# The EU Pharmacovigilance Risk Assessment Committee: First year experiences

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**Abstract**

*The European Pharmacovigilance Risk Assessment Committee began its work one year ago. The article provides an overview of the mandate, working practices and experiences of the new committee. It has been a challenging year for all stakeholders. The ultimate impact of the new legislative framework is yet unknown, but a thorough assessment is planned.*

## Introduction

The inaugural meeting of the Pharmacovigilance Risk Assessment Committee (PRAC) was held in Brussels in July 2012. This first PRAC meeting not only marked the coming into force of the new European pharmacovigilance legislation, it also saw the beginning of a new era within the European regulatory environment.

The new legislation is in many ways an appropriate response to identified needs, including:

- The need to facilitate the rational use of resources. One way in which this will be achieved is by strengthening the risk-based approach and expanding worksharing between committees and between member states.
- The need to coordinate activities within a system characterised by immense complexity. To achieve this, initiatives will include strengthening the coordinating role of EMA, which will be responsible for coordinated safety announcements, including for non-centrally authorised products.
- The need to increase transparency. This will be achieved through extensive publication of key information, which aims to increase insight and participation, legitimacy and trust in the pharmacovigilance system.
- The need to provide effective and appropriate risk communication. The key route to this will be by targeted communication, as well as the direct involvement of healthcare professionals and patient representatives.

## Internationalisation and legal framework

The PRAC is central to the new EU pharmacovigilance framework. Following decades where pharmacovigilance took place in a national environment, with decisions being based purely on national data, even in the smallest countries in the world, the establishment of a European Committee mandated to handle a wide range of pharmacovigilance procedures signifies that European pharmacovigilance finally has become truly internationalised.

The new legal framework has significantly changed the way EU member states cooperate within pharmacovigilance. Prior to the creation of the PRAC, the forum of cooperation between member states was the Pharmacovigilance Working Party (PHVWP), in which each member state was represented by one delegate. The PHVWP did not have a legal basis, but was an informal group working according to non-legally binding timetables and delivering non-legally binding outcomes.

In contrast, the PRAC has a legal basis. All agenda items (eg, periodic safety update report (PSUR) assessments, signal evaluations, referrals, PASS) are based on a legal mandate. All procedures run according to clearly defined and legally binding timetables. Decisions are based on the cumulative international experience, and extensive harmonisation is anticipated. Also in contrast to the PHVWP, the PRAC mandate is not confined to the post-authorisation phase, as pre-authorisation risk management plans (RMPs) are also evaluated by the PRAC.

## Adapting to modern times

The creation of the PRAC helps adapt the pharmacovigilance system to the way citizens in the modern world interact and – due to the internet and modern communication tools – how individuals are able to exchange information and views across national borders. The new legislation also acknowledges the need to involve other stakeholders in the decision-making process, in particular healthcare professionals and patients or patients' representatives. These stakeholders are now represented in the PRAC, and they undoubtedly make a difference. Their presence and perspectives help ensure the quality of the regulatory decisions. As an example, the healthcare professionals and patient representatives often impact significantly on decisions regarding feasibility and appropriateness of risk minimisation measures.

Furthermore, the aim of the PRAC and the new procedures is to ensure rational use of scarce resources, by clarifying the roles and responsibilities of different stakeholders and avoiding redundancy and duplication of work.

## The PRAC's mandate

The new legislation provides clarity with regards to the mandate of the PRAC. The PRAC's responsibilities are as follows:

- Referral procedures for safety reasons (art 107i and art 31)
- Signals detected from EU spontaneous reporting systems
- RMPs (pre- and post-authorisation)
- PSUR assessments
- Post-authorisation safety and efficacy studies (PASS, PAES)
- Product-related pharmacovigilance inspections
- Safety issues at the request of the EMA's Committee for Medicinal Products for Human Use (CHMP) or by member states (eg, type II variations, renewals).

Furthermore, the PRAC discusses organisational, regulatory and methodological matters, either during the plenary meeting or via a teleconference. For example, the PRAC has had extensive discussions on the development of a wide range of templates for the various types of assessments (PSURs, RMPs, PASS, etc), on how identified signals should be handled consistently and risk-proportionately, on details of the additional monitoring system and criteria for initiating public hearings.

## PRAC working practices

The PRAC meets every month (except August), with the meetings lasting typically 3.5 days. The Committee works according to a high level of transparency. The agenda is published just before the meeting commences, and the minutes are published following adoption at the subsequent meeting. In between these times, the most important safety recommendations are included in press releases and highlights – in line with, for example, publications from the CHMP meetings. Prior to each meeting, the EMA provides an overview to national agencies of topics on which publication is expected. This enables the national agencies to prepare for communication to the public at national level.

The PRAC forwards recommendations to either the CHMP or the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The rule governing whether it is one or the other group is simple. If a particular procedure, eg, a referral, includes at least one centrally authorised product, then the PRAC forwards the recommendation to the CHMP. If a procedure only includes nationally authorised products, then the PRAC forwards the recommendation to the CMDh. The CHMP or the CMDh then formally adopt an opinion, which is then forwarded from CHMP to the European Commission or from the CMDh to member states. The latter is true if there is consensus within the CMDh; if this is not the case then the CMDh opinion is also forwarded to the Commission.

## PRAC workload

During the first year the workload of the PRAC has increased significantly, with an overwhelming number of Periodic Safety Update Reports (PSURs) and RMPs on the agenda each month, together with referrals, which – although relatively few in number – are quite complex to handle both from a scientific and legal point of view.

In order to manage the large number of PSURs and RMPs during a single meeting, the PRAC has developed sets of criteria for plenary and silent adoption respectively. For instance, PSURs where the PRAC advises that the marketing authorisation should be varied will always be presented and discussed in plenary. The remaining PSURs are adopted silently. Likewise, only RMPs with important unresolved issues will be discussed in plenary. These selection criteria are justified with reference to the aim of the new legislation – that is to apply a risk-based approach.

## Handling of signals

For the first time, a legal basis for a very important tool in pharmacovigilance – the signals – has been established. The PRAC has introduced a systematic evaluation process of all signals which are identified and – following an initial evaluation by the PRAC rapporteur – has sufficient strength to be prioritised for plenary discussion in the PRAC.

The most frequent outcome of a signal evaluation is to forward a request to the MAH to perform a cumulative review (within 30 or 60 days), which will be followed by assessment by the PRAC rapporteur and subsequent discussion in the PRAC. Eventually the PRAC will recommend that the MAH submit a variation application in order to add new safety information to the labelling. In a minority of cases, the PRAC considers that there is sufficient information to justify a variation without prior review. Alternatively, the PRAC recommends that the issue is monitored closely in the future PSURs.

## Handling of referrals – a case study

A wide range of referrals has been triggered during the first year. The initiation of a referral is announced immediately after the closure of the PRAC meeting. Likewise, the PRAC outcome of the referral is published in the highlights from the particular PRAC meeting. As mentioned above, the referrals are complex in many ways.

One illustrative example is the ongoing art. 31 referral on hydroxyethyl-starch (HES). This product is an infusion solution used, for example, in critically ill patients with sepsis to replace lost blood volume in hypovolaemia. The concern is that use of HES is associated with increased mortality and risk of kidney failure, as compared with use of crystalloids. Based on all of the available data, the PRAC recently recommended suspending the marketing authorisations for HES. The recommendation was forwarded to the CMDh for final adoption. However, before the CMDh could consider the case, the EMA became aware that at least one MAH would request re-examination of the PRAC decision. As a consequence, the finalisation was expected to be postponed by four months.

This prompted national authorities to consider whether there was a need to take regulatory action at national level, in order to protect public health. These considerations led to divergent outcomes across the EU. One member state suspended the marketing authorisations, which elicited an additional referral procedure (107i), which will now run in parallel with the art 31 referral. In a few member states it was decided to await the outcome of the re-examination without further action. In many member states, information was published on the respective national websites. In most instances the information included a summary of the state of play of the art 31 referral. In addition, interim – and not entirely similar – recommendations were provided to healthcare professionals.

## Safety referrals: A challenge

The above example highlights how challenging a safety referral procedure can be. All stakeholders have to apply to the legal framework. All stakeholders must respect the regulators' available tools as well as the legal rights of the MAHs. That is indisputable. However, ideally all serious safety concerns dealt with in a referral should lead to prompt, clear and unanimous outcomes, which are then conveyed to the public, without delay, in clear communications, thereby enabling healthcare professionals to implement change immediately and protect patients maximally.

In the present case there are, however, differing views with regard to the strength of the evidence. This fact reflects that it is extremely difficult to perform research in a critically ill patient population. There are also differing views with regard to the appropriate actions to be taken at national level. This can be explained by, for example, different consumption figures and treatment practices in different member states. Only the future can tell what the final outcome of these procedures will be, but it will be interesting to monitor. Undoubtedly there will be some important lessons learned, and based on these, the system can be further refined.

## Conclusion and future outlook

It is clear that this has not been an easy year, either for the industry stakeholders or for the regulators. The workload has been extremely challenging. The promise of a reduced administrative burden and a more rational use of resources have not yet been delivered. But realistically, taking into account that this legislative change is the most far-reaching change in European pharmaceutical sector since the creation of the EMA, what could we expect? Furthermore, a global financial crisis developed after launch of the legislative proposal, resulting in delays in implementation. We are still waiting, for instance, for the EudraVigilance system to become the single point of receipt of adverse drug reactions and for the PSUR repository to become established, as well as various provisions on transparency, for example, public hearings and the web portal have also not been delivered.

The ultimate impact of the new legislation is still unknown, but a thorough assessment is planned. It is important to capture as much experience as possible, enabling the improvement of future legislative reforms. Currently, key performance indicators for the assessment are being developed. Hopefully, the evaluation will document significant impact in terms of benefit to public health and to society overall. Furthermore, we would like to see that trust in, and legitimacy of, the pharmacovigilance system has improved significantly.