Module III– Regulatory Aspects of Pharmacovigilance

Contents

1. United States

United States (US) regulations and guidance:

Drug Safety in the US is covered under several sections of the Code of Federal Regulations (CFR).

Code of Federal Regulation (CFR)

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and agencies of the federal government of the US.

The CFR is divided into 50 titles that represent broad areas subject to federal regulation. The 50 subject matter titles contain one or more individual volumes, which are updated once each calendar year, on a staggered basis.

CFR Title 21

Title 21 of CFR governs food and drugs within the US for the FDA, the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP). It is divided into three chapters-

- Chapter I: Food and Drug Administration (Parts 1-1299)
- Chapter II: Drug Enforcement Administration (Parts 1300-1399) - combating drug smuggling and use within the United States.
- Chapter III: Office of National Drug Control Policy (Parts 1400 to 1499) - establish policies, priorities, and objectives to eradicate illicit drug use, manufacturing, and trafficking, drug-related crime and violence, and drug-related health consequences in the U.S.
- Important parts of Title 21 of CFR:

CFR Title 21 Part 310 New drugs

Subpart D - Records and Reports

Sec. 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications

CFR Title 21 Part 314 - Applications for FDA approval to market a new drug

Subpart B - Applications (New Drug Application: NDA)

Sec. 314.80 Post marketing reporting of adverse drug experiences

Subpart C - Abbreviated Applications (Abbreviated New Drug Application: ANDA) Sec. 314.98 Post marketing reports

CFR Title 21 Part 312 - Investigational New Drug Application (IND)

Subpart B - IND Sec. 312.32 IND safety reporting

CFR Title 21 Part 600 Biological products

(Biological product: any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man. e.g. vaccines)

Sec. 600.80 Post-marketing reporting of adverse experiences

CFR Title 21 Part 803 - Medical device reporting

CFR Title 21 Part 11 - Electronic records; electronic signatures

In United States (US), Food and Drug Administration (FDA) is responsible for:-

- Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labeled; ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective
- Protecting the public from electronic product radiation
- Assuring cosmetics and dietary supplements are safe and properly labeled
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations

FDA's responsibilities extend to the 50 United States, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions

Brief History of US FDA:

FDA is an agency within the Department of Health and Human Services and has its headquarters at Silver Spring, Maryland.

In 1906, the Pure Food and Drugs Act prohibited inter-state commerce of mislabelled and adulterated drugs and food within the U.S. This covered some safety aspects of drugs but not efficacy.

In 1912, the law was changed to cover false and fraudulent claims made for drugs. However, the law did not mandate safety and, in effect, unsafe products could be and were marketed.

In 1937, a company in US marketed elixir of sulfanilamide, which contained diethylene glycol (similar to antifreeze). More than 100 people died from this product. Because the law did not require safety testing for drugs, the company had done none.

As a result, the Federal Food, Drug and Cosmetic Act was passed into law in 1938 giving authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics.

FDA's Organization:

The FDA's organization comprises of Offices and Centers (around 223 field offices and 13 laboratories).

The FDA's organization consists of:

- Office of the Commissioner
- Four Directorates, overseeing the core functions of the agency:
    - Office of Foods and Veterinary Medicine
    - Office of Global Regulatory Operations and Policy
    - Office of Medical Products and Tobacco
    - Office of Operations

Various Departments under FDA are:

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Food Safety and Applied Nutrition
- Center for Tobacco Products
- Center for Veterinary Medicine
- National Center for Toxicological Research

Center for Drug Evaluation and Research:

- This is the prime centre in the FDA for handling drugs.
- CDER handles new drugs from the Investigaional new drug (IND) stage to the evaluation of the New drug application (NDA) for approval or rejection of the request to market the product in the US.
- CDER then evaluates the post marketing safety of the product
- There are more than 20 “offices” in CDER covering many areas including biotechnology, new drug evaluation, pediatric drug development, generic drugs, compliance, and, of course, drug safety.
- There is an advisory committee (consist of outside experts) on Drug Safety and Risk Management that looks at safety issues.
- In 2005, the FDA created the new Drug Safety Oversight Board (DSB), which advises the CDER Center Director on handling and communicating important and emerging drug safety issues.

MedWatch

The MedWatch program is the FDA’s National Pharmacovigilance Program.

It provides Clinical information about safety issues involving prescription and over-the-counter (OTC) drugs, biologics, medical and radiation-emitting devices and special nutritional products.

MedWatch Online Reporting Form

MedWatch form 3500: For use by healthcare professionals, consumers, and patients.

Form FDA 3500B - Voluntary Reporting for Consumers. A consumer-friendly version of the 3500 reporting form.

Form FDA 3500A - Mandatory Reporting-For use by IND reporters, manufacturers, distributors, importers, user facilities personnel

The FDA maintains several databases that contain safety information-

- FAERS: FDA Adverse Events Reporting System
- VAERS: Vaccine Adverse Event Reporting System
- MAUDE: Manufacturer and User Facility Device Experience Database

2. Europe

European Medicines Agency (EMA)

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London.

In 1995, the European Medicines Evaluation Agency (EMEA) was created, based in the Canary Wharf section of London, UK (with > 600 employees). From 1995 to 2004, it was known as European Agency for Evaluation of Medicinal Products.

In 2004, a new directive changed the name of the EMEA to EMA (European Medicines Agency).

For European Union (EU), each European member State has its own National Competent Authority (NCA), with more or less, same missions.

Responsibility of EMA: The protection and promotion of public and animal health through the evaluation and supervision of medicines throughout the EU, comprising 28 countries (Member States) and their more than 40 national authorities, as well as the three European Free Trade Area (EFTA) nations of Iceland, Liechtenstein and Norway.

Switzerland also works closely with the EMA, particularly in areas regarding inspections.

Mission of EMA:

- Provide independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines
- Scientific evaluation of applications for European marketing authorization for medicinal products
- Stimulating innovation and research in the pharmaceutical sector

EMA evaluates and supervises medicines for use in European market, which is conducted in close co-operation with WHO and its procedure provides a level of confidence that a product is safe and effective.

The EMA handles human and veterinary medicinal products (but not food, unlike the FDA).

EMA has the authority to approve the "Marketing Authorization" for a product via the "Centralized Procedure", thus, avoiding the need to gain approval in each of the 31 countries.

Marketing Authorization Process in Europe:

Clinical Trial Application (CTA) is filed to the national competent authority (NCA) of the state to conduct the clinical trial within EU

After the evaluation and approval of CTA, Clinical Trials are conducted

Post phase I, Phase II and Phase III Clinical Trials, Marketing Authorization Application (MAA) is filed

Marketing Authorization is granted post which Phase IV/ Post authorization safety study (PASS)/Post marketing study (PMS) are conducted (if required)

**By law, a company can only start to market a medicine once it has received a marketing authorization*

Marketing Authorization Application

Centralised Procedure (via the agency (EMA), which results in a single marketing authorisation valid throughout EU and EEA for 5 years, extension may be applied 3 months before expiry)	Nationalised Procedure (where individual EU Member States authorise medicines for use in their own territory)
Applications are submitted directly to the Agency	This type of authorization is granted on country-by-country basis by the national

	competent authorities, in each member state
Evaluation by the Agency's Scientific committees takes up to 210 active days plus 'clock stops', at the end of which the committee adopts an opinion on whether the medicine should be marketed or not.	For medicines that fall outside the scope of the centralised procedure and intended for one market
This opinion is then transmitted to the European Commission, which has the ultimate authority for granting marketing authorisations in the EU.	
When license is recommended, EPAR (European Public Assessment Report) is produced and MA is issued.	

The Agency (EMA) provides scientific opinions, but it is not responsible for issuing decisions on whether to grant, suspend or revoke a marketing authorisation for any medicine.

For centrally authorised medicines, this type of legal decision is issued by the European Commission.

For nationally authorised medicines, this type of legal decision is issued by the national competent authorities of the EU Member States.

For companies to get MA in > one country:

Decentralised Procedure (to obtain marketing authorizations in several member states for products with no previous MA in any of the member states) of EU:

- An application is submitted to competent authorities of each of the member states where authorization is sought

- Quality/Efficacy/Safety/Administrative info along with the list of CMS (concerned Member states) and the member state to act as Reference Member state(RMS)
- Draft Assessment report on the medicinal product prepared and the CMS and RMS validate the application (14 days)
- RMS to prepare draft Summary of Product Characteristics (SmPC), labelling and package leaflet within 120 days which can be approved within 90 days

Mutual Recognition Procedure (to obtain marketing authorizations in multiple member states for products with previous MA in one of the member states of EU)

- Application is evaluated by RMS (90 days instead of 120 days)
- After marketing authorization is granted, product may be marketed (Phase IV trials) where new uses or new populations, long term effects etc. can be explored.

The European Medicines Agency (EMA) has seven scientific committees that carry out its scientific assessments. Seven scientific committees, with members from all 31 states are as follows:

CHMP: Committee for medicinal products for human use

- The CHMP replaced the former Committee for Proprietary Medicinal Products (CPMP).
- In the 'centralised' or 'Community' procedure, it is responsible for conducting the initial assessment of medicines for which an EU-wide marketing authorisation is sought
- The CHMP is also responsible for several post-authorisation and maintenance activities, including the assessment of any modifications or extensions ('variations') to an existing marketing authorisation.
- In the 'mutual-recognition' and 'decentralised' procedures, the CHMP arbitrates in cases where there is a disagreement between Member States concerning the MA of a particular medicine ('arbitration procedure').
- Assessments are purely on scientific criteria and detrmine if the medicines meet Q/S/E requirements

- The CHMP can issue an 'urgent safety restriction' (USR) to inform healthcare professionals about changes as to how or in what circumstances the medication may be used
- The CHMP publishes a European public assessment report (EPAR) for every centrally authorised medicine that is granted a marketing authorisation.
- Scientific assessment work conducted by the CHMP is subject to an internal peer-review system to safeguard the accuracy and validity of opinions reached by the Committee

PRAC: Pharmacovigilance risk assessment committee

- Composition: The Pharmacovigilance Risk Assessment Committee (PRAC) is composed of:
    - a chair and a vice chair, elected by serving PRAC members;
    - one member and an alternate nominated by each of the 28 Member States;
    - one member and an alternate nominated by Iceland and by Norway;
    - six independent scientific experts nominated by the European Commission;
    - One member and an alternate nominated by the European Commission after consultation of the European Parliament to represent healthcare professionals;
    - One member and one alternate nominated by the European Commission after consultation of the European Parliament to represent patients organisations.
- Role of PRAC:
    - The PRAC is responsible for assessing all aspects of the risk management of medicines for human use. This includes the detection, assessment, minimisation and communication relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account.
    - It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audit
    - The main responsibility of the PRAC is to prepare recommendations on any questions relating to pharmacovigilance activities related to a medicine for human use and on risk-management systems, including the monitoring of the effectiveness of those risk-management systems.

- In addition the PRAC is responsible for providing advice either to the CHMP, CMDh, EMA Secretariat, Management Board and European Commission, as applicable.
- The PRAC meets once a month. The meetings of the PRAC are not public. The Agency publishes the agendas and minutes of the meetings. After each PRAC meeting, the Agency also publishes a table highlighting the main decisions taken in the meeting.

PRAC tasks common to both centrally and non-centrally authorised products:

- For urgent Union procedures, Article 31 and Article 20 procedures triggered for safety reasons: the PRAC shall issue a recommendation.
- For PSUR single assessment: the PRAC shall issue a recommendation.
- For PASS protocols: the PRAC shall issue a letter of endorsement or objection.
- For PASS study results: the PRAC shall issue a recommendation.
- For signals: the PRAC shall issue a recommendation.
- For the establishment and subsequent updating of the list of EU Reference Dates (EURD) and the frequency of PSURs submission: the PRAC shall be consulted.
- For the updating of the list of medicinal products requiring additional monitoring: the PRAC shall be consulted.
- For “for cause” pharmacovigilance inspections: the PRAC shall issue an advice.

PRAC tasks specific to non-centrally authorised products:

- For PSUR single assessment: the PRAC shall issue a recommendation.
- For risk management plans/systems, renewals, safety type II variations: the PRAC may issue an advice, at the request of a Member State.
- For Member States’ safety announcements and communications: the PRAC shall issue an advice, at the request of the EMA Secretariat, on the timing and message content.

Other PRAC tasks:

- For the functionalities of the EudraVigilance database and the PSUR repository: the PRAC shall issue an advice.
- For the choice of the black symbol for additional monitoring: the PRAC shall issue an advice.
- For literature ADR monitoring: the PRAC may issue an advice, at the request of the EMA Secretariat.

CVMP: Committee for medical products for veterinary use: responsible for preparing opinions on questions concerning medicines for veterinary use.

COMP: Committee for orphan medical products: responsible for reviewing applications from people or companies seeking 'orphan-medicinal-product designation'.

HMPC: Committee for herbal medical products: responsible for preparing the Agency's opinions on herbal medicines.

PDCO: Paediatric committee: To assess the content of paediatric investigation plans (PIPs) and adopt opinions on them.

CAT: Committee for advanced therapies: It is a multidisciplinary committee responsible for assessing the quality, safety and efficacy of Advanced-Therapy Medicinal Products (ATMPs: gene therapy/somatic cell therapy/tissue-engineered/combined advanced-therapy medicines), and to follow scientific developments in the field.

EU-QPPV

- QPPV: Qualified Person for Pharmacovigilance
- QPPV is an individual named by a pharmaceutical company as the main person responsible for ensuring that the company (the holder of the Marketing Authorisation for the product or MAH) meets its legal obligations for the monitoring of the safety of the product on the market.

QPPV roles and responsibilities:

- Single point of contact for the NCAs in member states and the agency on a 24-hr. basis and also for PV inspections
- Shall reside in EU or EEA
- Is responsible for the overall functioning of the PV system including its quality system (e.g. SOPs, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance).
- Responsible for ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP.

Regulatory Authorities in the EU and EEA:

- Austria - Austrian Agency for Health and Food Safety
- Belgium - Federal Agency for Medicines and Health Products (FAMHP)
- Bulgaria - Bulgarian Drug Agency
- Croatia - Agency for Medicinal Products and Medical Devices of Croatia
- Cyprus - Ministry of Health- Pharmaceutical Services
- Czech Republic - State Institute for Drug Control
- Denmark - Danish Health and Medicines Authority
- Estonia - State Agency of Medicines
- Finland - Finnish Medicines Agency (FIMEA)
- France - National Agency for the Safety of Medicine and Health Products
- Germany - Federal Institute for Drugs and Medical Devices (BfArM)
- Greece - National Organization for Medicines
- Hungary - National Institute of Pharmacy
- Iceland - Icelandic Medicines Agency
- Ireland - Irish Medicines Board
- Italy - Italian Medicines Agency
- Latvia -State Agency of Medicines

- Liechtenstein - Office of Health/ Department of Pharmaceuticals
- Lithuania - State Medicines Control Agency
- Luxembourg - Ministry of Health
- Malta - Medicines Authority
- Netherlands - Medicines Evaluation Board
- Norway - Norewegian Medicines Agency
- Poland - Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
- Portugal - National Authority of Medicines and Health Products
- Romania - National Medicines Agency
- Slovakia - State Institute for Drug Control
- Slovenia - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
- Spain - Spanish Agency for Medicines and Health Products
- Sweden - Medical Products Agency
- United Kingdom - Medicines and Healthcare Products Regulatory Agency

New PV Legislation

New Pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.

The new Pharmacovigilance legislation, which started to come into effect in July 2012, was the biggest change to the regulation of human medicines in the European Union (EU) since 1995. It had significant implications for applicants and holders of EU marketing authorizations.

With the application of the new pharmacovigilance legislation as of July 2012, volume 9A has now been replaced by the good pharmacovigilance practices (GVP) guideline, published by the European Medicines Agency (EMA). However, where GVP modules have not yet been finalised, and for some transitionary measures, the relevant parts of volume 9A of the rules governing medicinal products in the European Union remain the reference.

Background (EU and EU laws)

The European Union (EU) is a unique economic and political partnership between 28 European countries (Member States) as well as the 3 European Free Trade Area (EFTA) nations of Iceland, Liechtenstein and Norway. The 31 countries are also referred to as the European Economic Area (EEA).

The EU laws (**regulations, directives and decisions**) take precedence over national law and are binding on national authorities.

Regulations: Are the most direct form of EU law- self-executing

Have a binding legal force throughout the EU

Directive: Require member states to achieve a particular result without dictating the means of achieving that result

Decision: Are EU laws relating to specific cases.

Good Pharmacovigilance Practices (GVP)

Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU.

GVP apply to marketing-authorisation holders (MAHs), the European Medicines Agency (EMA) and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

Guideline on GVP

The guideline on GVP is divided into chapters that fall into two categories:

- Modules covering major pharmacovigilance processes (GVP modules I to XVI)
- Product- or population-specific considerations.

GVP Modules:

Module	Module Title	
I	**Pharmacovigilance systems and their quality systems**	This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorization holders, competent authorities of Member States and the Agency.
II	**Pharmacovigilance system master file**	This Module provides detailed guidance regarding the requirements for the pharmacovigilance system master file, including its maintenance, content and associated submissions to competent authorities, applicable from July 2012, during the transition period (as described in Article 2 of Directive 2010/84/EU and Article 3 of Regulation (EU) No 1235/2010), and after 2015.
III	**Pharmacovigilance inspections**	This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and outlines the role of the different parties involved.
IV	**Pharmacovigilance audits**	This Module provides guidance on planning and conducting the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity.
V	**Risk management systems**	This module includes the principles of risk minimization, and details of routine risk minimization measures.

VI	**Management and reporting of adverse reactions to medicinal products**	This Module addresses the legal requirements which are applicable to competent authorities in Member States, MAH and the Agency as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU).
VII	**Periodic safety update report**	This module provide guidance for PSURs which are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.
VIII	**Post-authorisation safety studies**	This Module concerns PASS (post-authorisation safety study) defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
VIII Addendum 1	**Post-authorisation safety studies:**	Member States requirements for transmission of information on non-interventional post-authorisation safety studies
IX	**Signal Management**	This module provide guidance and requirements on structures and processes involved in signal management.

X	**Additional monitoring**	This module provides general principles for assigning additional monitoring status to medicinal products and on communication and transparency aspects.
XV	**Safety Communication**	This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information in the EU.
XVI	**Risk-minimisation measures**	Selection of tools and effectiveness indicators

Product or Process-Specific Considerations:

The chapters on product- or population-specific considerations are currently under development. They are being released for public consultation one by one. The first GVP considerations chapter (see below) was published in December 2013, i.e. GVP P I on pharmacovigilance for vaccines for prophylaxis against infectious diseases.

- Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases
- Product- or population-specific considerations II (PII): Biological medicinal products.

GVP Annexes:

- GVP Annex I - Definitions
- GVP Annex II - Templates:
    - Direct healthcare-professional communication
    - Cover page of Periodic Safety Update Report (PSUR)
- Final GVP Annex III - Other pharmacovigilance guidance

- Final GVP Annex IV - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for pharmacovigilance
- Final GVP Annex V - Abbreviations

2.1 Brexit and UK PV

2.1.1 UK PV pre-Brexit

The MHRA has been a strong voice in European and global pharmacovigilance for many years since its expertise is recognized globally. It may be because of the MHRA's expertise that the European Medicines Agency (EMA) decided to set up in London when it was founded in 1995. The MHRA was instrumental in the development of the current EU pharmacovigilance system, and the first Pharmacovigilance Risk Assessment Committee (PRAC) chair, Dr June Raine, is the MHRA director of vigilance and risk management of medicines.

Currently, the MHRA takes quite a large proportion of the EU workload. Over the years, the MHRA has provided guidance and support to many other Member States and led the Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action group.

Pharmacovigilance is one area where it is acknowledged that a post-Brexit relationship with the EU is particularly important. After Brexit, the MHRA may not be part of the Pharmacovigilance Risk Assessment Committee (PRAC) or have access to EU systems, such as EudraVigilance. However, the Member States acknowledge that they already have relationships with non-EU countries and the UK comes from a situation of strength. PV has been standardised within the EU relatively recently, so the MHRA has the expertise required if the UK ends up with a 'no deal' Brexit.

2.1.2 MHRA Brexit preparations

The MHRA has a Brexit taskforce that has been and continues to take the time to look in detail at all areas of pharmaceutical legislation and take into account the needs of all stakeholders. It wants to avoid any unnecessary complexity in future UK-specific requirements, for example by following existing processes. However, Brexit is an opportunity for the MHRA to remove any unnecessary 'red tape'. This may mean that post-Brexit UK pharmacovigilance processes will be simpler than EU PV processes. The Brexit section of the MHRA website is titled 'Making a success of Brexit', and it has made it clear it is looking for the best options and opportunities available for the safe and effective regulation of medicines and devices in the UK post-Brexit.

The existing EU rules will be converted into UK pharmacovigilance law at the moment of exit, with changes where necessary to make sure the rules work in the UK. The current PV legislation would remain in UK law as 'secondary legislation' and would be transferred into 'primary legislation' at a later date. This essentially means that UK pharmacovigilance requirements would mirror EU requirements on Day one so PV will continue as normal in the UK as if it were still an EU Member State, at least initially.

2.1.3 EU QPPV versus UK QPPV

Arguably the biggest post-Brexit change for PV is who will have legal PV responsibility in the UK. During the transition period, the MHRA will continue to be treated as a Member State. This probably means that, for companies with a UK-based EU qualified person for pharmacovigilance (EU QPPV), the EU QPPV can remain in the UK during the transition per-iod, but clarification, from the EU, is awaited.

Currently, the MHRA doesn't require an individual responsible for PV in the UK since that role is covered by the EU QPPV. After Brexit, a UK QPPV will be a legal requirement. It will be possible for the EU QPPV to take on responsibility for UK marketing authorizations (MAs) until the UK QPPV can be established. MA holders (MAHs) that don't currently have any presence in the UK will have until the end of 2020 to establish a UK QPPV in the UK.

The deputy EU QPPV role isn't defined in EU legislation. As a result, many companies were wondering whether UK-based EU QPPVs could have a joint role of both UK QPPV and deputy EU QPPV. In June, the EMA clarified its position and stated that deputy EU QPPVs must be established and perform their tasks in the Union (EEA).6 For many PV professionals the UK QPPV role will be a development opportunity. For those who hold EU QPPV roles and intend to remain in the UK, this change may mean a reduction in their job responsibility, although some companies have already started changing job roles, presumably to help them retain well-respected PV staff and enable them to continue to share their expertise.

2.1.4 UK pharmacovigilance post-Brexit

The MHRA will only be invited to EMA meetings and working groups where there is a UK interest (although the MHRA says this will be most of them). However, they will not be able to vote. They also won't be able to be rapporteur, co-rapporteur or reference member state for licence applications, but will be a concerned member state.

Specifically, with reference to individual case safety reports (ICSRs), it was as recent as November 2017 that EudraVigilance was updated to allow central EU PV reporting. Until then, many Member States (including the MHRA) required ICSRs to be submitted to them as well as the EMA. It, therefore, doesn't seem to be a big change to revert to separate reporting to the MHRA post-Brexit, especially if they have the same reporting requirements as the EMA (although the 90-day reporting rule for non-serious cases wasn't an MHRA requirement prior to November 2017 and could involve quite a large case burden for many companies). In preparation for the potential loss of access to EU databases, the MHRA is developing databases similar to the EU systems and intends to have them up and running in March 2019. They will notify stakeholders and will ask for their help to test systems before March 2019.

The Pharmacovigilance System Master File (PSMF) was developed as part of the current EU PV regulations. In the UK it replaced the Summary of Pharmacovigilance Systems. The PSMF needs to be housed within an EU Member State, but tends to be electronic so accessible from all countries. The MHRA is, therefore, unlikely to ask for a separate UK PSMF. However, there may need to be UK-specific annexes.

All MAs would need to be converted to national licences. Centrally approved product (CAP) MAs will automatically be converted to UK MAs on 29 March 2019, a conversion process known as 'grandfathering'. Mutual recognition and decentralised MAs will be unaffected since they already hold national UK MAs. With regards to aggregate reporting, the MHRA is likely to follow the EU model with national submissions via a portal similar to the Common European Submission Portal (CESP). It's not yet clear how they will take decisions on safety data submitted. If the MHRA has visibility of EU decisions, they may be able to accept those decisions, especially where they have limited resource, but, as usual, they will take a risk-based approach.

The only thing that we can say for certain about Brexit at the moment is that no one really knows what the relationship between the UK and the EU will be and what implications that will have. As we move closer to March 2019, the UK Government, including the MHRA, is trying to provide guidance to cover all scenarios. As with many new PV systems, the processes are likely to develop with time, but the MHRA continues to give guidance and has made it clear that it is making allowance for the challenges that MAHs are facing.

3. India

Pharmacovigilance in India was initiated way back in 1986 with a formal adverse drug reaction (ADR) monitoring system, under supervision of the drug controller of India. India joined the World Health Organization (WHO) Programme for International Drug Monitoring in 1998, but was not successful. Later, the National Programme of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programme of India (PvPI) in 2010.

The **Pharmacovigilance Program of India (PvPI)** was re-launched with a broad objective to safe guard the health of people of India. Adverse drug Reactions (ADRs) are reported from all over the country to national Coordination centre (NCC)-PvPI, which also work in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden to contribute in the global ADRs data base. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India (CDSCO) in taking decision for safe use of medicines. I invite all the health care professionals and patients/consumers to join us in our mission to promote patient safety.

The Programme

The Central Drugs Standard Control Organisation (CDSCO), New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide pharmacovigilance programme in July 2010, with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordinating Centre (NCC) for monitoring Adverse Drug Reactions (ADR) in the country to safe-guard Public Health. In year 2010, 22 ADR monitoring centers (AMCs) including AIIMS, New Delhi had been set up under this Programme. To ensure implementation of this programme in a more effective way, the National Coordinating Centre was then shifted from the All India Institute of Medical Sciences (AIIMS), New Delhi to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, (U.P.) in April, 2011.

Mission of PvPI:

The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of use of medicine outweighs the risks associated with its use.

The purpose of the PvPI is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. The broadened patient safety scope of pharmacovigilance includes the

detection of medicines of substandard quality as well as prescribing, dispensing and administration errors. Counterfeiting, antimicrobial resistance, and the need for real time surveillance in mass vaccinations are other pharmacovigilance challenges which need to be addressed.

Scope and Objectives

- To create a nation-wide system for patient safety reporting
- To identify and analyse new signal from the reported cases
- To analyze the benefit - risk ratio of marketed medications
- To generate evidence based information on safety of medicines
- To support regulatory agencies in the decision-making process on use of medications
- To communicate the safety information on use of medicines to various stakeholders to minimise the risk
- To emerge as a national centre of excellence for pharmacovigilance activities
- To collaborate with other national centres for the exchange of information and data management
- To provide training and consultancy support to other national pharmacovigilance centres across globe
- To promote rational use of medicine

Goals

Short term Goals

- To develop and implement pharmaco-vigilance system in India
- To enrol, initially, all MCI approved medical colleges in the program covering north, south, east and west of India
- To encourage healthcare professionals in reporting of adverse reaction to drugs, vaccines, medical devices and biological products
- Collection of case reports and data

Long term Goals

- To expand the pharmacovigilance programme to all hospitals (govt. & private) and centres of public health programs located across India
- To develop and implement electronic reporting system (e-reporting)
- To develop reporting culture amongst healthcare professionals
- To make ADR reporting mandatory for healthcare professionals

ADR Monitoring Centres under PvPI

ADR Monitoring Centres (AMCs) under PvPI play a vital role of collection and follow-up of ADR reports from the patients. They are set up across India to collect the adverse event information from patients.

These AMCs are the Medical Council of India (MCI) approved medical colleges & hospitals, medical/central/autonomous institutes, public health programmes or corporate hospitals.

They are responsible for collecting the adverse event information from the patients, performing follow up with them to check the completeness of the ADR reports as per Standard Operating Procedures (SOPs), entering information in the prescribed software (Vigiflow) and sending them to NCC via the same software. Some AMCs are also responsible for providing training and technical support at regional level.

The PvPI started with the enrolment of 22 ADR monitoring centres across the country in the year 2010, which has increased to 90 by the end of 2012, 60 of which are phase I (FY2010-FY2011) AMCs and 30 are phase II (FY2012-FY2013) AMCs. All the 90 AMCs are categorized into four zones i.e. North, South, East and West as per zonal offices of CDSCO in India and are functioning under NCC.

There are more than 2000 pharmacy colleges 90 Institute of Pharm.D, more than 200 dental institutes and more than 320 nursing institutes all over India. All PharmD, pharmacy practice, dental and paramedical colleges are associated with patients care by providing safe and effective medication. For robust pharmacovigilance, these colleges will be included as ADR Monitoring Centres under this programme in the years to come.

There are more than 360 MCI approved medical colleges in India, of which 194 colleges are private. All MCI approved colleges and Pharmacy Council of India (PCI) approved pharmacy colleges having pharmacy practice and Pharm.D will be included in PvPI through proper channel. All MCI approved medical colleges and hospitals in the programme covering north, south, east and west of India will be enrolled and ultimately, all government and corporate hospitals will be enrolled in the programme covering the entire India.

ADR Reporting under PvPI:

The National Coordination Centre was shifted from New Delhi to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad in 2010. The PvPI works to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use.

The culture of reporting of ADRs has achieved remarkable success, with 250 PvPI-established adverse drug monitoring centres all over India and provision of training to healthcare professionals. The programme is striving hard to build trust between the physician and the patient, thereby increasing patient safety and the confidence of people in the country's health system, in addition to the detection of substandard medicines and prescribing, dispensing and administration errors.

The IPC-PvPI has now become a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services.

In spite of these achievements, several challenges are faced by the PvPI, like the monitoring of generic drugs, biosimilars, and disease-specific ADRs of antidiabetic, cardiovascular and antipsychotic drugs and, above all, creating awareness, which is a continual process. At the same time, the PvPI is trying to address other challenges like counterfeit drugs, antimicrobial resistance, and surveillance during mass vaccinations and other national programmes.

4. Australia

Drug safety in Australia is regulated via the Office of Medicines Safety Monitoring (OMSM) (synonymous with Adverse Drug Reaction Advisory Committee), a branch of the Therapeutic Goods Administration (TGA).

Therapeutic Goods Act 1989 provides a national framework for the regulation of therapeutic goods in Australia to ensure quality, safety and efficacy of medicines.

The **Therapeutic Goods Administration (TGA)** is a unit of the Australian Government Department of Health and Ageing that is responsible to ensure the administration of the provisions of the legislation, Therapeutic Goods Act 1989.

The TGA carries out assessment and monitoring activities to ensure that therapeutic goods available in the Australian market are of acceptable standard.

The TGA Office of Medicines Safety Monitoring receives reports of suspected adverse reactions to prescription medicines, vaccines, over-the-counter medicines and complementary medicines. All reports are reviewed by professional staff. Reports involving serious reactions or recently marketed drugs are reviewed by the Adverse Drug Reactions Committee (ADRAC). The Adverse Drug Reactions Committee (ADRAC) is a subcommittee of the Australian Drug Evaluation Committee (ADEC) which was formed in 1970 to advise TGA on the safety of medicines.

The Australian pharmacovigilance requirements have been implemented using the following Guidelines:

Spontaneous Reporting: "Australian guideline for pharmacovigilance responsibilities of sponsors for registered medicines regulated by Drug Safety and Evaluation Branch," July 2003, Amended May 2005.

Clinical Safety Reporting: "Access to unapproved therapeutic goods – clinical trials in Australia," Oct 2004.

It is expected that drug Sponsors/Manufacturers must ensure that an appropriate system of pharmacovigilance be in place in order to assume responsibilities and liability for its products on the market and to ensure that the appropriate action can be taken when necessary.

Spontaneous adverse event reporting is voluntary in Australia. Domestic reports, serious expected and unexpected received by sponsors/manufacturers from healthcare professionals, patients and consumers are to be reported to ADRAC in an expedited manner (15 days). Cases from worldwide literature and reports from post-registration studies are also reported to ADRAC within 15 days upon receipt of reports.

Domestic clinical trial cases are to be reported within 7 days for fatal/life-threatening serious unexpected adverse reactions and all other serious unexpected adverse reactions (SUA's) within 15 days. Special access scheme, authorized prescriber mechanism and use of unapproved products through personal importation are also reportable to ADRAC.

PSURs (Periodic Safety Update Reports) are submitted annually for the first 3 years after the date of the approval letter. The first must be submitted no later than 15 calendar months after approval. Subsequent reports must be submitted at least annually from the date of the first submitted report.

Minimum reporting criteria for reporting of ADRs to ADRAC are:

- Identifiable patient
- Medicinal product
- Identifiable reporter
- Event

One of the features of the Australian pharmacovigilance system is the high proportions of direct reporting by health professionals using the ADRAC "Blue-Card." Cases received by ADRAC are subjected to medical review and new safety information is circulated to the healthcare professionals via the Australian ADRAC Bulletin.

Recently, the TGA embarked on several initiatives: Web-based electronic report form in Australia with reporting facility in GP software; dedicated pilot consumer reporting line; Risk Management Plans being introduced and Life cycle management of products. These

initiatives are important for TGA to further fulfill its pharmacovigilance commitment to the Australian community.

Like all other regulators, the TGA are faced with challenges and here are some of these challenges:

- Pharmacovigilance still largely limited to spontaneous reporting: Limitations include difficulties with adverse event recognition, underreporting, biases, estimation of population exposure, and report quality
- Data-mining potentials and pitfalls: No current guideline on standards for the use of these methods in routine pharmacovigilance
- Risk management: Ongoing “monitoring” and “fine-tuning” required to ensure value to public health
- Pharmacoepidemiology: Practice guidelines required for conduct of pharmacoepidemiology studies
- Global problems: global responses

5. Japan

The Ministry of Health, Labor and Welfare (MHLW) is one of the cabinet level Ministries in the Japanese government. This government body provides regulations on maximum residue limits for agricultural chemicals in foods, basic food and drug regulations, standards for foods, food additives, etc.

The **Pharmaceuticals and Medical Device Agency (PMDA)** of Japan is the foremost agency in Japan, and is the counterpart to the FDA in the USA and is responsible for the operational aspects of drug development. The PMDA, along with The Pharmaceutical Affairs Law, provides the legal basis for PV requirements in Japan, supplemented by a variety of communications issued by the Ministry of Health, Labor, and Welfare (MHLW). The MHLW is the Japanese counterpart of the Department of health and human services (HHS), and is ultimately responsible for drug approval.

Institute for Safe Medication Practices (ISMP) is a national, confidential medication error reporting system, that distributes hazard alerts and other medication safety information to 6,00,000 providers every other week.

What is reported: ISMP is a focused system for adverse drug events and hazards in medication delivery and management.

Who reports: Reports are accepted from HCPs, organizations or patients.

How they report: Reports from organizations or professionals can be submitted online, electronically, by telephone, mail or fax.

General requirements for PV in Japan

- All Japanese companies must make provisions for the conduct of post marketing surveillance (PMS):
- Establish PMS management departments with qualified staff and independent sales and marketing departments
- Appoint a responsible person for PMS management
- Prepare and comply with relevant standard operating procedures

- Japanese expedited reporting for investigational products is generally consistent with the ICH E2A guidelines. However, the requirements also specify that fatal or life-threatening expected ADRs qualify 15 day reports, regardless of the country of origin.

Investigational products: Japanese expedited reporting requirements

Report

ADRs that qualify for reporting

- 7 day Fatal or life-threatening unexpected
- 15 day Fatal or life threatening expected

In addition to the above, 15 day reports should also be filed if results from clinical trials indicate an increased frequency of ADRs, lack of efficacy or the possibility of an association with the onset of cancer, important medical events, disability/incapacity or a fatal outcome.

PMS activities for marketed products

Once a company gets the approval to market a drug in Japan, it should evaluate the product's safety over 4, 6, or 10 years “re-examination” period, dependant on the nature of the drug. The activities that should take place in the early post-marketing phase are as follows:

Early post-marketing phase vigilance (EPPV)

Companies are required to conduct EPPV for the first 6 months after the launch of a new product in Japan. The main objective of conducting EPPV is to assure that appropriate information has been provided to the prescribers to encourage caution, promote understanding of the appropriate use of the product, and report spontaneous ADRs and infections to implement the consequent safety measures and minimize the associated public health risk.

Clinical Experience Investigation (CEI) studies: CEI studies are also a post-marketing requirement to detect unlabeled ADRs, to understand the development of ADRs during the actual use of the drug, and to define the factors suspected to influence the product's safety and efficacy profile.

Special studies and post-marketing clinical trials as instructed by the MHLW at the time of approval may include

Drug utilization studies

Studies arising from pre-approval clinical trials, reports of ADRs, communicable diseases, etc.

Studies for identifying, validating, or confirming information about the appropriate use of the product

Expedited reporting for marketed products

In Japan, expedited reporting requirements for marketed products are dependent on the country of origin and seriousness and severity of the ADRs.

Infections:

The Pharmaceutical Affairs Law requires that all domestic and foreign reports of fatal/life-threatening or other serious infections associated with possible contaminations of the drug to be notified immediately to the MHLW as preliminary reports followed by written report within 15 days, irrespective of whether the event is labeled or not. All domestic cases of moderate unexpected infection must be notified within 30 days.

Periodic safety reports

All PSURs in Japan should be submitted to the MHLW for all marketed products in accordance with ICH E2C and include all foreign data. Each PSUR should contain a full section on the safety information presented in the Japanese prescribing texts for the product. The PSURs should be submitted every 6 months for 2 years following approval of the Japanese new drug application (JNDA) and on an annual basis thereafter during the defined “re-examination” period. Following completion of “re-examination,” the PSURs can then revert to a 5 year periodicity.