TCP Transl Clin Pharmacol
2016;24(2):63-65
http://dx.doi.org/10.12793/tcp.2016.24.2.63

EDITORIAL

Problems within the post-marketing surveillance system in Korea: Time for a change

Hyoyoung Song and Dong-Seok Yim*
Department of Clinical Pharmacology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Korea
*Correspondence: D. S. Yim; Tel: +82-2-2258-7327, Fax: +82-2-2258-7885, E-mail: yimds@catholic.ac.kr

Keywords
Post-Authorization Safety Study, Post-Marketing Surveillance, Korea

pISSN: 2289-0882
eISSN: 2383-5427

Post-marketing safety studies are an important tool for understanding and monitoring the safety profiles of drugs in the clinical setting. Their importance has attracted not only the attention of regulators for reinforcing legislation but also led to recent changes in European Union (EU) regulations; these regulations have influenced the practice of Post-Authorization Safety Study (PASS) by marketing authorization holders. Korea conducts post-marketing surveillance (PMS) studies, but their execution is very different. This editorial reviews the PMS system in Korea in comparison with the recent legislative changes affecting the EU system. Ultimately, it suggests that changes to the PMS system are necessary to obtain quality safety data while maintaining a global standard of operation. Such efforts to refine the system will enhance the credibility of the PMS in Korea and, in due course, produce safety profiles that will be valuable for public health.

Pharmacovigilance seeks to minimize the risk related to drugs and maximize their benefit by monitoring drug safety during clinical trials and in real practice settings. Due to limitations of the clinical trial setting, such as the limited sample size and controlled conditions of drug use, further monitoring of drugs after market authorization is necessary for a comprehensive understanding of their safety.[1] Therefore, thorough knowledge of safety profile requires a structured system of safety monitoring in the market and rationalized regulations.

Recently, public concerns raised following the withdrawal of high-profile drugs and an increase in the amount of data to be handled through diverse sources have driven regulatory authorities to reinforce and streamline pharmacovigilance systems. For example, the European Medicines Agency (EMA) has made major legislative changes regarding safety monitoring since 2012. As a result, the focus of profiling drug safety has shifted from pre-authorization to post-authorization.[2] Consequently, the EMA has strengthened its Post-Authorization Safety Studies (PASS) system to acquire detailed information. To rationalize decision making, the Pharmacovigilance and Risk Assessment Committee (PRAC) was established through an amended EMA regulation. The PRAC is composed of pharmacovigilance experts and representative stakeholders, such as doctors and patients. The PRAC evaluates PASS protocols and results, and the findings are published in the EU portal for transparency.[1] Such actions to improve the post-marketing safety of approved medicinal products affect health care professionals and pharmaceutical companies.

Similarly, Korea has a post-marketing surveillance (PMS) system, which conducts post-marketing surveillance of new drugs under the regulations of the re-examination system. It was established by the Ministry of Food and Drug Safety (MFDS) of Korea in 1995, emulating the Japanese PMS system. The PMS system has made it mandatory for marketing authorization holders (MAH; *i.e.*, pharmaceutical companies) to conduct post-marketing studies if they wish to retain their licenses for new drugs or vaccines in Korea.[3] The PMS system in Korea aims to parallel the EMA PASS system to determine safety profiles in clinical settings to protect public health. However, many stakeholders are concerned that the Korean PMS system has failed to accomplish its objectives in real-world situations and has sometimes been misused, which might have had detrimental effects on public health rather than protected it.

Before legislative change in PMS on Oct 30 2015, the sample size had been predefined as either ≥ 600 or ≥ 3,000 based on certain criteria of the PMS guideline. After the amendment in legislation, the predefined sample size (≥ 600 or ≥ 3,000) is applied unless MAH provides reasonable evidence on change to it.[4] Because the figures of 600 or 3,000 are not based on the

statistical calculation, they cannot provide statistical power for every licensed products. To collect data enough to provide meaningful conclusions, the sample size should be determined based on the anticipated rate of a certain risk, product characteristics, patient pool in the market, *etc*. Furthermore, the methodology of data collection is not clarified in the Korean PMS guideline and there are no other comprehensive regulations or standards to collect high quality data from PMS to avert biases. Thus, scientifically-sound interpretation of PMS results has been virtually impossible under the current system. Furthermore, the regulators have not provided proper oversight for the operation of PMS studies; the studies are not controlled under good standards of operation, such as Good Clinical Practice (GCP) in Korea. Consequently, the integrity of the data and ethical practices within the PMS are not ensured. If inappropriate statistical methodologies are used to collect adverse events (AEs), lower AE rates could be listed on product information labels, commercially benefiting pharmaceutical companies. Some companies may also exploit regulatory loopholes in the PMS system, using it as a promotional tool to compensate doctors while expending little effort to conduct proper studies. In summary, without proper oversight or standards, the PMS is apt to be misused as a mere means of retaining a license, rather than as a tool for safety profiling, which may jeopardize its ability to ensure the safety of drugs on the market.

Safety information can differ in quantity or quality for similar products, depending on the AE collection methods used in the studies.[5] This is commonly exemplified by the AE rates of vaccines listed on their product information (labels) because the AE rates are updated as PMS results are obtained.

Consider the safety information on vaccines publicly available at the MFDS portal site.[5] Of the 94 vaccines licensed from 1995 to April 2008, 35 had safety profiles obtained from the PMS using the same format, including the overall AE rate, the number of all AEs for which a causal relationship with the study vaccine could not be ruled out, unexpected AEs, and serious AEs. Assuming that the vaccines licensed by the MFDS should have comparable safety profiles if they were within the same categories, we compared their overall AE rates. Interestingly, there were discrepancies in the AE rates of MAHs, as shown in Table 1. Since the details for each PMS protocol or methodology used were not disclosed to the public, information on how the safety data were collected and interpreted remains obscure. However, considering the tendency of general PMS practice in Korea, the discrepancies in the AE rates can be attributed to inconsistent methodologies rather than the inherent differences in the safety profiles of the vaccines.

Differences in the methods used to collect safety data can lead to discrepancies in the results. Hatz *et al*. reported that safety results differed significantly depending on the AE collection method used (*e.g*., solicited vs. unsolicited/open questioning) even for the same vaccine.[12] Another example is the PMS for hepatitis A vaccines: the subjects who did not return their diary cards were retrospectively interviewed by telephone and they reported fewer solicited and unsolicited symptoms than those who returned their diary cards.[13] Therefore, it seems likely that unsolicited questioning or retrospective collection of AEs without use of a diary card may risk under-reporting of AEs, while collecting data using solicited events may risk over-reporting of AEs that might not be related to the vaccines.[12] Consequently, it is advisable to disclose which method was used for data collection when PMS results are updated in the product information. The most appropriate data collection method should also be adapted for PMS for the purpose of monitoring safety.

PMS studies are a time-consuming, resource-intensive process. Since a PMS is mandatory for retaining licenses for new drugs/vaccines, conducting a PMS is a waste of resources if it does not follow a rational protocol and methodology. PMS practice and regulations should be changed not only to save resources but also to obtain high-quality data for public health. Dealing with execution problems within the current PMS system will be the first step to establish a sound, structured system of pharmacovigilance in Korea.

Conflict of interest

There are no conflicts of interest to declare.

Table 1. Examples of large discrepancies in the adverse events (AE) rates obtained after PMS in Korea

Vaccine Category	MAH*	Brand Name	AE rate (%)	Reference
Hepatitis A	Sanofi Pasteur	Avaxim®	1.4	[6]
	Berna Biotech Korea	Epaxal® Berna	39.4	[7]
Inactivated influenza	Sanofi Pasteur	Vaxigrip®	1.2	[8]
	Berna Biotech Korea	Inflexal®	42.2	[9]
Haemophilus influenzae type b	SK Chemical	Firsthib®	9.7	[10]
	Novartis Korea	Vaxem® Hib	66	[11]

*market authorization holder.

References

1. Borg JJ, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to? A review of the new EU legislation on pharmacovigilance. Drug Saf 2011;34:187-197.
2. Borg JJ, Tanti A, Kouvelas D, Lungu C, Pirozynski M, Serracino-Inglott A, et al. European Union pharmacovigilance capabilities: potential for the new legislation. Ther Adv Drug Saf 2015;6:120-140.
3. Choi NK, Park BJ. Adverse drug reaction surveillance system in Korea. J Prev Med Public Health 2007;40:278-284.
4. Ministry of Food and Drug Safety (MFDS). Provision of safety information management regulation of drugs. MFDS Notice No. 2015-79 (Amended on Oct 30, 2015).
5. Ministry of Food and Drug Safety (MFDS). Product license information. http://www.mfds.go.kr/index.do?searchkey=title:contents&mid=686&pageNo=9&seq=10094&cmd=v (Accessed 10 May 2016).
6. Sanofi Pasteur. Avaxim® 80U Pediatric inj. package insert. Seoul: Sanofi Pasteur, 2013a. http://www.sanofi.co.kr/l/kr/ko/layout.jsp?scat=10454F71-A809-4756-8DE2-CC39058A486D (Accessed Jan 20, 2016).
7. Epaxal® Berna prefilled syringe inj. Package insert. Seoul: Berna Biotech Korea. http://www.bernabiotech.co.kr/home/da/epaxal_berna.pdf (Accessed May 16, 2016).
8. Sanofi Pasteur. Vaxigrip® package insert. Seoul: Sanofi Pasteur. http://www.sanofi.co.kr/l/kr/ko/layout.jsp?scat=70037095-FBA3-47A5-9282-66B6C399653A (Accessed Jan 20, 2016).
9. Inflexal® V prefilled syringe inj. Summarized Information. http://www.druginfo.co.kr/cp/msdNew/detail/product_cp.aspx?cppid=186717 (Accessed May 18, 2016).
10. FIRSTHIB INJ. Summarized Information. http://www.druginfo.co.kr/detail/product.aspx?pid=50149 (Accessed May 18, 2016).
11. Song H, Bock H, Guadagno A, Costantini M, Baehner F, Kim YH, et al. Safety of a CRM197-conjugated Haemophilus influenzae type b vaccine in Korean children. Southeast Asian J Trop Med Public Health 2015;46:743-752.
12. Hatz C, Beck B, Steffen R, Genton B, d'Acremont V, Loutan L, et al. Real-life versus package insert: a post-marketing study on adverse-event rates of the virosomal hepatitis A vaccine Epaxal® in healthy travellers. Vaccine 2011;29:5000-5006.
13. Choi JW, Kim MS, Ma SH, Kang JH, Ok JJ, Ng LT, et al. Post-marketing surveillance study of hepatitis A vaccine in Korean population. Korean J Pediatr Infect Dis 2008;15:115-120.