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

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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

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.”

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...
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 Pharmacovigilance responsible body (Centre for regulatory pharmacovigilance) Guidelines | Article 106 of directive 2001/20/EC, directive 2001/83/EC and article 26 of Regulation (EC) No. 726/2004. 21CFR 314.80; 314.98, guidance for industry GVP and pharmacoepidemiologic assessment | To CDER for drug products and CBER for biological products | CDSCO, NCC PvPI, IPC | Health Canada Marketed health products, directorate of the health products and food branch |
| Process for reporting | 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 | Via PADE inspections | Via risk assessment strategy |
| Pharmacovigilance system master file | | Not mentioned | Not mentioned | Not mentioned |
| Serious ADR reporting time period | Within 24 h of occurrence | Within 15 calendar days of occurrence | WHO ICSR Database (VigiBase) | Within 15 calendar days of occurrence of ADR Canva vigalence Adverse Reaction Online Database |
| Types of different ADR reporting form | | 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 | | |
| Data lock point for PSUR | 6 months after the commission date | 30 days of the last reporting period | | Communicated via Health Canada website |
| Safety communication | Communicated via MHRA website and press release | Communicated via CDSCO press release and also PvPI newsletters | | |
| Risk minimization measures | Not mentioned | Not mentioned | | Guidance document - submission of risk management plans and follow-up commitments |
| Toll-free/helpline number Connection with UMC | Yes 1-800-322-1088 Yes, FAERS data are communicated to WHO UMC | Yes 0808-100-3352 Yes, yellow card reports are reported to UMC after causality assessment | Yes 1800-180-3024 Yes, The ICSRs are directly reported to UMC database via VigiFlow | Yes 1-866-337-7705 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.[1] 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[5] 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.”[1] 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.

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Conflicts of interest

There are no conflicts of interest.

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