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Review Article

A NEW ERA OF DRUG SAFETY – NEW EU PHARMACOVIGILANCE (PV) LEGISLATION AND COMPARISON OF PV IN EU, US AND INDIA

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ABSTRACT

A series of public health disasters (Thalidomide in the 1960s to Rofecoxib (Vioxx) at the beginning of this century have served to remind us that effective Pharmacovigilance (PV) is crucial for protection of citizens. The introduction of new PV legislation in July 2012 is the biggest change to the regulation of human medicines in the European Union (EU) since 1995. New requirements and procedures for Post-Authorization Safety Studies (PASS) open the gateway for development of real-world effectiveness outcomes. Similarly, the United States Food and Drug Administration (USFDA) has become more open to inclusion of non-safety data collection in its safety surveillance mandates and more proactive risk management approach. In addition, the Marketing Authorisation Holders (MAHs) need to be more efficient with their post-authorisation activities to maximize their utility. The main goal of this new PV path is to strengthen the public health. However it is also concerned with improved efficiency, clear decision-making processes, reduce duplication and better use of Information Technology in PV process.

Keywords: Pharmacovigilance, European Medicine Agency, Good Pharmacovigilance practice, New EU PV Legislation, Food and Drug Administration, Signal detection, Risk Management Plan.

INTRODUCTION

In accordance with data of European Commission (EC), adverse drug reaction (ADRs) are responsible for 5% of all hospital admissions, 5% of all patients in hospital experience an ADR and lastly ADRs cause minimum of 1.91 extra days of hospitalization. In United States (US), more than 100,000 deaths annually are because of ADRs [2]. Hence, this scenario itself makes clear the importance of pharmacovigilance (PV), as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or other drug related problems" [3]. PV is crucial in all phases of drug development process and is based on effective systems and processes that are dependent on regulations in various countries and regions.

New eu pv legislation

On December 10, 2008, EC published proposals to amend European Union (EU) PV legislation contained in the Directive 2001/83/EC and Regulation 726/2004/EC. In July 2012, new legislation with Directive 2010/84/EU and Regulation 1235/2010 substantially amended the EUs PV requirements by strengthening and consolidating the PV system [4, 5]. The legislation is the biggest change to the regulation of human medicines in the EU since 1995. The EU PV system is now one of the most advanced and comprehensive systems in the world and represents a robust and transparent instrument to ensure a high level of public health protection.

New definition of adverse drug reaction:

An adverse drug reaction is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- The use of a medicinal product within the terms of the marketing authorisation.
- The use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse, medication errors and occupational exposure [6].

Need for new eu pv legislation

As ADRs are the fifth most common cause of hospital death and they are accountable for EU societal cost of £79 billion per year [7], hence a change was required in the existing legislation to protect public health. This would have been possible with a high level objective with clear roles and responsibilities; risk based/proportionate approach; increased proactiveness and proper planning resulting in integrated benefit and risk of products. With the recent changes, the EU intends to promote and protect public health by reducing burden of ADRs and optimizing the use of medicines.

What about volume 9a?

The key to the success of the legislation is the Good Pharmacovigilance Practice (GVP) document which replaced Volume 9A. The Figure 1 shows various GVP Modules and these were made modular to enable easier amendments. All key modules were available by July 2012 [8].

Main pillars of new pv legislation

Reduction in administration burden/increased work-sharing

This new legislation clearly states the roles and responsibilities of European Medicines Agency (EMA), member states and the Marketing Authorization Holders (MAHs). The EMA and member states remain central to the operation of the PV with increased co-operation and work sharing. The role of the MAH is more clarified in reference to obligation to monitor the safety of the products and to ensure that all information available is shared with Competent Authorities (CAs) [9].

Greater transparency - medicines web-portals (EU & national) and products subject to 'additional monitoring'

The regulatory agencies and member states have the substantial powers to make following information of medicinal products from MAHs available on web portal and in public domain [10]:

– Summaries of Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) with issues.

– Information pertaining to Public Assessment Reports (PARs), Summary of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs).

– Publicly available list of medicinal products subjected to additional monitoring. It includes identification of these products by

black symbol, a PRAC recommendation to EC and explanatory note in SmPCs and PILs.Online ADR reporting forms and information pertaining to various ways of reporting ADRs by Health Care Professionals (HCPs) and Patients. The MAHs and MSs are supposed to report serious ADRs within 15 days and non-serious ADRs within 90 days to Eudravigilance.

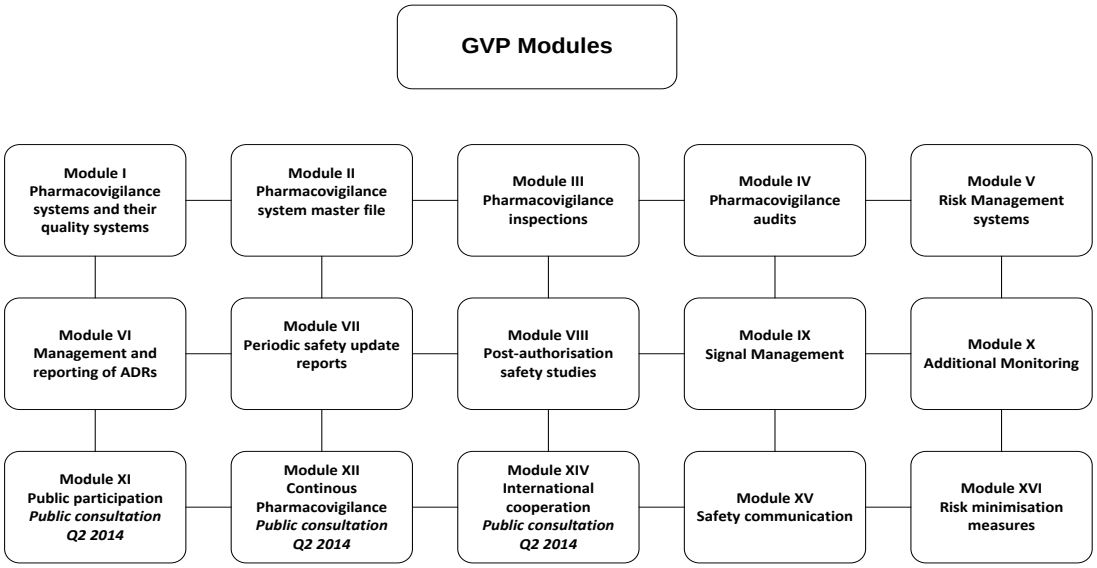

Fig. 1: GVP Modules [8]

Pharmacovigilance Risk Assessment Committee (PRAC)

The creation of PRAC has an important role in all aspects of Risk Management (as shown in Figure 2) of the use of medicinal products. This includes detection, assessment, minimisation and communication relating to the risk of adverse reactions, due regard to the therapeutic effect of the medicinal product, the design/evaluation of the PASS and PV audit. For specific activities of signal management, the PRAC appoints a rapporteur from amongst its members. The role of the PRAC rapporteur is to prepare a recommendation or an advice together with an assessment report on the relevant issue pertaining to signal detection that is raised to PRAC, taking into account the timeframe laid down in the relevant legislation. The PRAC rapporteur also provides recommendations to Committee for Medicinal Products for Human Use (CHMP) or the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh) lead Member State/Reference member state for the concerned medicinal product [11].

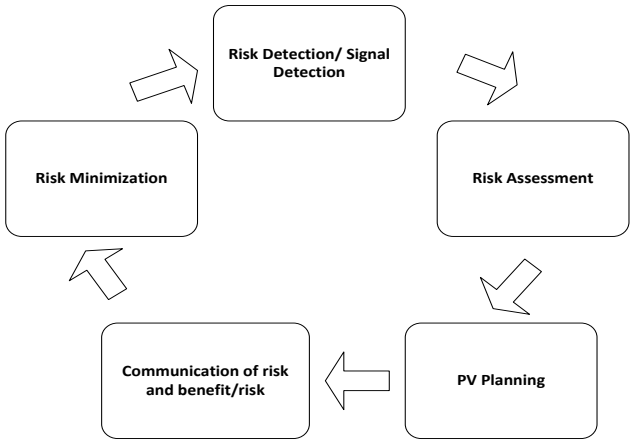

Fig. 2: Role of PRAC in Risk Management [12]

In relation to specific activities of the PRAC, rapporteur contacts with representatives of patient organizations' and relevant health-care professionals' associations and rapporteur provides a report on the outcome of such contacts to the PRAC, which is reflected in assessment report.

The PRAC also plays a crucial part in handling of direct ADR reporting by consumers irrespective of medical confirmation. Lastly, PRAC has a big role in monitoring of RMPs and assessment of list of harmonised frequencies pertaining to submission of PSURs/PBRERs [12].

PV system Master File (PSMF)

As per the new legislation, Detailed Description of Pharmacovigilance System (DDPS) will no longer be required and is replaced by PSMF. On request, the PSMF should be provided within seven days to CAs. The annexes of the PSMF contain comprehensive data demonstrating the current state of the PV system, including [13]:

– An overview of all marketing authorisations covered by the PSMF together with information on presence on the market (also outside EU) and specific safety monitoring requirements

– Results of the current performance assessment [e.g. timeliness of Individual Case Safety Reports (ICSRs) reporting and PSUR submission, safety variations and adherence to RMP requirements]

– An audit schedule and critical findings from previous PV audits

– A detailed overview on the company's written procedures

Risk Management Plans (RMPs)

RMP is defined as, "a set of PV activities and interventions designed to identify, characterize, prevent or minimize risks related to a medicinal product, including the assessment of effectiveness of those activities and interventions". In accordance to new legislation, RMP should be risk proportionate and needs to be submitted for all new products. The authorized products require RMP if there are issues affecting the risk benefit balance. The new legal requirement states that "EMA and MS's shall monitor the outcome of risk minimisation measures contained in the RMPs." [14].

Signal Detection

The GVP clearly sets out the concept of signal detection, validation, prioritization, evaluation and communication. The MAHs needs to have documented processes for signal detection in accordance with the level of reports received and portfolio of medicinal products. It may include individual case review, statistical analysis or a combination of both [15].

Periodic Safety Update Reports (Addendum to Clinical Reports and PSURs)

The concept of Addendum to the Clinical Overview reports has been expanded and these reports should include a benefit/risk evaluation in renewal applications. The PSURs will not be required for generic and traditional herbal medicinal products. However, CAs can request PSURs for these products on the basis of various safety concerns. In addition, PSUR is replaced with Periodic Benefit Risk Evaluation Report (PBRER) and MAHs shall submit PBRERs/PSURs containing summaries of data relevant to benefits and risks of the product. The new features of the PBRER are [16]:

– Focus on benefit and risk

– Emphasis on analysis and evaluation, in reference to active substance

– Focus on cumulative data, with no case line listings (no individual case line listings, no tables of listed vs. unlisted)

– The submission frequency is determined by drug's risk profile

Pharmacovigilance in united states

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) of the USFDA monitor and review safety information throughout life cycle of the medicinal product, from application for MA through approval of the application and after entry of drug in the market. The Food and Drug Administration Amendments Act (FDAAA), has a pivotal role in safety of drugs during post-marketing phase. It provides FDA with the authority to require labeling changes with respect to new safety information. The FDAAA also gives FDA the authority to require certain post-marketing studies and clinical trials for new drugs approved under Food, Drug and Cosmetic Act (FDCA) or for biological medicinal products.

The routine PV activities in US i.e. compliance with applicable post-market requirements under the FDCA and USFDA implementing regulations includes post-marketing surveillance and risk assessment. The PV plan describes efforts beyond the routine post-marketing spontaneous reporting and is designed to enhance and expedite the sponsor's acquisition of safety information. The sponsors have to develop a PV plan for products for which; serious safety risks have been identified post-approval and/or already identified safety risks need more evaluation or risk populations have not been adequately studied. Under USFDA, guidance to cover the different phases of the risk assessment and risk management for industry is divided into three parts [17]:

Premarketing risk assessment

The MAH is responsible for reviewing all information pertaining to safety of the drug obtained or otherwise received by the MAH from any sources or from any clinical or epidemiological investigation. The MAH needs to notify USFDA and all participating investigators in Investigational New Drug (IND) safety report of all serious and unexpected serious risk from clinical trials or any other sources that has not previously been reported to the Agency [17].

Post-marketing Pharmacovigilance and Pharmaco epidemiologic Assessments

The PV in US encompasses all scientific and data gathering activities relating to the detection, assessment, and evaluation of safety signals [17]:

– Safety signal identification

– Pharmacoepidemiologic assessment and safety signal interpretation

– Pharmacovigilance plan development

Risk Evaluation and Mitigation Strategies (REMS)

The USFDA has obligation for manufacturers to implement special risk management programs, called REMS. The Secretary, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety of the drug, determines the requirement of REMS. If the benefits of drug outweigh the risks, then the applicant having an approved application for new drug or abbreviated new drug or biological medicinal product has to submit REMS. The proposed REMS must be submitted within 120 days of the USFDA notification for the protection of public health [18]. The risk assessment and risk minimization together is called as Risk Management and it is an iterative process throughout a product's lifecycle which consists of [18, 19]:

– Assessing a product's benefit-risk balance;

– Developing and implementing tools to minimize its risks while preserving its benefits;

– Evaluating tool effectiveness and reassessing the benefit-risk balance;

– Making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance [19].

In US, under Title 21 of Code of Federal Regulation (CFR) §§ 314.80, 314.98, 600.80, Periodic adverse drug experience reports (PADERs) shall contain among other data, information about all serious expected and non-serious adverse events, which are not reported through the post-marketing "15-day Alert reports" or their follow-up reports. These periodic reports also include a narrative summary of information in the report and an analysis of "15-day Alert reports" submitted during the reporting intervals [20].

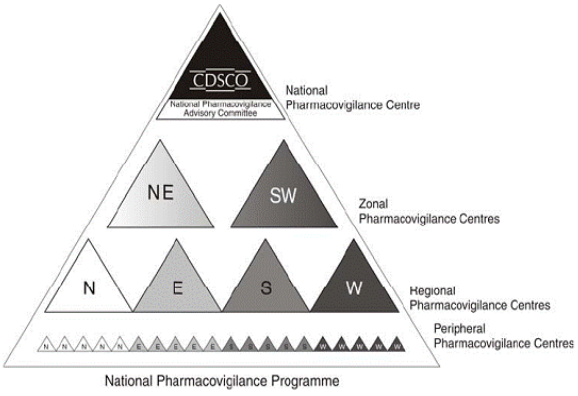

Fig. 3: National Pharmacovigilance Program (NPP) of India [21]

Pharmacovigilance in india

The Legislative requirements of PV in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945. The National Pharmacovigilance Programme (NPP) shown in Figure 3 was launched by Central Drugs Standard Control Organization (CDSCO) on 23-Nov-2004 which became operational from 01-Jan-2005. However, due to some technical difficulties the NPP was closed in 2008. It was again resurrected as the Pharmacovigilance Programme of India (PVPI) on 14-Jul-2010 [21].

In order to ensure implementation of the programme in a more effective way the National Co-ordination centre (NCC) at AIIMS, New Delhi was shifted to CDSCO in collaboration with Indian Pharmacopoeia commission, Ghaziabad on 15-Apr- 2011 [21]. The Figure 4 shows elements of PVPI. To streamline the growth of the PVPI programme further, the commission has planned to include all medical colleges across the country under its fold. The commission aims to expand PVPI and attain its goal of setting up 350 ADR centers across the country [22].

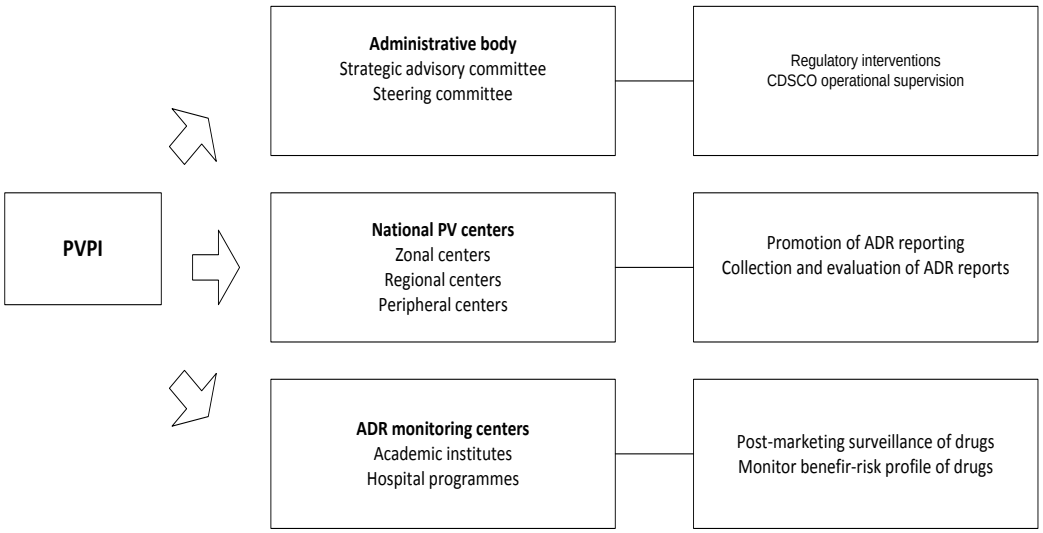

Fig. 4: Pharmacovigilance Programme of India [23] (PVPI)

The role of various Regulatory agencies in India [23] is summarized in Table 1 below:

Table 1: Roles of various regulatory agencies of India

Agencies	Role of agencies
Drug Controller General of India (DCGI)	Implementation the NPP in India
Central Drugs Standard Control Organization (CDSCO)	Operate under the supervision of National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory interventions.
Indian Council of Medical Research (ICMR)	Brought out the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000 as the 'Ethical guidelines for Biomedical Research on Human Subjects'.
Ministry of Health and Family Welfare (MHFW)	An autonomous body for setting of standards for drugs, pharmaceuticals and healthcare devices and technologies in India.
National Pharmacovigilance Advisory Committee (NPAC)	To collate, analyze and archive adverse drug reaction data for creating healthy environment for the regulatory authorities to analyze drugs to be marketed in India
Central Bureau of Narcotics (CBN)	Closely monitor all clinical trials, which require additional narcotics compliances relating to storage, import-export quotas and movement of the investigational drug.
Department of Biotechnology (DBT)	Provides product evaluation and validation through support for field trials for agriculture products and clinical trials for health care products.

Pharmacovigilance concepts in eu, us and india

In both EU and US, PV activities cover the whole life-cycle of medicinal products for human use.

The full safety profile of medicinal products can only be known after marketing of the products and in this period, pharmacovigilance activities become especially important for the protection of public health.

The EMA and the National CAs in EU and USFDA are empowered to impose certain obligations on authorized medicinal products with respect to new safety information, to ensure appropriate changes to medicinal product's labeling and to conduct post-authorization safety studies.

The PV system in both areas demand expedited and obligational recording and reporting of all available data about the serious unexpected adverse events, medication errors and any suspected transmission of an infectious agent through the medicinal products.

The PV is still in its infancy in India and is likely to expand in accordance with time. The entry of new drugs in market demands more PV activities.

The PV concepts in EU, US and India [4, 5, 11-21, 23] are summarized in Table 2 below:

Table 2: Comparison of PV in EU, US and India

Topics	EU	US	INDIA
Regulatory Structure	EMA & EC	FDA,CDER,CBER	CSDCO (DCGI), Schedule Y
Legislation & Regulation	Regulation 1235/2010 and Directive 2010/84/EU	21 CFR §§ 314.80,314.98, 600.80	DGHS, Ministry of Health & Family Welfare
Description of PV System	PSMF is required and it is aimed to strengthen and rationalize the monitoring of safety information of medicinal products in EU market and to harmonize the PV activities throughout EU.	In accordance with CFR, which demand from the applicants having approved new drug applications (NDAs) or approved abbreviated new drug applications (ANDAs) and from manufacturer having licensed biologic applications to archive and retain records of all adverse events, known to them, including raw data and any correspondence relating to adverse drug experience.	The CDSCO in collaboration with Dept of Pharmacology, AIIMS, New Delhi launched the nation-wide Pharmacovigilance programme for protecting the health of patients by assuring drug safety. The programme is coordinated by Department of Pharmacology at AIIMS as a NCC. The centre operates under the supervision of a Steering Committee.
Electronic Databases	Permanently accessible electronic database (the Eudravigilance Database) for collection, collation and dissemination of information on suspected adverse reactions to medicinal products for human use authorized by the Union. The Eudravigilance database is equipped to immediately forward reports on suspected adverse reactions received from MAHs to the MS, on whose territory the reaction occurred.	FDA's Adverse Event Reporting System (FAERS) and FDA's Vaccine Adverse Event Reporting System (VAERS) are computerized information databases designed to support FDA's post-marketing safety surveillance program for drugs/biological products and for vaccines, respectively.	Vigiflow software provided by WHO-Uppsala Monitoring Centre is utilized as the safety database, where all data originating from India is maintained in a secure and confidential manner.
PV Plan	In Europe, ICH E2E guideline on PV Planning suggests that a "PV plan" would routinely be developed, even when the sponsor does not anticipate that enhanced PV efforts are necessary.	In US, for most products routine PV activities (i.e. compliance with applicable post-market requirements under the FDCA and FDA implementing regulations) will be sufficient for post-marketing surveillance and risk assessment, and a PV plan describes PV efforts beyond the routine post-marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.	The PVPI NCC is collaborated with the WHO-UMC Collaborating Centre based in Sweden.
Risk Management System	The medicinal products for pediatric use and those involving a significant change in the MA, including a new manufacturing process have to implement a risk management system and all new marketing authorization application (MAA) have to contain a RMP with a detailed description of the risk management system used by MAH.	The applicant having an approved application for new drug or for abbreviated new drug or for a biological medicinal product has to submit REMS. If FDA believes that REMS is necessary to assure that the drug's benefits outweigh its risk, the manufacturers have to implement REMS for the drug.	No Specific Guideline
Spontaneous Case reports	To be reported by MAH within 15 Calendar days	Serious and unexpected, foreign and domestic are to be reported by MAH within 15 calendar days	To be reported by MAH within 10 Calendar days
Case reports from the worldwide literature	To be reported by MAH within 15 Calendar days	Serious and unexpected, foreign and domestic are to be reported by MAH within 15 calendar days	To be reported by MAH within 10 Calendar days
Case reports from post-authorization studies/ pharmaco-epidemiologi-cal study	All serious adverse reactions within or outside the EU should be reported within 15 days.	Serious and unexpected adverse experiences (domestic and foreign) should be reported within 15 calendar days	No Specific Guideline
Fatal or Life Threatening Unexpected ADRs	As soon as possible but no later than 7 calendar days after first knowledge followed by a complete report as possible within 8 additional calendar days.		
All Other Serious, unexpected ADRs	As soon as possible but no later than 15 calendar days		As soon as possible but no later than 10 calendar days.
Periodic safety reports	The PBRER does not work anymore as a detailed listing of ICSRs. The	The PADERs shall contain among information about all serious expected	The PSURs are submitted every 6 monthly for the first 2 years of

	submission of periodic reports is also exempted for MAHs of generic, well-established used, homeopathic or traditional-use herbal medicinal products. Frequency of submission is 6-monthly continued until two full years then, once a year for the following 2 years and thereafter at 3- yearly intervals.	and non-serious adverse events, not reported through the post-marketing "15-day Alert reports" or their follow-up reports. A narrative summary of the information in the report and an analysis of the "15-day Alert reports" is also included in these reports. The periodic reports are submitted quarterly for first three years, then annually.	marketing in India, and annually for the subsequent 2 years.

In addition, both REMS and RMPs provide positive guidance for identification, monitoring, and minimization of risk to patient safety. A summary of elements [24] of RMPs and REMs are described in Table 3 below:

Table 3: EMA-RMP and USFDA-REMS

EMA-RMPs	USFDA-REMS
Patient alert cards	Medication guides
Patient information leaflet	Patient information sheet
SmPC contraindications	Container labels
SmPC special warnings and precautions for use	
SmPC contraindications	Provider communication plan
	Provider information sheet
Educational programmes	Highlighted information for prescribers
	Training of healthcare professionals
Prospective observational studies	Monitoring of patients receiving medication
Additional trial and study data	Prescriber and patient database
Specific adverse event and pharmacovigilance surveillance reporting requirements	Post marketing studies

Challenges for new eu pv legislation

Besides being the biggest change to PV pertaining to human interest, the new legislation has some following challenges [25]:

- Inconsistent requirement across member states, for e.g. the reporting requirements for ICSRs are revised thrice since July-2012.
- Significant implications for ability to monitor & maintain compliance, inconsistency with legislation with respect to no additional requirements unless for PV reasons.
- Submission of non-serious cases to Eudravigilance.
- Delay in transposition of directive in most member States, inconsistencies in adoption and rejections of requests in line with Directive and inconsistencies between finalized modules.
- Lack of harmonization with developing countries.
- Ad hoc requests for spontaneous data reviews that are not consistent with new principles, format and content:

– requests to continue cumulative /interval reviews of spontaneous data, even they have proved to be negative on many previous occasions

– provision of line listings of case reports with a fatal outcome

- Reporting of ADRs to be done in a structured manner and to the highest possible quality standards to support accurate detection and analysis of drug safety signals.
- Specific guidance is required on how to handle "invalid reports" and reports identified through social networking websites, web blogs and other such sources of data.

Achievements of new eu pv legislation

After implementation of this legislation from July 2012, a huge change has been delivered for better public health improvement [26].

- Better public participation

– increase of patient reports by 10,000

– Patients and HCPs voting on PRAC

- Better planning: RMPs are now routinely submitted
- Better evidence: routine identification of data needs for referrals
- Faster decision-making

– PRAC referrals are now finalized in 1 to 8 months

– PSURs/PBRERs directly result in label changes

- Greater transparency: agendas, minutes, signals of PRAC meetings
- Better information: black triangle, ADR reporting, warnings in SmPCs/PILs

CONCLUSION

This EU PV legislation represents the most extensive change to the EU PV requirements for over a decade and biggest changes to human medicines since the establishment of EMA in 1995. As a result, there is a major impact on earlier regulatory processes and numerous new processes replaced the older ones.

In addition, the current sets of USFDA and EMA guidance are driven by similar objectives for identification, monitoring and minimization of risk to patient safety. As a result, they frequently lead to the generation of similar data needs. In today's global market environment such similar data requirements facilitate the exchange of information between the regulators. The central concept for both agencies is assessing risk and determining if it is acceptable. Both USFDA REMS and EMA RMPs currently provide comparable comprehensive post approval guidance for the identification, monitoring and minimization of risk to patient safety with some differences in respective implementation toolkits [24].

The PV system in India is still not well developed. Despite of recent implementation of a well structured PVPI in accordance with the objectives and recommendations of WHO by CDSCO, desired success is still a distant dream. However, the reporting rate of ADRs is increasing as compared to previous programmes. The NCC is making efforts to enhance the visibility of PVPI by regularly publishing the PVPI Newsletters and distributing them within India and overseas [27].

The new EU PV Legislation has resulted in major implications on human resources in the field of PV, information technology and regulatory in addition to financial resources. The MAHs have played a crucial role to re-engineer processes and databases, revise procedures, and train staff etc. after implementation of the

legislation from July 2012. The work of the EU regulatory network is intensifying and the changes from new legislation are significant. The EU regulators are working with industry and patient and healthcare groups to deliver better public health protection through better PV. "The full implementation of new EU PV Legislation is estimated to save between 591 and 5910 lives, while providing savings to society of some €2.5 billion per year across the EU" [28].

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