EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 September 2012
EMA/PRAC/520121/2012
Patient Health Protection

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the inaugural plenary meeting 19-20 July 2012

Centre Albert Borschette, Conference Room AB-0C

Rue Froissart 36, 1040 Brussels, Belgium

1. Introduction

1.1. Welcome and keynote address by the EMA, Executive Director

Speaker: Guido Rasi

The EMA Executive Director welcomed all participants to the inaugural meeting of the PRAC and thanked the European Commission for hosting it in Brussels.

He explained that the first meeting of the PRAC would focus mainly on addressing aspects relating to the mandate of the PRAC and on adopting its Rules of Procedures.

Prof Rasi reminded the PRAC that the European Medicine Agency (EMA) has a strict policy on the handling of conflicts of interests for its staff, scientific experts including committee members and Management Board representatives. Further details are provided under item 2.4.

Regarding the role of the new Committee, the Executive Director underlined that the PRAC will deliver outcomes which will be turned into binding regulatory decisions. This is why it is particularly important that outcomes are clear, scientifically robust and provide the public and stakeholders with a full rationale.

The PRAC will focus on the processes outlined in the legislation. In this regard, the agenda of the PRAC will be designed to show the adherence of PRAC discussions with the tasks outlined by the new pharmacovigilance legislation.

Finally the EMA Executive Director concluded announcing that the election of the Chair and vice-Chair of the PRAC will take place at the September 2012 meeting. EMA will launch a call for expression of

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

interest for the Chair and vice-Chair position in August 2012 to allow for their election at the September 2012 PRAC meeting.

1.2. Keynote address by the European Commission, Director General of DG Health and Consumers (SANCO)

Speaker: Paola Testori Coggi

The Director General of DG Health and Consumers opened her keynote address emphasising how the adoption of the new pharmacovigilance legislation in 2010 was the result of a collective effort of the EU Member States, the European Parliament and the European Commission. The new legal framework supports a move to truly harmonised pharmacovigilance systems across the EU, optimised with a clear and strengthened focus on public health protection.

Key elements of the new pharmacovigilance legislation provide for strengthened transparency, communication and patient involvement. In order to promote patients' compliance to treatment, patients should be empowered to understand better and to be more involved in their own healthcare. For this reason Authorities should encourage patients to become actors in this area. The new legislation recognises this new role, for example by empowering the patient to report adverse reactions to medicinal products.

The new legislation also enables harmonised decisions and efficient use of resources. The PRAC will have a key role in this. The Committee will analyse and prioritise better incoming safety information for medicinal products to identify those signals that require regulatory follow-up. It will support Marketing Authorisation Holders (MAHs) in developing appropriate risk management plans for their products or when post-authorisation studies are considered necessary.

The Director General pointed out the importance of the PRAC in effectively supporting the system. This could be achieved by concentrating on key deliverables of the new legislation and focussing on the safety of individual medicinal products. Good cooperation between PRAC and other scientific Committees / Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) would be key.

The Director General advocated, given the current economic climate in the EU, the most efficient use of available resources. For instance, whilst it was recognised that regular physical meetings of a Committee remain necessary, the use of new technologies to support deliberations should be explored on some occasions. The Director General appealed to EMA in order to set up flexible working procedures and working methods which allow Regulators to reach their objectives with the minimum of complexity and administrative burden.

The Director General concluded by informing the PRAC that the European Commission was not in a position to appoint representatives for patient and health care professional groups for the first meetings due to the small number of applications received for the initial call for expression of interest. A new call for expression of interest was launched at the beginning of July 2012 with a 1 October 2012 deadline for nominations. The call was being widely disseminated with a view to increase the number of potential candidates.

Questions were raised concerning transparency of the nomination process for members to be appointed by the European Commission to the PRAC. Explanations were provided by the DG indicating that the process applied followed normal operating procedures established by the EC for such nominations.

Finally it was announced that DG Health and Consumers is proposing a 'Joint Action' from 2013 to 2016. The objective is to help the Member States to apply the new pharmacovigilance requirements. If

the DG Health and Consumers proposal is agreed, the formal call for projects will be launched by the end of 2012.

1.3. Membership of the Committee

Tour de Table / Introduction and Expertise

The Members and Alternates of the PRAC, as well as EMA and European Commission representatives introduced themselves to the Committee.

1.4. General Introduction to the EU Regulatory Framework and Opportunities offered by the new Pharmacovigilance Legislation

Speaker: Peter Arlett (EMA)

The EMA gave a presentation providing an introduction to the EU regulatory framework, the new legislation, and the opportunities it offered for public health. The main objective of the whole framework aims at promoting and protecting public health. The new legislation covers the main regulatory steps of the lifecycle of a product including risk management planning and benefit risk monitoring. Patients, healthcare professionals, pharmaceutical industry, and medicines regulators are key actors in the process.

The EMA reminded that the preparation of the new EU pharmacovigilance legislation followed a process which took approximately nine-years, starting in 2004 with the European Commission launching an independent study assessing the strengths and weaknesses of the then current EU Pharmacovigilance system.

Current opportunities for public health given by the new legal framework have included various initiatives. For example, the creation of lists of all EU products and substances has been an important step forward to support EU medicines databases (e.g. EudraVigilance) and the coordination of safety monitoring.

It was noted that Marketing Authorisation application requirements are impacted. The pharmacovigilance system description will be reduced in the authorisation and the Pharmacovigilance System Master File (PSMF) will be maintained by every company and this will allow for prompt checks, as appropriate.

Every new Marketing Authorisation application will need to include a Risk Management Plan (RMP) and, when justified by public health, post-authorisation studies will become legally binding. Moreover studies in the RMPs may cover both safety and efficacy of the product (the inclusion of efficacy studies being an important evolution of post-authorisation product research planning). All these measures will contribute in ensuring that high quality information on the benefits and risks of medicines is generated pre- and post-authorisation for the benefit of public health.

As for Periodic Safety Update Reports (PSURs) the new legal provisions see their scope modified as their main objective is to present a comprehensive and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information, in the context of cumulative evidence. Their submission is proportionate to possible risks and allows also for a more proportionate use of resource by Industry and Regulators.

There are also new legal obligations to analyse data to detect new safety issues, for EMA and national Regulatory Agencies. For Industry this means that new or changing safety issues should be detected more rapidly and that new advice and warnings will be implemented in product information more

rapidly. With the outcome of its scientific evaluation for product reviews, the PRAC will be supporting this mechanism for fast efficient updates to all product information.

The EMA concluded by emphasizing that the new transparency and communication measures will lead to increased coordination of information between Member States the provision of detailed and easily accessible information on new safety issues and on benefits and risks of medicines. Finally the new processes for inspections and audits will provide greater assurance of the quality of pharmacovigilance performed by industry and Regulators.

1.5. Presentation of EMA, its Scientific Committees and key interactions between PRAC, CHMP and CMDh

Speaker: Anthony Humphreys (EMA)

The EMA is a decentralised body of the EU responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products. With the addition of the PRAC, the EMA counts seven scientific Committees conducting the main scientific work of the Agency: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee for Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT).

The main responsibility of the PRAC is to prepare recommendations and advice, according to the type of procedures, 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.

The different PRAC outputs depend on the existence of a formal decision-making phase or not as defined in the pharmacovigilance legislation. For the processes with a formal decision-making phase, the PRAC output is a recommendation and applies to safety referrals, PSURs single assessments and Post Authorisation Safety Study (PASS) results assessments. These recommendations are transmitted to the CHMP when a procedure concerns at least one centrally authorised product (CAP). The PRAC recommendations lead to CHMP Opinions and one or more Commission Decisions. When there is no CAP involved in the PRAC procedures, the recommendations are transmitted to the CMDh. These PRAC recommendations lead to a CMDh consensus that the Member States shall follow, or a CMDh majority that leads to a Commission Decision.

Where the position/opinion of the CMDh/CHMP differs from the recommendation of the PRAC, the CMDh/CHMP shall attach a detailed explanation of the scientific grounds for the differences together with the recommendation.

The meeting schedule of the PRAC allows for a full week gap between PRAC and CHMP/CMDh meetings which are organised concomitantly. This allows for contributing to the robustness of the outcome of the scientific review and for the finalisation of the PRAC assessment and conclusions, enhancing the quality of the PRAC output. It also allows for the preparation of the CHMP/CMDh discussions in order to ensure sufficient review time at CHMP/CMDh level and facilitate interaction at national level between the CHMP/CMDh and PRAC members. Finally this will facilitate discussion and decision at CHMP/CMDh level.

1.6. Key processes and deliverables of the PRAC

Speaker: Peter Arlett (EMA)

The EMA, in anticipation of discussion on the Rules of Procedure of the PRAC, presented key processes and a list and categorisation of deliverables (or outputs) of the Committee.

A full list of deliverables was presented along with their legal references. Deliverables may differ depending on the authorisation status of the products concerned. Different processes have been set-up to support the different outputs of the PRAC for centrally and non-centrally authorised products.

It was explained how the PRAC outputs will be followed-up, in some cases, by a formal decision-making phase. In this situation the PRAC output is a "Recommendation". This means that the recommendations of the PRAC will be providing grounds to other bodies (e.g. CMDh or CHMP) for further decision making, which will in turn transmit their outputs to the Member States or to the European Commission where they become legally binding.

In cases when the outputs of the PRAC do not lead to a formal decision making phase, its output could be either directly applicable, as is the case for protocols of PASS. Alternatively the PRAC will be providing advice to the Member States or the CHMP.

Following comments raised by some members it was specified that PAES (Post-Authorisation Efficacy Studies) will not be routinely presented to the PRAC. However processes are still under discussion in the case of PAESs which are a part of the RMP. Measures for implementation will be proposed in the next wave of release of the draft Good PharmacoVigilance Practices (GVPs).

1.7. Transparency aspects

Speaker: Roberto De Lisa (EMA)

The EMA presented the current transparency provisions applicable to the PRAC in accordance with the new legislation. The Agenda and Minutes of the PRAC as well as the conclusion of the assessments, recommendations and advice will be published on the EMA website. The minutes and the agenda will be published in full. However the level of information provided in the PRAC agendas and minutes will respect the EMA policy on publication of information on on-going evaluations, as well as the protection of Commercially Confidential Information (CCI) as per the EMA/HMA recommendations in this field.

The Agenda will be published prior to the meeting and the minutes will be published after their adoption (after the following meeting). The publication of a document highlighting high-level outcomes of the PRAC's main scientific discussions will take place without undue delay after the meeting. PRAC recommendations and advice will be published together with the final outcome of the CHMP and CMDh procedures after these meetings have finished.

2. Rules of Procedure of the PRAC

Discussion led by Noel Wathion (EMA)

2.1. Draft Rules of Procedure

- Mandate
- Membership and Chairmanship
- Voting process
- Rapporteurship

Speakers: Anthony Humphreys (EMA), Sheila Kennedy (EMA)

The EMA presented the content of the different articles of the draft Rules of Procedure of the PRAC.

EMA had already incorporated into the latest version circulated for discussion preliminary input provided by the European Commission who, in accordance with the legislation, will also be invited to give a favourable opinion on the Rules of Procedures following adoption by the PRAC.

The special nature of some rules as regards membership and voting process, in comparison to other Committees of the EMA, were described in detail and comments of the members addressed. For instance, EMA underlined that PRAC should aim at agreeing its recommendations and advice by consensus and voting would not be performed routinely. However if consensus cannot be achieved, the Chair is responsible for deciding whether a vote is necessary. PRAC members also have the facility at any time to request a vote. Should this request be refused, this will be referenced in the minutes of the meeting stating clearly any grounds for refusal.

Major comments focused on the fact that according to the latest version of the draft Rules of Procedure (RoP), members nominated by the European Commission would be unable to act as Rapporteurs for products. The European Commission representative clarified that those members are appointed as independent scientific experts or representatives of patients and healthcare professionals. This implies that they would need to have a different role in the PRAC from that expected from those nominated by the Member States.

Finally, it was clarified that currently there are as yet no provisions to define who will present and discuss PRAC recommendations/advice at the CHMP/CMDh meetings as well as, other groups or Committees. This aspect will be further addressed in the development of processes for a strengthened interaction between EMA Committees and CMDh.

2.2. Draft Rules of Procedure

- PRAC tasks
- Roles and responsibilities of the PRAC and EMA Secretariats
- Other arrangements

Speakers: Roberto De Lisa (EMA), Geraldine Portier (EMA)

The EMA presented the content of the different articles of the draft Rules of Procedure of the PRAC. The Rules of Procedure include a list of the tasks and deliverables of PRAC as specified in the legislation.

The role of the PRAC co-rapporteur is subject to further discussion driven by growing experience in the coming meetings. PRAC co-rapporteur will be directly involved in the production of assessments in referral procedures, but for other procedures deliverables have to be agreed subject to best use of resources.

2.3. Adoption of the Rules of Procedures

The PRAC adopted by majority its own Rules of Procedures (25 members in favour out of 31) with some refinements. Those members not in favour expressed concerns in relation to the fact that members appointed by the European Commission would not be able to act as Rapporteur. Noel Wathion explained that, as per the process outlined in the legislation, the adopted PRAC rules will now be provided to the European Commission and the EMA Management Board in order to obtain a favourable opinion, after which the PRAC rules can be implemented. In order to ensure availability of these rules at the September 2012 PRAC meeting a written procedure will be initiated at the level of the Management Board during August 2012.

2.4. EMA Policy for handling of Conflict of Interests and Confidentiality Agreement

- Guarantees of Independence and Code of Conduct

Speaker: Sheila Kennedy (EMA)

The EMA presented its policy on the handling of conflicts of interests for its scientific experts, including Committee members and alternates. The aim of the policy is to ensure that experts and Committee members do not have any financial or other interests in pharmaceutical industry that could affect their impartiality. EMA proactively ensures the early identification of potential conflicts of interest, restricting or excluding expert's involvement where necessary, and is committed to search for alternative experts when needed. Prior to involvement in the EMA activities experts must complete an annual declaration of interests form (and as soon as changes to current declared interests are applicable) which is subject to EMA's review. It assigns each expert a risk level based on whether the expert has any interests, and whether these are direct or indirect and determines if an expert's involvement should be restricted or excluded in the EMA's specific activities. In March 2012, the EMA's Management Board endorsed a revised policy taking into account lessons learned, as well as a breach-of-trust procedure to deal with incorrect or incomplete declarations of interests.

3. Orientation on key tasks

3.1. Rapporteurship Appointment process

Speaker: Anthony Humphreys (EMA)

EMA explained that PRAC Rapporteur appointment principles are based on maintaining and enhancing the robustness of the scientific review process including the continuity of the scientific knowledge throughout a product's lifecycle, and the need for checks and balances. The Rapporteurship appointment process, whilst recognising the need for the best possible available scientific expertise, also fosters the creation of multi-national Rapporteur teams. The selection criteria applied will take into consideration the best possible available scientific expertise and, where possible, will favour the participation of a different Member State in the PRAC work compared to the CHMP Rapporteur and CHMP Co-Rapporteur.

The process will take into account the need to avoid duplication of work and will strengthen the sustainability of the system.

The appointment process will be implemented immediately for new Marketing Authorisation applications. For medicinal products already authorised, the same principles will apply but the appointment procedure will be staggered from 4Q2012 to 2014.

To support the exercise a list for PRAC Rapporteurs appointments in relation to all CAPs that are due for PSUR assessment or PASS results under evaluation in 1Q2013 will be prepared. The preparation of this list will also follow a risk-based approach.

It was clarified that for EU Community Procedures a similar but distinct process will be in place and more details on the implementation plan to progress the Rapporteurship appointment will be presented during the following meetings.

3.2. Pharmacovigilance Working Party (PhVWP) Legacy

Speaker: Geraldine Portier (EMA)

EMA gave a presentation on the PhVWP legacy safety issues which were still under discussion at the time of the termination of the PhVWP activities, and for which follow-up is to be provided under the new legal framework. The PhVWP has carried out a re-classification and prioritisation exercise to ensure issues can be addressed at the PRAC or national level as appropriate under the appropriate legal provisions.

3.3. List of Union Reference Dates and frequency for submission of Periodic Safety Update Reports (EURD list)

Speaker: Geraldine Portier (EMA)

The EMA gave a presentation on the EURD list which consists of a comprehensive list of active substances and combinations of active substances for which PSURs should be submitted in accordance with the EU reference dates and frequencies determined by the CHMP and the CMDh following consultation with the PRAC. The EU reference dates list has been built by the EMA and National Competent Authorities and following public consultation, to facilitate the harmonisation of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances subject to different Marketing Authorisations, authorised in more than one Member State. The list is intended to optimise the management of PSURs assessments within the EU while supporting transparency, and to provide predictability to the various stakeholders in terms of workload related to PSURs taking into account the currently known safety profile of the active substances and combinations of active substances. On a national basis, competent authorities still have the possibility to request a PSUR (for innovators or generics).

This list will be dynamic and will be amended whenever considered necessary by the PRAC, CHMP or CMDh and upon request of MAHs. The list will take effect 6 months after its publication date on the EMA website (until the EU web-portal is available) following endorsement by the CHMP/CMDh after consultation of the PRAC. This consultation is scheduled at the September 2012 PRAC meeting.

3.4. Signal Management

Speaker: Peter Arlett (EMA)

The EMA gave a presentation on the Signal Management process defined as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed. The signal management process covers all steps from detecting signals, through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made. Roles and responsibilities of the EMA and National Competent Authorities were described and further details on the technical tools, periodicity of monitoring and processes were given.

3.5. Additional Monitoring and Black Symbol

Speaker: Peter Arlett (EMA)

The EMA described the objectives of the additional monitoring as per the new legal provisions. The concept of additional monitoring focuses on the need to address uncertainty regarding the knowledge

of the benefit-risk balance of a given product at the time of authorisation or at any stage during its lifecycle. The medicinal products subject to additional monitoring will be included in a list according to determined criteria as defined in the pharmacovigilance legislation, to be made publicly available together with the black symbol and the explanatory sentence included in the product information to increase transparency and enhance communication with healthcare professionals, patients and consumers. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and to increase awareness about the safe and effective use of certain medicinal products.

The PRAC will be consulted on the draft proposals reviewed by the EMA, National Competent Authorities and following public consultation on a black symbol and the new standardised statements. The PRAC advice will be subsequently transmitted to the European Commission for selection of the black symbol.

4. Organisational matters

4.1. Operational aspects related to the handling of unforeseen urgent Safety Issues (possibilities for ad-hoc PRAC meetings and operation of the Incident Review Network)

Noel Wathion explained the process for the handling of any unforeseen urgent safety issues if these arise before the meeting of the PRAC in September 2012 and if these would require discussion at EU level. The Incident Review Network established within the frame of the EU Regulatory Network Incident Management Plan will review any emerging information and take the necessary actions as per its revised mandate.

PRAC meeting dates in 2012

The calendar for the meeting dates 2012 was circulated to the PRAC members and alternates.

Preparation of the PRAC meeting of 3-6 September 2012

EMA announced that procedural and technical training of PRAC members and alternates will take place before the beginning of the September 2012 PRAC plenary meeting. The plenary meeting will start with the election of the PRAC Chair and vice-Chair.

Regarding discussions on medicinal products to take place in September, EMA explained that due to agreed proposals for phasing-in for PRAC involvement for on-going and newly submitted procedures for centrally authorised products, nationally authorised products and safety-referrals, the agenda of the PRAC will mainly focus on the evaluation of new signals. A gradual involvement of the PRAC in other procedures, in accordance with its mandate, will begin as of October 2012.

4.2. Any Other Business

None