PEER REVIEWED

Developing Global Solutions for Product Safety

Recent Changes in EU Requirements and New Directions in PV Globalisation

Over the past 20 years, the level of globalisation in the pharmaceutical industry increased significantly for both innovative and generic drugs. International cooperation between regulatory bodies and the harmonisation of regulatory requirements are key elements supporting the effective development of medicines, wide access to advanced therapies and ensuring sufficient safety oversight.

Since 2012, when European (EU) pharmacovigilance (PV) legislation came into effect, we can observe continuous dynamic improvement of safety data quality, credibility and transparency. More strategic groundbreaking changes in drug safety are planned for Q3/Q4, 2017. The European Medicines Agency (EMA) is about to finalise the process of a European pharmacovigilance legislation implementation and to introduce enhanced functionalities of a EudraVigilance database. At the same time, EMA is constantly extending and enhancing the cooperation with competent authorities outside the EU to facilitate the exchange of information, knowledge and experience between some of the world's largest regulatory bodies.

Harmonisation of Pharmacovigilance Legislation

The European regulatory system for medicines monitors the safety of all medicines that are available on the EU market through the entire lifecycle of the products. The European pharmacovigilance legislation that came into effect in 2012 fulfilled the growing need for harmonisation of requirements and standards across all EU countries. Since that time, Good Pharmacovigilance Practice (GVP) guidelines have been evolving dynamically under EMA experts' regular observations and public consultations with the stakeholders.

In 2017, EMA is going to finish the implementation of the pharmacovigilance legislation, enhancing the coordinating role of the Agency in safety monitoring and safety data analysis. Following the public consultations, EMA has already published the following GVP guidelines (Q1 and Q2, 2017):

- GVP Module II - Pharmacovigilance System Master File (Rev. 2)
- GVP Module V – Risk management systems (Rev. 2)
- GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)
- GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev. 2)

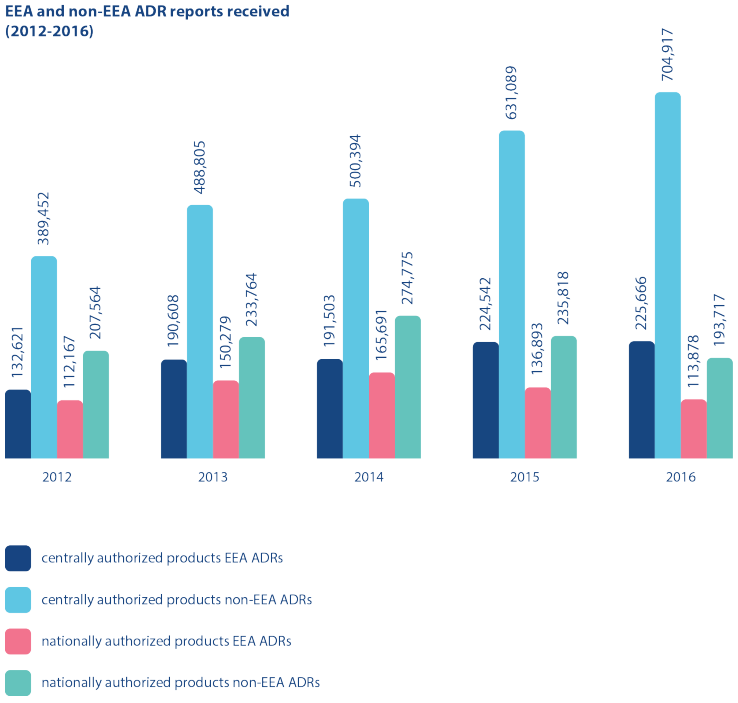
Additionally, the following updated documents are expected to be released in Q3, 2017 by EMA:

- GVP – Annex I – Definitions (Rev. 4)
- GVP Module XV – Safety communication (Rev. 1)
- GVP Module IX – Signal management (Rev. 1) and revised guidance on statistical methods
- GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev. 2)[1,2].

Centralised Vigilance for Global Safety Oversight

The EudraVigilance (EV) system launched by EMA has enabled a harmonised process of safety reporting and safety data assessment across Europe. Regulatory authorities, marketing authorisation holders (MAH) and clinical trial sponsors all use the same format, timelines and terminology for the electronic submission of suspected adverse drug reactions (ADRs) that occurred in European Economic Area (EEA) and in non-EEA countries. More than 1.2 million ADRs were reported to EudraVigilance in 2016; the majority of ADR reports were non-EEA reports for centrally authorised products.

EMA is going to introduce enhanced functionalities of the EudraVigilance database in November 2017. EudraVigilance changes were driven by the need to simplify the reporting process, improve the quality of data, and enhance analysis and tracking functionalities. A modified EudraVigilance system will require submission of individual case safety



Graph 1. Increase of ADR reporting in 2012-2016 for products authorised in EEA and non-EEA (source: European Medicines Agency, Annual Report 2016)

reports (ICSRs) that occur inside or outside the EU, only to EMA, without separate reporting to other national competent authorities. The ICSRs submitted to EudraVigilance will be automatically transmitted to the competent authority of the member state where the event occurred. This will significantly decrease the regulatory burden concerning safety submission processes and limit the number of duplicated reports.

Additionally, EMA implemented a new requirement to report all non-serious cases of suspected adverse drug reactions that occur in the EEA into the EudraVigilance database. This modification will streamline the signal-detection and data-analysis processes.

EMA continues to enhance the collaboration with the World Health Organization and has announced that safety data reported via EudraVigilance will be automatically directed in electronic format to the WHO Collaborating Centre, the Uppsala Monitoring Centre (UMC). Member states will no longer be responsible for transferring this data. New EudraVigilance functionalities will come into effect on 22nd November 2017[3,4].

The detailed change management plan released by EMA presents information on the technical changes of the EudraVigilance system, as well as business process changes required to work with the new system[5].

Common Language for Global Solutions

Globalisation of safety standards and systems requires the development of widely acceptable and flexible tools supporting data unification, analysis and reconciliation.

The best example of a standardised international solution is the Medical Dictionary for Regulatory Activities (MedDRA), developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the late 1990s. Since that time MedDRA has been regularly upgraded to become a highly specific tool for sharing medical information and is recognised worldwide.

Currently MedDRA is commonly used through all phases of the medicinal product development cycle in regulatory communication, safety monitoring and reporting (E2B Individual Case Safety Report), as well as product registration (within the ICH's Electronic Common Technical Document (eCTD)).

The MedDRA Maintenance and Support Services Organization (MSSO), as well as the Japanese Maintenance Organization (JMO), recently reported the number of subscribing organisations, which is currently over 5000 in 103 countries. This reflects the successful adoption of MedDRA as a worldwide standard in the protection of public health. The future focus is to explore interoperability between MedDRA and other medical terminologies[6].

Open Access to Big Data – Towards Global Knowledge and Transparency
There is a common understanding that the value of safety data is strictly dependent on completeness, credibility and transparency. Increased data transparency supports global innovations, improvement of quality and better efficiency of medicine development programmes.

The European Medicines Agency is the first regulatory authority worldwide to provide such broad access to clinical and safety data in accordance with transparency commitments. Information on suspected side-effect reports is publicly available in the European database of suspected adverse drug reaction reports [http://www.adrreports.eu/]. The system demonstrates the total number of individual suspected side-effect reports submitted to the EudraVigilance database for each centrally authorised medicine. Information on registered clinical trials is available in a public register called EU Clinical Trials Register [https://www.clinicaltrialsregister.eu/]. In October 2016, EMA additionally implemented an innovative policy and facilitated open access to clinical reports for new medicines for human use authorised in the European Union [https://clinicaldata.ema.europa.eu/]. This was a crucial step undertaken for greater transparency of clinical and safety data.

Innovative initiatives that focus on the use of mobile technologies and social media in pharmacovigilance are currently under evaluation. New technologies have been found to be powerful in adverse reaction reporting and the monitoring of the safety of medicines. Requirements regarding data transparency and data protection, accountability for data processing and some ethical principles still trigger challenges around the legal framework. EMA plans the further strengthening of the regulations on safety data transparency over the coming years.

Area	Medium term objective	Initiative(s)	Start	End	Performance indicator(s)
Harmonisation of international standards and approaches	**Improve application of equivalent standards of good manufacturing and clinical practices throughout the world**	Develop (through relevant inspector working groups) and apply an integrated and consistent approach to cooperation with key authorities (such as China and India)	Continious	Continious	- Network approach to inspections and training collaboration agreed, with particular focus on China and India - agreed procedures for cooperation
International cooperation mechanisms	Ensure appropriate representation in relevant fora, to ensure convergence of standards	Implement mechanisms to ensure representative and consistent representation of the network in international fora, and to provide feedback to the network, including ICH, VICH, WHO, OIE, IRCH and PIC/S, ICMRA, IPRF, IGDRP	2017	2019	Mechanism to ensure participation and feedback through pharmaceutical committee and HMA agreed
Efficient use of global resources	Expand work-sharing and mutual-reliance initiatives	Support the Commission with the establishment of a Mutual Recognition Agreement with the US	2016	2018	Principles of mutual recognition agreed and implemented for certain group of medicines
		Increase information-sharing between regulators responsible for the conduct of clinical trials and pharmacovigilance activities	Continious	Continious	- GCP initiative with PMDA established - Pharmacovigilance inspection initiative with FDA established
Training and capacity-building for non-EU regulators	Support capacity-building of non-EU regulators	Organise regular training courses for GXP inspectors, with participation of non-EU regulators	Continious	Continious	- Number of training sessions organised with non-EU regulator participation - Number of non-EU regulators' representatives trained

Table 1. EMA contribution to the global regulatory environment – examples (source: EMA Work Programme 2017, EMA/583016/2016, 17 January 2017)

International Collaboration for Global Health

The European Medicines Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines across the European Union (EU) and also cooperates with many of the world's largest regulatory bodies outside the EU (United States of America, Canada, Japan, Switzerland, Australia, New Zealand, Israel). Main areas of collaboration and information exchange include: inspections, safety of medicines and issues of mutual concern.

The process of sharing information on medicinal products safety between the US Food and Drug Administration (FDA) and the Committee for Medicinal Products for Human Use (CHMP) Pharmacovigilance working party started in 2003 (announced formally in 2014)[7]. The EMA-FDA international pharmacovigilance cluster activities include the exchange of information on: policies, guidance documents and regulations, risk assessment, concerns over marketing authorisation holder's pharmacovigilance systems and inspection findings, views on impacts, priorities and goals for pharmacovigilance activities. The pharmacovigilance cluster aims also at complementing the activities of the World Health Organization (WHO), the Council of International Organization of Medical Sciences (CIOMS), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the Drug Information Association (DIA)[8].

Further activities to strengthen the collaboration on pharmacovigilance compliance and inspections activities between EMA, FDA and other non-EU regulators is planned for the next years[9].

Next Step: Optimising Safety Requirements

While the protection of patients' safety is critically important, unnecessary data collection may be burdensome, and a disincentive for patients to participate in clinical research. In June 2017, ICH announced the development of a new safety data collection guideline (ICH 19) consistent with risk-based approaches and quality-by-design principles applicable for some late-stage pre-marketing or post-marketing studies.

This guidance will deliver recommendations whether selective safety data collection may be considered and how to maintain a balance between eliminating the unnecessary data and maintaining an adequate characterisation of the drug safety profile at the same time.

The aim of the new ICH guideline is to provide the first internationally harmonised guidance on targeted safety data collection to further increase clinical research efficiency and global participation in clinical development[10].

Since the European pharmacovigilance legislation came into effect, we can observe a continuous dynamic improvement of safety data quality, credibility and transparency. Unfortunately, such desired modifications entail a significant increase of regulatory burden and complexity. The need for adequate optimisation of the safety data collection process has recently been widely recognised.

Current changes in PV legislation and guidelines are driven mainly by the need to simplify the safety reporting process and improvement of the quality, transparency and usefulness of safety data collected throughout the entire lifecycle of the medicinal product. Nevertheless, further improvements for mutual benefits would be impossible to achieve without strengthened global collaboration and effective exchange of knowledge and experience between the regulators, manufacturers and patients.

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