequate resources. An overarching principle throughout the PSUR process is the need for a proactive approach in order to identify the critical steps in the process and to have a clear understanding of the consequences of any critical 'mis-step'.

With this information comes appropriate planning, building quality into each step of the PSUR process and monitoring performance will maximize the likelihood of generating a quality report. Any failure of a key PSUR process will have the opposite effect - a poor quality report that will give little insight into emerging safety signals or provide misleading information that can adversely affect public health. A pragmatic approach that will avoid or minimize these pitfalls includes the following: adequate resource planning, training, development of 'scripts' designed to maximize the capture of key information for

medically important reactions, standardized and harmonized Medical Dictionary for Regulatory Activities (MedDRA) coding procedures, pre-specified search criteria for data retrieval, ongoing medical review, and metrics to evaluate the effectiveness and efficiencies of these processes. With these quality measures in place, the utility of the PSUR as an effective pharmacovigilance tool is enhanced.

GENERAL PRINCIPLES

GENERAL SCOPE OF INFORMATION

MAHs must include in the PSURs of all VMPs, details of all adverse events arising in the EEA and in a third country. The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR, providing a basis for conclusion whether further investigations or changes in the SPC will be necessary. For this purpose the PSUR should include information on the following types of adverse event reports/case histories received during the period of review:

- All adverse events in animals and in human beings, sent spontaneously to the MAH and occurring in the EEA and in a third country, including information from literature.
- All adverse events forwarded to the MAH by an NCA;
- Any suspected transmission of an infectious agent via a VMP;
- Serious and non-serious adverse event reports from post-authorization safety studies;
- Any available information on investigation of the validity of a withdrawal period or any potential environmental problems, caused by the product under the normal conditions of use;
- Any available information on investigation of adverse events related to off-label use;
- Any available information on lack of expected efficacy, as specifically for VMPs used in the treatment of life-threatening conditions and for certain other VMPs, e.g. antibiotics or vaccines, lack of expected efficacy may represent a significant hazard and in that sense may give rise to a safety concern;
- Any data from previously requested close monitoring.

FREQUENCY AND TIMING OF PERIODIC SAFETY UPDATE REPORTS

SUBMISSION OF PSURS

The periodicity for submission of PSURs is established in point 2 of Article 110.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, from 28th October. Unless other requirements have been laid down as a condition of the granting of the MA, a PSUR should be prepared immediately upon request or at least every six months after authorization until the placing on the market. Following the initial placing on the market, PSURs shall be submitted

Immediately upon request, or at the following intervals:

- 6-monthly for the first 2 years
- Annually for the subsequent 2 years, and
- Thereafter, at three-yearly intervals.

For products authorized through the MRP or DCP, the PSUR submission schedule should be agreed on and be the same for all involved NCAs. The PSUR cycle should be based on the EU Birth Date (EBD, date of the first marketing authorization within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorization for the product granted to the MAH in any country in the world), or the EU HBD (EU Harmonized Birth Date for VMPs included in the work sharing initiative on PSUR assessments, provided it is not against National Legislation).

Once a VMP is authorized in the EU, even if it is not marketed, the MAH is required to submit PSURs at 6-monthly intervals, until initial placing of the VMP on the market. When launch dates are planned, this information should be reflected in the forthcoming PSUR. The PSUR covering this period during which the product is launched is considered the last of the six-month PSURs to be submitted before 'initial placing on the EEA market'.

After this initial placing of the product on the EEA market, the MAH should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the product on the EEA market are covered through provision of 6-monthly PSURs, while keeping the DLP according to the EBD, EU HBD or IBD.

PSUR REPORTING PERIOD

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP. Gaps are not allowed. Overlapping should be avoided. DLPs should be set according to the EU Birth Date (EBD, date of the first marketing authorization within the European Union) of a VMP or its International Birth Date (IBD, date of the first marketing authorization for the

product granted to the MAH in any country in the world), or the EU HBD (EU Harmonized Birth Date for VMPs included in the work sharing initiative on PSUR assessments).

PREPARATION OF PSURS ACCORDING TO THE INTERNATIONAL BIRTH DATE

VMPs, which are also authorized outside the EU, will have an IBD. This is the date of the first marketing authorization for the product granted to the MAH in any country in the world. For VMPs first authorized in the EU, the EBD is the IBD. For administrative convenience, if desired by the MAH, the IBD may be designated as the last day of the same month.

In order to harmonize PSURs internationally, the MAH may use the IBD to determine the DLPs in the EEA rather than the EBD. If the IBD is used, the first DLP must be within 6 months of the EBD, unless other requirements have been laid down at the time of granting the MA. Regardless of whether the IBD or EBD is used, the PSUR should be submitted within the 60 days following the DLP, taking into account that the date of submission of the PSUR is in compliance with the stipulated submission schedule

For purely nationally authorized VMPs that are marketed, the MAH may wish to synchronize national birth dates with the IBD. Such a step may be feasible and should be discussed with DGV. For nationally authorized VMPs, including those authorized through the MRP or DCP, where national birth dates are used to determine the submissions of PSURs, the MAHs and NCAs voluntarily may agree on an EU HBD which may be the IBD.

Thus the first PSUR to be submitted in the EU should be based on the EU HBD and should cover a period in accordance with the life cycle of the VMP in the EU (6 months, 1 year or 3 years). When PSURs have previously been submitted in MS based on different national birth dates, DGV accept that there may be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD

CONTENT OF PERIODIC SAFETY UPDATE REPORTS – MARKETED PRODUCTS

For marketed VMPs, the PSUR should fulfil the following format and content: MAH and product details. Each PSUR should include:

- i) The VMP name(s)
- ii) The name of the MAH
- iii) The MA number(s)

- iv) Procedure number, if applicable
- v) EBD / Start date for PSUR-submission cycle
- vi) The period covered by the PSUR
- vii) The date of initial placing of the product on the EEA market, understood as the date when the first presentation of the product was first placed on the market in any MS.
- viii) Chronological order of PSUR (e.g. 1st 6 month PSUR after initial placing on the market)

UPDATE ON REGULATORY OR MAH ACTIONS TAKEN FOR SAFETY REASONS

An overview of regulatory and MAH actions taken for safety reasons (e.g. follow-up measures, specific obligations and variations) since the last period covered in the PSUR indicating scope, status and date should be given. Significant changes in the wording of the SPC should be explained, where of relevance to safety.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The latest version of the relevant SPC must be included for reference in the report. It is recommended that when the SPC changed significantly in matters relevant to safety during the covered period, the nature of the change(s) should be succinctly explained in 5 the PSUR. If evaluation of safety data leads to any proposed changes in the SPC, these should be described, see Part I Section 3.1.9.

- For VMPs authorized through MRP or DCP, this will be the mutually accepted SPC in English.
- For nationally authorized VMPs, the specific national SPC in Portuguese language should be included.

If no SPC is available, e.g. in cases of old non-reviewed/renewed VMPs, an explanation should be given and the package leaflet should be provided. It is preferable that the SPC(s) are included in an annex.

ESTIMATIONS OF EXPOSURE

SALES VOLUME

Each PSUR should contain the number of doses/amount of VMP sold within the reporting period in the relevant Member State(s) and third countries, if applicable. The sales information should be expressed per presentation in an appropriate form. The following forms are suggested:

- Vaccines- to be expressed in numbers of doses;
- Liquid- to be expressed in litres;
- Powder- to be expressed in kilograms;
- Tablets- to be expressed in numbers of tablets;
- Sprays- to be expressed in litres or kilograms;
- Flea collars- to be expressed in numbers of collars;
- Paste- to be expressed in kilograms
- Pipettes for spot-on solution - to be expressed in numbers of pipettes.

INCIDENCE OF ADVERSE EVENTS

A PSUR must address the relationship between the sales volume of a VMP and the numbers of adverse events reported. An overall incidence should be calculated for all spontaneous adverse reactions (A, B, O, including O1) that occur after recommended or non-recommended (off-label) use in the target species. For clarity, adverse reactions from post-authorization safety studies should be excluded. In this respect the use of a VMP in non-authorized species under specific conditions laid down in Article 78.º of Decreto-Lei n.º 148/2008, from 29th July, as amended by Decreto-Lei n.º 314/2009, is regarded as off-label use. In addition, an incidence for lack of efficacy in target species after recommended use should be calculated, when relevant.

When a VMPs is indicated for more than one target animal species, it is suggested that in addition to the ratio of all animals expressing an event the ratio be computed for each species based on the estimated conditions of use of the VMP (sales/species) (see 3.1.4). This information is of importance to NCAs although the arbitrary nature of such calculation based on assumptions is recognized. For the calculation of incidence of adverse reactions it is suggested that MAHs adopt the following two-tier approach:

CALCULATION 1 – RATIO OF ANIMALS EXPRESSING AN ADVERSE EVENT

In the first instance, the ratio of the number of animals expressing an adverse event (reports assigned a causality code of A, B, O, including O1, N) during a period to the amount of VMP sold during that period should be computed:

No of animals with adverse event during period

Ratio of animals with adverse event = No of doses sold during the period

This calculation is based on data that tends to be accurate and can be used reliably to monitor trends from one PSUR to the next. Any increase in this ratio relative to previous PSURs may signal a problem and the need for more detailed evaluation of the pharmacovigilance data.

CALCULATION 2 – INCIDENCE

The incidence (%) of adverse reactions (reports of adverse events assigned a causality code of A, B or O, including O1) should be calculated by dividing the total number of animals reacting during the period by an estimate of the number of animals treated during the period of the report and multiplying by 100.

No of animals reacting during period (coded A, B or O and O1) x 100 % Incidence = Estimated No of animals treated during the period

For VMPs authorized in multiple MS, incidence should be calculated individually for each MS where sales have occurred. This calculation may then be revised to exclude O and O1 coded reports (that is, this calculation would focus on A-probable - and B-possible -coded reports only).

The values included in the calculation of incidence must be justified.

It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the VMP. All assumptions used for calculation should explicitly be stated. Overall incidences are calculated for the EEA in total, regardless of the route of authorization of the VMP

DATA REVIEW

The report should include a data review based on the MAHs analysis (including causality assessment) of the individual adverse events reported during the period concerned by the PSUR. The analysis of the adverse events reported should be supported by tables or tabulations summarizing the main findings. It may be helpful, especially for PSURs which contain a large number of adverse events, to introduce summary tabulations and prepare separate tables e.g. for serious expected reactions, serious unexpected

reactions, non-serious unlisted reactions (not mentioned in the SPC), or on basis of VEDDRA categories on organ level (e.g. System Organ Class (SOC) or Preferred Term (PT) level).

The data review should be structured as follows:

- Adverse events in target species, including events of lack of efficacy and those events occurring after off-label use in target species;
- Adverse events reported in humans;
- Other pharmacovigilance fields:
- Adverse events after use in non-target species;
- Investigations of the validity of the withdrawal period;
- Transmission of any infectious agent via a veterinary medicinal product;
- Potential environmental problems arising from the use of the VMP.

NON-SPONTANEOUS REPORTS

A narrative overview of available data from other sources (e.g. post-authorisation safety studies, published adverse event reports, user experience studies) should be included in this section. The data should be analysed and discussed as part of the benefit-risk assessment. The overview should include a review of all adverse event reports eligible for expedited reporting that were received during the PSUR period from post-authorisation safety studies. Summaries from post-authorisation safety studies should be included once final results become available, and should consider all adverse events reported from the study

OBJECTIVITY:

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of authorisation status information for initial and renewal applications, and data on serious, unlisted adverse reactions. These should be provided for both the period in question and as cumulative summary tabulations starting from the International Birth Date (IBD).

The main focus of the report should be adverse reactions. Unless indicated otherwise by the reporting health-care professional, all adverse experiences reported spontaneously should be considered adverse reactions; for clinical study and literature cases, only those judged not related to the medicinal product by both the reporter and the MA holder should be excluded. The PSUR should include a scientific evaluation of the risk: benefit balance of the product(s), and should be generated according to the ICH E2C guidelines.

CONCLUSION

Any failure of a key PSUR process will have the opposite effect - a poor quality report that will give little insight into emerging safety signals or provide misleading information that can adversely affect public health. A pragmatic approach that will avoid or minimise these pitfalls includes the following: adequate resource planning, training, development of 'scripts' designed to maximize the capture of key information for medically important reactions, standardized and harmonized Medical Dictionary for Regulatory Activities (MedDRA) coding procedures, pre-specified search criteria for data retrieval, ongoing medical review, and metrics to evaluate the effectiveness and efficiencies of these processes. With these quality measures in place, the utility of the PSUR as an effective pharmacovigilance tool is enhanced

REFERENCES

1. Holm, G., Snape, J R., Murray-Smith, R., Talbot, J., Taylor.D., & Sörme. P.,(2013). Implementing Ecopharmacovigilance in Practice: Challenges and Potential Opportunities. *Drug Safety*, 36(7): 533–546. [doi: 10.1007/s40264-013-0049-3,available from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691479/>, accessed March 25, 2014]
2. Hoffmann, E., Fouretier, A., Vergne, C., et al. (2012). "Pharmacovigilance Regulatory Requirements in Latin America". *Pharm Med* 26 (3): 153–164.doi:10.1007/bf03262389.
3. Ruhoy, I.S., & Daughton, C.G., (2008). Beyond the medicine cabinet: An analysis of where and why medications accumulate. *Environment International*, 34 (8): 1157-1169.
4. Lindquist, M., & Vigibase, (2008). The WHO Global ICSR Database System: Basic Facts. *Drug Information Journal*, 42:409-419.
5. Herper, M., (2012). Why Big Pharma Won't Get Its Piece Of The \$1.2 Trillion Global Drug Market. Available from <http://www.forbes.com/sites/matthewherper/2012/07/12/the-global-drug-market-will-swell-to-1-2-trillion-while-big-pharma-treads-water/>, accessed March 28, 2014.
6. Rahman, S.Z., Khan, R.A., Gupta, V., Misbah Uddin, (2008). "Pharmacoenvironmentology – Ahead of Pharmacovigilance". In Rahman, S.Z., Shahid, M., & Gupta, A., *An Introduction to Environmental Pharmacology* (1st ed.). Aligarh: *Ibn Sina Academy*. pp. 35–52.
7. Rahman., S.Z., Khan, R.A., (2006). "Environmental pharmacology: A new discipline". *Indian J Pharmacol*. 38 (4): 229–30. doi:10.4103/0253-7613.27017.

8. Rahman, S.Z., Khan, R.A., Gupta, V., Uddin & Misbah, (2007). "Pharmacoenvironmentology – A Component of Pharmacovigilance". *Environmental Health* 6 (20). doi:10.1186/1476-069X-6-20. PMC 1947975. PMID 17650313.
9. Rahman, S.Z., & Singhal, K.C., (2002). Problems in pharmacovigilance of medicinal products of herbal origin and means to minimize them, Uppsala Reports, WHO Collaborating Center for ADR monitoring, *Uppsala Monitoring Centre*, Sweden, Issue 17: 1-4 (Supplement)
10. Sackman, J.E., (2013). Navigating Emerging Markets -Latin America: Latin America's diverse growing market seeks regulatory harmonization. *BioPharm International* 26(4), 60-63.
11. Sara Gambrill, (2011). China's Pharmacovigilance System: The Hunger For Safety Insights, *Clinical Leader*,
12. Retrieved _____ from http://www.paho.org/hq/index.php?option=com_content&view=category&layout=blog&id=1156&Itemid=513, accessed March 28, 2014.
13. <http://ireminder.com/products/medtrigger>
14. <http://se-fc.org/gestor/farmacovigilancia/generalidades.html>
15. http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf
16. <http://www.cdsc.nic.in>
17. <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm>
18. <http://www.ipc.gov.in>
19. <http://www.pv.pharmacyboardkenya.org>
20. www.pv.pharmacyboardkenya.org
21. <http://www.who-umc.org/DynPage.aspx?id=13140&mn=1514>, accessed 10 February 2009.
22. <https://www.swissmedic.ch/bewilligungen/00155/00242/00327/00345/index.html?lang=en>, accessed March 28, 2014.