Review Article

Comparative evaluation of pharmacovigilance regulation of the United States, United Kingdom, Canada, India and the need for global harmonized practices

Mohit Hans, Suresh Kumar Gupta[1]

Department of Clinical Research, Delhi Institute of Pharmaceutical Sciences and Research, [1]Department of Clinical Research, Delhi Pharmaceutical Sciences and Research University, New Delhi, India

Abstract

The primary focus of the pharmacovigilance (PV) practice has been on the collection, assessment, and reporting of the adverse drug reactions to medicinal products. Globalization of the pharmaceutical industry has prompted efforts to toward harmonization of PV practices worldwide to enable improved knowledge of medicine's benefit-risk profile and risk communication. Even as PV has evolved over the past decade, there still exist few areas of discordance across global PV practices. This article compares the PV legislation in the United States, United Kingdom, Canada, and India with a view to understand areas of harmony in the current legislation across regions and further compare health authorities' requirements with recommendations made by international organizations. Identification of potential areas of disharmony would pave the way to design solutions and strategies toward creation of a comprehensive PV system, which can be easily implemented across the globe, thus promoting the safer use of medicines.

Keywords: Adverse drug reaction, drug safety, harmonization, pharmacovigilance

Address for correspondence: Prof. SK Gupta, Department of Clinical Research, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi - 110 017, India.
E-mail: skgup@hotmail.com

INTRODUCTION

The World Health Organization (WHO) defines pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects or any other possible drug-related problems."[1] The international efforts to address drug safety issues worldwide were initiated soon after the thalidomide disaster in 1961. Earlier, PV and related activities included reactive techniques to respond to risks associated with medicines once they had been marketed. In recent years, the scope and objectives of PV have expanded manifold due to changes in the global pharma environment, improved access to medicines, varied utilization of medicines and availability of newer, more powerful tools and databases for tracking and analyzing data; however, the discipline needs to evolve further to meet both public health system needs and consumer expectations.

Thalidomide was first marketed in 1957 and thereafter was widely prescribed in Europe, Australia, Asia, Africa, and the United States of America. In 1961, severe birth defects were noted in children born to mothers who had been prescribed

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.PICR_89_17

How to cite this article: Hans M, Gupta SK. Comparative evaluation of pharmacovigilance regulation of the United States, United Kingdom, Canada, India and the need for global harmonized practices. Perspect Clin Res 2018;9:170-4.

thalidomide during pregnancy and these were found to be associated with thalidomide. More than 10,000 cases of birth defects were reported in over 46 nations and included children born with missing or abnormal limbs, spinal cord defects, cleft lip or palate, absent or abnormal ears, heart, kidney and genital abnormalities and abnormal formation of the digestive system. Nearly, 40% of the thalidomide victims died within a year of birth. In 1961, thalidomide was withdrawn from the market in many countries.[2]

New regulations and spontaneous reporting systems were put in place after the thalidomide tragedy. The WHO International Programme for adverse reaction monitoring led to the identification of the rare adverse drug reactions (ADRs) that could not be identified through the limited scope of clinical trials. Initially, the adverse events were reported through the British Yellow Card system and the Food and Drug Administration's form. Since then, PV practices have progressed from a reactive mode to a more proactive approach, where the safety of medicines is studied and tracked from the earlier stages of development through the entire product lifecycle including postmarketing.

Reports of the ADRs continue to be largest source of safety information with ADR reporting at the core of PV systems, extending through the entire product lifecycle from early developmental phases through post-marketing safety monitoring. The Adverse event reporting is required in the clinical trials, while spontaneous reports and reports from postmarketing studies are used to identify rare adverse effects that could not be identified during the clinical trial program as well as for signal detection.

The Council for International Organizations of Medical Sciences (CIOMS) and the International Council on Harmonization (ICH) initiatives have provided new direction to PV through guidance on risk management. Risk management comprises systematic discovery and communication of specific known and unknown risks of medicine as well as the plan to address and minimize those risks. PV is now viewed as a dynamic practice, involving safety data reporting, analysis and then communication to help implement comprehensive strategies for potential safety issues associated with marketed products. These multiple regulatory initiatives over the years demonstrate a clear understanding and solutioning in response to the new demands within PV. Yet the current regulations, systems, and tools for drug safety monitoring and public health protection have considerable room of improvement.

COMPARISON OF THE PHARMACOVIGILANCE REGULATIONS

On studying the evolution of PV trends over the past decade, it is evident that there has been a clear shift from a primarily reactive approach to more proactive PV approach with keen focus on risk mitigation and communication strategies. However, direct comparison of specific components of PV regulations, systems, and processes across the four regions (namely, US, UK, Canada, and India), shows many areas of disparity and disagreement. For example, with respect to the adverse event reporting, major discrepancies exist between the specific data, collected by international regulatory agencies with different types of safety data being collected/reported in different formats and at different frequencies. Risk management is also often conducted disparately, for example, although specific aspects of ICH good clinical practice recommendations are included in various sections of the regional legislation, the same aspects are neither always integrated across the four regions nor are they always integrated/presented in the same ways.

Table 1 depicts a comparison of PV regulations; compared across eighteen distinct parameters, which clearly highlights the multiple key areas of disharmony that exist across the regulations in these four regions.

THE NEED FOR HARMONIZATION

The recent efforts directed to enable the shift toward proactive PV and establishing global PV practices show that harmonized PV practices are required to meet the needs of the various stakeholders in PV (including health authorities, the pharmaceutical industry, health-care professionals, and consumers). In addition, harmonization would also promote the safer use of medicines and public health protection. The existing working practices of a particular region are directly correlated to the PV legislation that exists in that region. By defining the minimal requirements and practices, PV legislation thereby helping define how safety information about medicinal products is reported to enable adequate benefit-risk assessment.

Differences in implemented practices mean that rates and quality of adverse reaction reporting and risk management policies vary among countries. When drug safety reporting requirements differ among health authorities, different sets of data become available in different regions. When risk management is implemented in inconsistent ways, information known about the safety of medicines and the ability to manage new safety information remains isolated

Table 1: Comparison of pharmacovigilance regulations

Parameter	United states	United kingdom	India	Canada
Regulatory authority	FDA	MHRA	CDSCO	Health Canada
Pharmacovigilance responsible body (Centre for regulatory pharmacovigilance)	CDER and CBER	CHM	NCC PvPI, IPC	Marketed health products, directorate of the health products and food branch
Guidelines	21CFR 314.80; 314.98, guidance for industry GVP and Pharmacoepidemiologic assessment	Article 106 of directive 2001/20/EC, directive 2001/83/EC and article 26 of Regulation (EC) No. 726/2004.	Schedule Y of Drug and Cosmetics Rules, 1945	GVP guidelines (GUI-0102)
Process for reporting	Through medwatch form and online through FAERS	Through yellow card form or via online reporting through yellow card portal, or via email	Paper ADR reporting Form, through Mobile app, or via email	Canada vigilance program (MedEffect Canada) either online, by fax/mail or through telephone at Canada vigilance regional office
Pharmacovigilance system master file	Not mentioned	Maintained by EU for each member countries	Not mentioned	Not mentioned
Pharmacovigilance inspection	Via PADE inspections	Via risk assessment strategy	Not mentioned	GVP inspection program Inspection strategy for GVP for drugs (POL-0041)
Pharmacovigilance audit	Via postapproval audit inspections	In accordance to EU GvP guidelines	Not mentioned	In accordance with the GVP guidelines (GUI-0102)
Risk management system	Given in risk management guidance under guidance for industry GVP and pharmacoepidemiologic assessment	Follows risk management plan as per EMA guidance	Mentioned in guidance document for spontaneous adverse drug reaction reporting	Mentioned in guidance document - submission of risk management plans and follow-up commitments
Serious ADR reporting time period	Within 15 calendar days of occurrence	Within 15 calendar days reporting by QPPV	Within 24 h of occurrence	Within 15 calendar days of occurrence of ADR
Database	FAERS database	Yellow card database	WHO ICSR Database (VigiBase)	Canada Vigilance Adverse Reaction Online Database
Types of different ADR reporting form	Three 1. Form 3500 2. Form 3500A 3. Form 3500B	MHRA Yellow Card adverse Drug reaction Reporting form	Two: Suspected ADR reporting form for Healthcare personnel Medicines side effect reporting form for consumers	Two: Form for suspected adverse drug reaction to marketed products by industry Form for suspected adverse drug reaction reporting by consumers
PSUR submission	To CDER for drug products and CBER for biological products	To PSUR repository	To DCG (I) and PvPI	To submission and information policy division Therapeutic products directorate Health Canada
Data lock point for PSUR	70/90 days	6 months after the commission date	30 days of the last reporting period	70/90 days
Safety communication	Solicited communication via FDA website release	Communicated via MHRA website and press release	Communicated via CDSCO press release and also PvPI newsletters	Communicated via Health Canada website
Risk minimization measures	Done through risk MAP guidelines	Not mentioned	Not mentioned	Guidance document - submission of risk management plans and follow-up commitments
Toll-free/helpline number	Yes 1-800-332-1088	Yes 0808-100-3352	Yes 1800-180-3024	Yes 1-866-337-7705
Connection with UMC	Yes, FAERS data are communicated to WHO UMC	Yes, yellow card reports are reported to UMC after causality assessment	Yes, The ICSRs are directly reported to UMC database via VigiFlow	Yes, via MedEffect program

FDA=Food and Drug Administration's, ADR=Adverse drug reactions, EU=European Union GVP=Good pharmacovigilance practices, QPPV=Qualified Personnel for Pharmacovigilance, PADE=Postmarketing Adverse Drug Experience, UMC=Uppsala Monitoring Centre, WHO=World Health Organization, FAERS=FDA Adverse Event Reporting System, PvPI=Pharmacovigilance Programme of India, IPC=Indian Pharmacopoeia. Commission, NCC=National Coordination Centre, DCG=Drugs Controller General, CDER=Center for Drug Evaluation and Research, CBER=Center for Biologics Evaluation and Research, PSUR= Periodic safety update report, MHRA=Medicines and healthcare products regulatory agency, ICSRs=Individual case safety report, CDSCO=Central drugs standard control organization, CHM=Commission on human medicines, EMA=European medicines agency

and varying. Hirst *et al.* outline 22 drugs that were withdrawn in US and EU between 1997 and 2005. In 10 cases, there was disparity in the regulatory decision between the two authorities which demonstrated the disagreement on major risk management decisions across international borders.[3] These inconsistencies lead to a disparity and disjunction between what is known about the safety of medicine as well as what medicines are available in different parts of the world. The goal of harmonization has always been to protect public health. The pharmaceutical industry shares responsibility in the communication of drug safety information, which would be enhanced by a global system that allows manufacturers to communicate new safety information to regulatory agencies in all countries where the drug concerned is marketed. In addition, regulatory agencies should have harmonized standards, requirements and practices for dealing with emerging safety issues and public safety concerns. An agreed-on understanding of what is a safety concern versus a crisis and what is required for reporting of safety information between industry and regulators would minimize miscommunications and allow for greater worldwide drug safety and utilization. International organizations have shifted from developing guidelines and systems for gathering safety data on medicines to a focus on a worldwide PV system with a unified approach to drug safety. The three most influential international groups– The WHO, The ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use and the CIOMS-and their efforts toward harmonization of pharmaceutical regulation specific to PV and other efforts toward safer medicines is of great importance.

THE NEED FOR INTERNATIONAL HARMONIZATION

The ICH, CIOMS, and WHO initiatives have made great strides toward unification of global PV practices, however, a level of complete harmonization of the adverse event reporting systems and risk management strategies[3] does not yet exist. Definitions and reporting requirements still vary among regulatory authorities creating an environment where different data on the same product is submitted by manufacturers and health-care practitioners to different authorities. When this happens, reactions to public health and safety can be varied or delayed. The keys to successful PV in a modern world include enhanced global sharing of data, more effective communication of safety and efficacy of medicines to all parties involved from manufacturers to health-care professionals and patients, increased PV education in colleges and universities and a more dramatic shift away from reactive reporting of negative effects toward the proactive sharing of safety information on drugs and risk management.

Truly harmonized PV practices cannot be achieved until the areas of disharmony are identified, and best practices are agreed-on and implemented globally. While the idea of a harmonized system is widely discussed and studied,[4,5] health authorities have failed to fully adopt policies and guidelines of global organizations such as ICH in their entirety. The tools are available for an environment where safety data of medicine are shared and known in all areas where that medicine is available.[6,7] Studies have explored the use of technology in PV. In Cambodia, a pilot study of text-message based the adverse event reporting system was tested from a single vaccination center.[8] The amount of safety data on medicines available to regulatory agencies, industry, health-care professionals, and consumers will continue to grow. Moore reported that "Social media will certainly play a major role in the early identification of alerts. It is possible that Google trends will be the future alerting system. How individual medical files will be incorporated into the Cloud and made available remains uncertain. One certainty is that as computing grows even more powerful, the capacity to identify minute differences may overtake the capacity to identify or include biases, resulting in the distinct risk of being overwhelmed by statistically "significant" differences that are clinically irrelevant. This might have the good effect of placing more importance on common sense and medical judgment.[9] The modes for collecting adverse event data are directly correlated to the need for harmonized PV practices. PV professionals must use these trends to their advantage and the enhancement of public health. International health authorities should use these tools in the same ways to allow for a truly global system. In all four regions, PV regulations exist that define not only how the health authorities of these regions will address and manage the risks of medicinal products, but also how the industry, health-care professionals and consumers will be involved in those processes. These regulations shape the use of PV tools and are the key to unlock existing disharmony and improve the national systems.[10-12]

CONCLUSION

While much progress has been made in PV practices, many deficiencies and issues still exist in the efforts to ensure safe medicine usage. Harmonization of PV practices beyond regulation requires defining and implementing "best suitable practices" for the health-care professionals, industry and the regulatory authorities. It requires formal training for PV professionals and better communication tools. Safety information is communicated between different

regulatory agencies, regulatory agencies and manufacturers, healthcare professionals and manufacturers, agencies and healthcare professionals, healthcare professionals and consumers. All parties in communication utilize different tools– from product labeling to adverse event reports. In today's technological environment these communications are occurring more frequently over the internet, through social media and the cloud. For PV practices to become truly global, there is a further need to integrate these PV best practices with these new modes of communication.

Identifying the discrepancies in existing practices is also only a first step. More work is required to establish the best practices, tools and infrastructure that will be required to address the needs of PV in the future. International organizations must continue to advance their understanding of PV and establish guidelines for shifting away from a focus on finding harm and more toward extending knowledge about safety to all appropriate stakeholders. Wallace and Evans write, "Pharmacovigilance should operate in a culture of scientific development. This requires the right balance of inputs from various disciplines, a stronger academic base, and greater availability of basic training and resource which is dedicated to scientific strategy."[13] Of course, implementing such strategies will require legislative change; thus, the process that begins with the legislation to identify where disharmony exists, must also end with the legislation to create a framework at a national level that allows for an international harmonization of practice.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products. Available from: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf
2. Pannikar V. The Return of Thalidomide: New Uses and Renewed Concerns. The World Health Organization, WHO Pharmaceuticals Newsletter No. 2; 2003. p. 11-2.
3. Hirst C, Cook S, Dai W, Perez-Gutthann S, Andrews E. A call for international harmonization in therapeutic risk management. Pharmacoepidemiol Drug Saf 2006;15:839-49.
4. Moscou K, Kohler JC, MaGahan A. Governance and pharmacovigilance in Brazil: A scoping review. J Pharm Policy Pract 2016;9:3.
5. 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;6:120-40.
6. Hughes RG. Tools and strategies for quality improvement and patient safety. In: Hughes RG, ed. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
7. Drug Safety Priorities 2016: Initiatives and Innovation. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm522941.htm#social. [Last accessed on 2017 Mar 10].
8. Baron S, Goutard F, Nguon K, Tarantola A. Use of a text message-based pharmacovigilance tool in Cambodia: Pilot study. J Med Internet Res 2013;15:e68.
9. Moore N. The past, present and perhaps future of pharmacovigilance: Homage to Folke Sjoqvist. Eur J Clin Pharmacol 2013;69 Suppl 1:33-41.
10. World Health Organization. Available from: http://www.who.int. [Last accessed on 2017 Mar 20].
11. International Conference on Harmonisation. ICH Harmonized Tripartite Guideline, Pharmacovigilance Planning E2E; 18 November, 2004.
12. Council for International Organizations of Medical Sciences. Available from: http://www.cioms.ch. [Last accessed on 2017 Mar 30].
13. Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003;12:17-29.