Pharmacovigilance in 2020: Boldly Shaping the Future An overview

Part 1:

Where we are

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Abstract

Since the start of the modern pharmacovigilance era in the 60s (sparked by the Thalidomide tragedy) the discipline has been steadily gaining importance in the pharmaceutical industry.

The changing role of pharmacovigilance (PV) has been most notable over the past few years with a "paradigm shift" that moved PV-related regulatory requirements away from simple "event counting" to "benefit/risk" evaluation and more recently to "proactive risk management".
While regulators will keep the emphasis on adequate collection of key information on medicines, PV functions will also be expected to conduct analysis of both safety and effectiveness data and information, and undertake corrective/proactive actions to safeguard public health. This will be expected across all phases of the product life cycle.
Examples of the European Medicine Agency's (EMA's) more all-encompassing approach to safety include the fairly recent creation of the Pharmacovigilance Risk Assessment Committee (PRAC) and the sharp increase of regulatory inspections.

At a company level, PV departments are finding their roles have become increasingly strategic. Not only must they respond to a higher number of more complex regulatory requirements but they are also involved in some high-level business and inter-departmental activities within their own companies. Examples of these new activities include greater collaborating with medical information and medical affairs departments, increasing involvement in the conduct of PV intelligence, involvement with vendors assisting patient support programmes, supporting mergers and acquisitions (M&As) negotiations, and involvement with non-interventional studies. Other future challenges will include the use of web and social media networks for PV purposes or personalised medicine. As a result, the "traditional" boundaries between the different phases of the life cycle of a drug are becoming more and more blurred, with a greater degree of overlapping between traditional regulatory, medical, and PV activities.

Managing the current and growing demands on PV departments requires team members to have multiple and diverse operational and management skills. For small and mid-sized companies, this adds enormous resource pressure. In such cases, outsourcing part or all the PV-related activities could be the most efficient and cost-effective strategy.

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Introduction

Pharmacovigilance (PV) is probably the area of drug development and commercialisation that has witnessed the greatest amount of change in the past few years.
Based on current developments, it's reasonable to assume that the trend towards, first, increased complexity of the whole field of PV, and second, towards an expansion of the scope of this area will continue. This paper is the first of a planned series of discussions regarding the increasing complexity of pharmacovigilance. It aims to provide an overview of some of the most significant areas of PV development in Europe and to offer an analysis of the possible consequences of such developments, especially from the point of view of the PV departments of a pharmaceutical company operating in the international market. Information shared in this paper are gathered from conferences and publications, EMA, institutional websites, Medline, and from industry and CRO experience.

Where we started

Even though "Pharmacovigilance" can be dated back to 1848 the start of its "Modern Era" can be considered 1961, when an Australian physician posed a question to "The Lancet" about the possible correlation between thalidomide and birth defects (see figure 1).

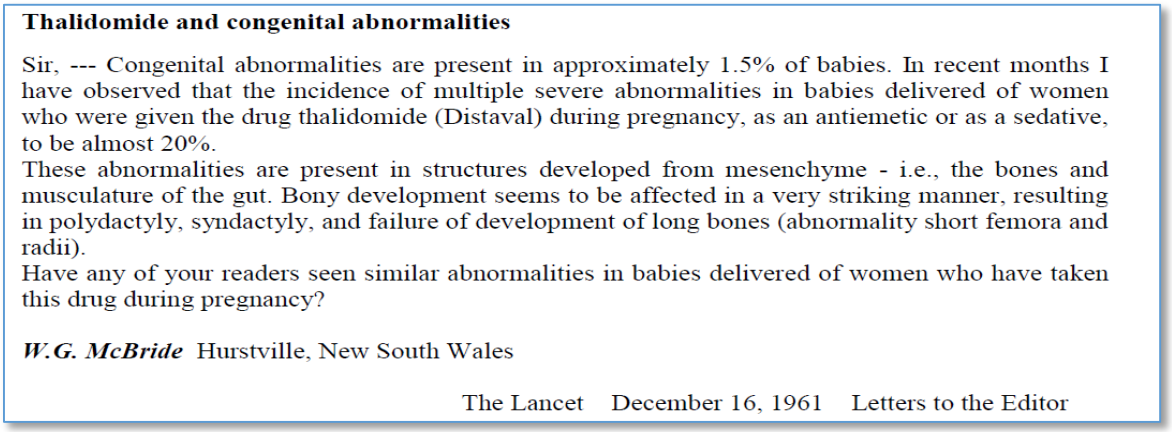
In 1962, the United States Congress enacted laws requiring tests for safety during pregnancy before a drug could receive approval for sale in the U.S. Other countries enacted similar legislation.

In 1968, the World Health Organization (WHO) started the "*Program on International Drug Monitoring",* to which most countries now participate, and since then PV has become an essential element of drug development.
Sparked by "incidents" that receive extensive media attention, such as the association of statins and rhabdomyolysis or heart risk associated with prolonged use of COX-2 inhibitors, PV legislation and guidelines have continued to evolve worldwide.
In recent history, this evolution was spearheaded by the European Medicines Agency (EMA).
The development of the most recent EU PV legislation was based on the observation that – as reported by EMA - adverse drug reactions (ADRs), defined as "*noxious and unintended responses to a medicine*", were causing around 197,000 deaths per year in the EU.

In 2005, the European Commission began a review of the European system of safety monitoring (i.e. Regulation (EC) No 726/2004 and Directive 2001/83/EC), including sponsoring an independent study, as well as extensive public consultation through 2006 and 2007.
This process resulted in the adoption of amended or new Directives and Regulations by the European Parliament and Council of Ministers in December 2010 (Directive 2010/84/EU, Regulation (EU) No 1235/2010) bringing about significant changes in the safety monitoring of medicines across the EU when this legislation became effective in July 2012. Other updates of legislation included Directive 2012/26/EU as well as Commission Implementing Regulation (EU) No 520/2012 and Regulation (EU) No 1027/2012.

Since 2012, a set of Good Pharmacovigilance Practices (GVP) guidelines have been developed and are regularly revised to support the implementation of the new PV legislation.

Figure 1



Thalidomide and congenital abnormalities

Sir, --- Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (Distaval) during pregnancy, as an antiemetic or as a sedative, to be almost 20%.
These abnormalities are present in structures developed from mesenchyme - i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormality short femora and radii).
Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

W.G. McBride Hurstville, New South Wales

The Lancet December 16, 1961 Letters to the Editor

Where we are

Presently, the "working definition" for PV used quoted by EMA in a pharmacovigilance brochure published in 2015 (see figure 2) and in many other official publications is:
"*Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions and other medicine-related problems.*"

Figure 2

This is essentially the definition previously adopted by WHO in 2002.

This is clearly a very broad definition that encompasses not only the traditional activity of collecting safety-related data, but also the concept of "prevention", which implies "pre-emptive" action. In addition the concept of "*other medicine-related problems*" is introduced ensuring that pharmacovigilance includes not only adverse events but "special situations" such as safety in the context of medication errors, abuse, misuse, foetal exposure, overdose, occupational exposure or off label use.

Benefit/risk ratio: the common denominator

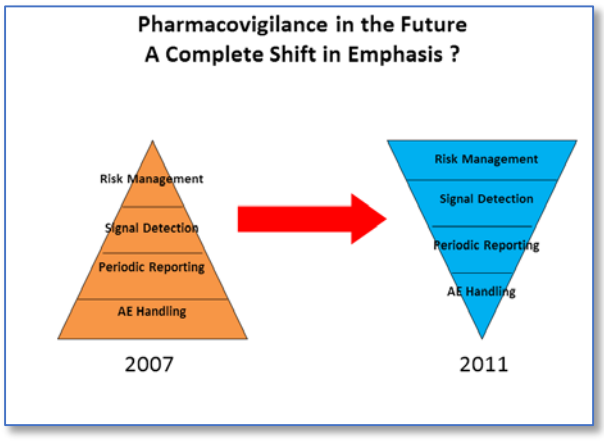
The concept of the "benefit/risk" ratio (no longer called "risk/benefit", which itself is a significant change) has become the common denominator not only of PV, but also of practically all drug-related regulatory activities throughout the life cycle of a medicine, from preclinical to post-marketing.
This is a scientifically sound approach and is in line with current clinical practice, however, it has made PV activities significantly more complex, since it implies that all benefit and risk data about a drug have to be put in context before any decision can be made on how to proceed. In addition, the concept of benefit has been extended beyond the traditional proof of efficacy demonstrated in an interventional clinical development programme to a much broader concept of effectiveness in the 'real world', where medicines are prescribed off-label, patients are not compliant with treatment, poly-pharmacy and poly-morbidities complexities exist, etc. Now PV experts have to become benefit experts, analysing complex data from different sources with highly variable quality.

The "pyramid paradigm"

The two most recent "Stakeholders Forums" organised by EMA have clearly indicated the agency's shifting perspective on PV (EMA, 2015 b; EMA, 2016 b).

As Sini Eskola (Eskola, 2015), official representative of EFPIA (European Federation of Pharmaceutical Industries and Associations), presented at the 9th stakeholder forum on the PV legislation, held on 15 September 2015, the first "paradigm shift" occurred between 2007 and 2011 (see figure 3).

Figure 3



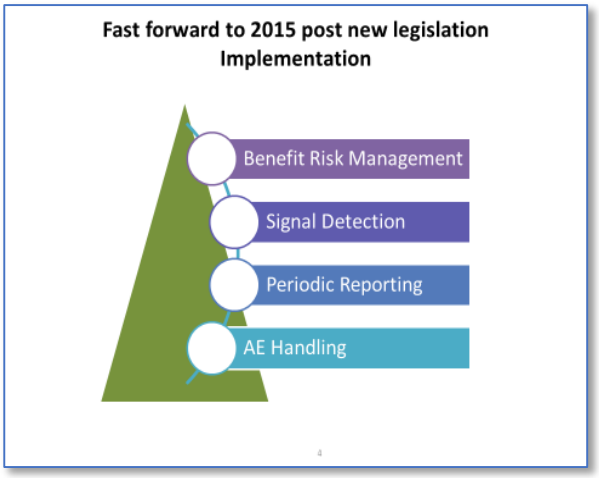
The focus, in fact, shifted from an "event-based" approach, i.e. making sure that all necessary data were collected properly and in a timely manner, to

an approach in which adequate collection of information was somehow "taken for granted", with the emphasis instead being placed on what could be done with the available information.
In fact, activities such as signal detection and signal management, along with Risk Management Plans (RMPs) have become core pharmacovigilance activities. The increasing number of RMP reviews undertaken by the PRAC underscores this: from 48 RMPs in the second half of 2012 to 637 in 2013 and 597 in 2014.
RMPs are a clear example of "proactive PV", since they give great importance not only to managing risk, but also to what we do not know about a medicine and to what can be done to minimise the possible consequences and/or to fill knowledge gaps.

Benefit/risk ratio: again the common denominator

In Sini Eskola's presentation (see figure 4) the new approach to PV is aptly summarised in a new "pyramid".

Figure 4



This is mirrored, with the addition of some regulatory detail, by what is published on the EMA website, which lists the key areas on which EMA is focusing its activities, such as:

- Collection of key information on medicines
- Analysis and understanding of data and information
- Regulatory action to safeguard public health
- Communicating with stakeholders

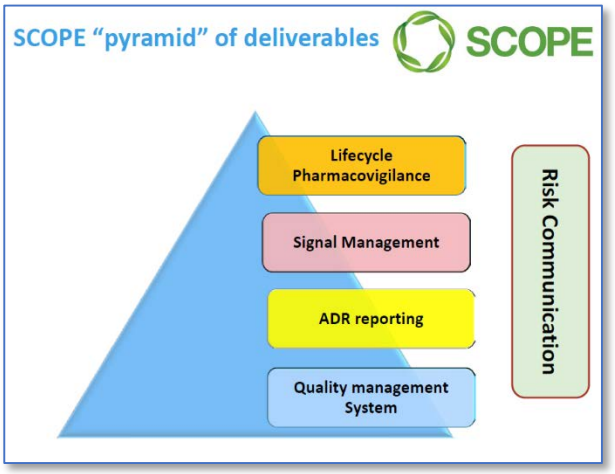
(see EMA website: Implementation of the pharmacovigilance legislation).

During his presentation, again at the 9th Stakeholder forum on the PV legislation, Peter Arlett (Head of the PV Department at EMA) confirmed that the situation in the past was characterised by "reactive monitoring" and sub-optimal processes (Arlett, 2015). The key priorities for EMA are "proactivity", improvement of processes and involvement of stakeholders, including the use of social media.

During the 10th Forum (held on September 21st, 2016) Dr. Arlett emphasised again the need for a proactive approach to pharmacovigilance, an approach that should make use of all available sources and data (Arlett, 2016).

The "pyramid paradigm" was taken one step further at the same meeting by Dr. June Raine, Chair of the PRAC) who presented the results of the SCOPE project (The Strengthening Collaboration for Operating Pharmacovigilance in Europe).

Figure 5



The aim of this international project (summarized in Figure 5) is "*shaping the communication in pharmacovigilance for the future by:*

- *evidence-based use of risk communication practices and tools*
- *maximising new mechanisms and media*

- *working in partnership with patients, healthcare professionals, and academia*
- *delivering measurable public health benefits" (Raine, 2016)*

It is likely that in the future there will be a need for a greater uniformity and "alignment" of PV reporting systems, which will have to be part of a quality management system.

This could represent a serious challenge for multinational companies with several affiliates. Cultural diversity, in fact, is an asset but can become a real hurdle when it comes to aligning different affiliates with a common set of processes and procedures that have to fulfil the requirements of multiple regulators with different priorities.

PRAC: present and future

PRAC – established in the second half of 2012 -- is responsible for assessing all aspects of the risk management of medicines for human use across the European Economic Area, from signal management to periodic safety update reports (PSURs) and risk management plans (RMPs). It is also involved in the design and evaluation of some post-authorisation safety studies (PASS), and coordinates the European PV agency inspection programme.

The main responsibility of PRAC is to prepare recommendations on any questions relating to PV activities of a medicine for human use, on signal management, and on risk-management systems, including monitoring of the effectiveness of such systems. Where appropriate, the PRAC can impose a PASS to the Marketing Authorisation Holder of a medicinal product as a condition of the marketing authorisation or a specific obligation under exceptional circumstances. PASS may be also be required by the PRAC to investigate a safety concern in the product risk management plan or to evaluate the effectiveness of risk minimisation activities (see GVP Modules V, VI and VIII).

If we needed another example of how quickly the scenarios in PV are changing, we could mention the fact that, in July 2017, EMA published 13 new "PASS: Questions and Answers". The PRAC work plan for 2017 (PRAC, 2017) was published on March 23rd 2017.

The document indicates that activities related to RMPs and safety referrals will be further enhanced, along with an increase in post authorisation safety study- (PASS) and post authorisation efficacy study- (PAES) related activities. A particular focus for 2017 will be signal management, with the introduction of enhanced EudraVigilance functionality on 22-Nov-2017 and associated requirements for the industry to forward all validated signals to PRAC for evaluation. A recently published document from EMA (April 21, 2017) states that since its establishment in September 2012, PRAC has discussed and published the results of its discussions on more than 600 signals.

This document essentially confirms and extends the lines already indicated in the previous work plans (PRAC, 2015; PRAC, 2016).

Given the emphasis placed by most of the presenters at the 9th and 10th stakeholders meetings on "real-life usage" medication errors management, epidemiological data, and involvement of stakeholders, it is quite likely that the next two to three years will also see PRAC taking a more focused approach to these areas.

The "external" role of PV

The role of PV has gained importance in recent years and has shifted from simple "event counting" to an active (and sometimes even assertive) interaction with stakeholders outside and within the company.

Requirements from Regulatory Authorities

Based on the trends seen in the past and from the official statements from EMA and other regulatory officials we can soon expect a higher number of inspections and audits, where all aspects of PV will be scrutinised. This is in stark contrast to statements made by EMA before the introduction of the new GVP that it was intended to ease the burden on industry and reduce duplicative activity.

We have seen, and will continue to see, an increase in follow-up inspections, where the inspectors will expect to find that the findings of previous inspections have been addressed and

corrected by means of Corrective and Preventive Action (CAPA) plans. Collaboration among national authorities, sharing findings from audits and inspections, will continue. One such example is EMA's EudraGMDP database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing-practice (GMP) and good-distribution-practice (GDP) certificates. The database is not only fully open to all regulatory authorities in the European Economic Area, but also to several international regulatory partners. A public version of the database gives members of the public access to the information in the database that is "not of a commercially or personally confidential nature." (EudraGMDP)

Most likely, the starting point of all inspections will continue to be the Pharmacovigilance System Master File (PSMF) which, many of which inspectors have said are still a long way from being considered adequate.

Some regulatory authorities, such as the Austrian Agency for Health and Food Safety (AGES), have recently emphasised the importance not only of having key performance indicators (KPIs) but also of monitoring them regularly from a signal detection point of view, assessing the situation, and proactively taking a CAPA whenever a trend is noticed.

Impossible expectations

The role and responsibilities of the Qualified Person for PV (QPPV) are clearly indicated in Section I.C.1.1. ("*Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU*") of the Guideline on GVP Module I – Pharmacovigilance systems and their quality systems.

The idea of having one person, resident in the EEA, who is directly and "*ad personam*" responsible for the PV structure and operation of a Marketing Authorisation Holder (MAH), is undoubtedly sound, since this person has a very personal interest in assuring that all processes and procedures are in order and that the existing regulations are complied with.

The burden placed on the QPPV, however, is already very heavy, both in terms of workload and responsibilities. Many activities -- RMP management, referrals, signal management, review and sign-off of PASS protocols, audits, and inspections – are expected to increase in frequency and detail.

Similarly, as clearly stated in PRAC recent work plans, a significant increase both in the number and in the complexity of PAES as PASS is quite likely.

In addition, new areas are going to be regulated, leading to further responsibilities and management resources, in the not-too-distant future. These include "social network listening", integrated knowledge management or measuring the impact of PV-related activities, which to some extent is already required with RMPs, but will become an even greater requirement in the future.

Further compounding the challenges faced is the fact that a large percentage of EEA QPPVs are based in the UK. Brexit could, therefore, have huge ramifications for the role.

Local Pressures

In addition to the QPPV, relevant authorities in the Member States have the option to request the nomination of a PV contact person at the national level reporting to the QPPV.

In principle, this approach could improve communications and relieve the QPPV of some of his/her workload. In reality, this poses an additional relevant burden on small and medium companies.

For larger enterprises. moreover, , having different local contact points could make standardisation and alignment between headquarters and affiliates difficult, and could well lead to additional management resources and control procedures being needed.

This is especially true in emergency situations, such as product recalls, where alignment between central and local procedures is required. In many companies, this will probably require re-analysis of some processes and procedures.

The role of outsourcing:

It is clear that the proper management of all PV obligations and requirements requires a team of skilled and experienced professionals and that the expectation, which is still the norm in some small to medium pharma companies that a single person can handle everything, is completely unrealistic.

Outsourcing can help to alleviate these pressures, though it's important that companies consider their specific needs to determine the best fit for their situation during a thorough request for proposal process.

In one example, a small North American company needed to update its PV system to European standards after a GVP inspection, conducted by the MHRA on behalf of the EMA, returned critical findings. The company began working with an external QPPV, who over the course of a year updated the company's entire PV system. When the next GVP inspection was held a year later, the EMA inspector returned no critical findings.

The example demonstrates how working with the right outsourcing partner can help small companies overcome challenges without having to take on full-time internal resources.

Outsourcing to an appropriate partner is also a very good opportunity for small and medium companies to obtain local and global PV and regulatory intelligence, knowledge that could be very useful for planning and executing strategies.

The "internal" role of Pharmacovigilance

In addition to the "external" requirements, coming from national, international, and regional regulatory authorities, PV groups are now involved in a series of strategic decisions within the company and must act in close collaboration with top management.
This adds to the workload of these groups, but also to the opportunities for PV professionals as they take on a more involved a strategic role within a company.
Indeed, the increasingly important role PV can and does play at a business level led to one person posing the rather provocative question: "*Are we ready for a CPVO (Chief Pharmacovigilance Officer)*?" That implies that pharmacovigilance expertise should be involved more and more extensively in top level strategies in all pharma companies.

PV beyond the EU

A detailed analysis of the situation outside the EU is beyond the scope of this paper, however, the fact that many countries (China, India, Korea and Japan, just to name a few) require a RMP implies a growing interest in many other parts of the world in a PV-approach based on risk minimisation and risk management rather than on simple "event reporting". It is notable that a number of countries are developing legislation and regulatory guidance that is inspired by the EMA's Good Pharmacovigilance Practices.

Egypt, Jordan, the United Arab Emirates, and Saudi Arabia already require a RMP.
In addition, a document on GVP for Arab countries has been published (effective in 2015), describing the respective obligations of the MAH and National Medicines Authority (NMA) to set up a PV system.

Russia, Belarus, Armenia, Kazakhstan, and the Kyrgyz Republic formed the "Eurasian Economic Union" (Eurasian Union, 2015), and in January 2016 a GVP document – applicable only to products registered under the "common procedure" – became effective, with some very specific requirements, such as a "Eurasian" QPPV and the need to submit "Eurasian" RMPs, PSURs, and PSMFs, along with ICSRs.
Inspections are expected to become operational as of January 2017.

It is logical to expect that more countries will add this type of requirement, most likely along with signal detection and benefit/risk analysis activities in general.
Exporting in those countries will therefore require greater involvement of the PV groups within companies.

Conclusions

In recent years, the role of PV has become more and more relevant and strategic in the pharmaceutical industry.

The new regulatory requirements have considerably increased the workload of PV, but have also changed the nature of PV work from simple “event counting” to “risk management”.

In addition to this, companies are increasingly viewing PV as less of costly necessity and financial burden and more of a possible source of savings and even revenue potential, for example through the development of products that have a better safety profile.
This is especially true in a scenario where mergers and acquisitions are frequent and Health Technology Assessment/Market Access activities have become essential to the success of a drug.

The focus on risk management-related activities will continue, however, the new challenges instigated by web and social listening or by the fact that regions outside of the EU, such as Eurasia or the Arab countries, are also becoming more focused on risk management, will require a more holistic approach to PV.
PV managers will likely have to become “knowledge managers” and be able to exploit in the most effective way the new available technologies.
PV is also going to have to become even more cross-functional, playing an increasingly important role across the life cycle of a drug.
This implies that all processes and procedures should be periodically re-evaluated for adequacy and, if needed, improved, modified, or altogether substituted.
The common denominator for this re-evaluation should be the adoption of a proactive safety approach integrated as much as possible on top and across departments/divisions, but with provisions to include also affiliates and partners/vendors.

If these challenges are met, PV will allow MAHs not only to be compliant with existing and future regulations (no small feat in itself), but also to gain a competitive edge.

As we have already said, all the present requirements, and the certainty that the situation will become more and more complex in the future, are probably “too much for one person” and possibly also “too much for a single group”, with the possible exception of the largest companies.

This complexity has led to a growth in outsourcing of PV-related services. For most companies, delegating (wholly or in part) PV activities to organisations with specialist knowledge and expertise will become the most cost-effective solution.

Publication of Part 2 expected DEC 2017

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