EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Countdown to July 2012: the establishment and functioning of the PRAC

Status report 28 June 2012

1. Purpose

The purpose of this document is to present the activities supporting the establishment and functioning of the Pharmacovigilance and Risk Assessment Committee (PRAC).

2. Establishment of the PRAC

2.1. Nomination of PRAC members

- With respect to the nomination process for PRAC members, appointed by the Member States (MSs), nominations from all MSs have been received. Three MSs (Cyprus, Luxembourg and Lithuania) only nominated a member but not an alternate. It should be noted that Liechtenstein delegated its PRAC tasks to Austria.
- The nomination process for members appointed by the European Commission has been finalised, except for civil society representatives (one member and one alternate representing healthcare professionals, and member and one alternate representing patient organisations).

2.2. Election of PRAC Chair and Vice-Chair

- The election of the PRAC Chair and Vice-Chair will take place at the September 2012 PRAC meeting.
- In July 2012, following the PRAC inaugural meeting, PRAC members will formally be invited to submit nominations in writing to the EMA no later than the start of the September 2012 meeting. A brief résumé in support of the candidature needs to be provided by each candidate.

3. Functioning of the PRAC

The following aspects are discussed:

- PRAC Rules of Procedure.

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- PRAC mandate and tasks.
- PRAC outputs.
- PRAC Rapporteur appointment principles.
- PRAC transparency and communication.
- PRAC – CHMP – CMD(h) interaction.
- Other arrangements.

3.1. PRAC Rules of Procedure

- The PRAC Rules of Procedure (ROP) will be presented at the July 2012 PRAC inaugural meeting for adoption. The ROP shall enter into force after receiving a favourable opinion from the European Commission and the EMA Management Board (MB). In order to allow the ROP to enter into force at the September 2012 PRAC meeting, a written procedure at the level of the MB will be initiated prior to the September 2012 PRAC meeting.
- The PRAC ROP are based on the CHMP ROP. There are, however, a number of differences between these ROP, taking into account specific legislative provisions applicable to the PRAC. The main differences are as follows:
  - Alternates to nominated PRAC members: alternates my act as Rapporteurs at any time with the exception of alternates representing healthcare professionals and patient organisations.
  - Delegation of tasks: a MS may delegate its tasks in the PRAC to another MS. Each MS may represent no more than one other MS. Delegation is subject to mutual agreement between two MSs and can be withdrawn at any time. A delegate representing another MS in the PRAC will have two votes and will be counted as two present members.
  - Tasks of the PRAC: see chapter 3.2 of this document.
  - Public hearings versus oral explanations: in addition to oral explanations public hearings may be held (further details will be provided once the concept of public hearings has been further elaborated upon taking into account the outcome of the March 2012 MB meeting). Of note is that for referral procedures initiated for safety reasons, where a Marketing Authorisation Holder (MAH) or another person intends to submit confidential data, the concerned party may request permission to present such data to the PRAC in a non-public part of the hearing.
  - Transparency: see chapter 3.5 of this document.

3.2. PRAC mandate and tasks

- Regulation (EU) No 1235/2010 provides the following mandate for the PRAC:

  "All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit".
- In addition to this specific mandate, both Regulation (EU) No 1235/2010 and Directive 2010/84/EU provide additional references to tasks to be performed by the PRAC and for some of these tasks specific procedures are laid down in the legal texts. However, while some tasks are associated with very precise procedures and timelines, for others business processes had to be developed without direction from the legislation.

- The PRAC tasks common to both Centrally Authorised Products (CAPs) and non-CAPs are as follows:
  - Assessment of any urgent union procedures (Article 107i) triggered due to safety concerns identified in medicinal product(s) authorised in more than one MS. Assessment of any Article 31 and Article 20 procedure triggered for safety reasons.
  - Assessment of non-interventional safety study protocols and study reports if the need for a non-interventional post-authorisation safety study (PASS) is identified.
  - Periodic Safety Update Report (PSUR) single assessment where at least one of the Marketing Authorisations (MAs) has been granted in accordance with the centralised procedure.
  - Establishment of a list of EU Reference Dates (EURD) and frequency of submission of PSURs.
  - Recommendations on the need and scope of "for cause" pharmacovigilance inspections related to medicinal products of Community interest. Review of the outcome of pharmacovigilance inspections and assessment of Corrective and Preventive Action Plans (CAPAs). Input in the preparation and agreeing on the risk-based programme for routine pharmacovigilance inspections.
  - Advice on including a medicinal product in the list or removing a medicinal product from the list of medicinal products requiring additional monitoring in case these fall under the optional scope. Advice on the necessity for the extension of the additional monitoring period beyond the agreed initial time period.
  - Recommendations in terms of signal assessment.
- The PRAC tasks specific to CAPs are as follows:
  - Regulatory oversight of Risk Management Plans (RMPs) and assessment of the outcome of risk minimisation measures contained in RMPs and of conditions of the MA.
  - Assessment of PSURs for individual CAPs.
  - Advice to the CHMP on other medicinal product related procedures such as renewals, annual re-assessments and safety type II variations (as regards the latter, at the request of the CHMP).
- The PRAC tasks specific to non-CAPs are as follows:
  - PSUR single assessment where no MA has been granted in accordance with the centralised procedure.
  - Advice on a particular RMP and/or outcome of risk minimisation measures at the request of a MS.
  - Advice on renewal and safety type II variations at the request of a MS.

3.3. PRAC outputs

PRAC outputs are classified as follows:

- PRAC output with a direct formal decision-making phase. In such situation the PRAC output is a "Recommendation". This applies to:

  - Pharmacovigilance referrals (including the possibility for temporary measures).
  - PSUR assessments.
  - PASS results assessments.
- PRAC output without a (direct) formal decision-making phase. In such situation the PRAC output is either
  - Directly applicable. This applies to PASS protocols (initial or amendments to ongoing study).

    or
  - A "Recommendation". This applies to signals.

    or
  - An "Advice". This applies to:
    - RMPs.
    - Renewals.
    - Type II safety variations.
    - Annual re-assessments.
    - Pharmacovigilance inspection requests or results.
    - Pharmacovigilance audits.
    - Timing and message content in relation to MS safety announcements.
- Other PRAC advice:
  - Functionalities of EudraVigilance and PSUR databases.
  - Additional monitoring.
  - Literature ADR monitoring.
- Lists, i.e.:
  - EURD list for PSURs.
  - List of medicinal products under additional monitoring.

3.4. PRAC Rapporteur appointment principles

Principles:

The PRAC Rapporteur appointment principles are based on:

- The robustness of the scientific review process in terms of scientific and specific knowledge including the continuity of such knowledge throughout a medicinal product's lifecycle.
- The need for checks and balances through the availability of a 3rd opinion on the basis of the best possible and available expertise.

These principles should also allow to:

- Open-up PRAC Rapporteurship to all PRAC delegates (including co-opted members) whilst emphasising the need for the best possible and available scientific expertise.
- Foster the creation of multi-national Rapporteur teams.
- Avoid duplication of work.
- Strengthen the sustainability of the system.

Applying these principles to the lifecycle of medicinal products results in the following:

- For CAPs, in terms of "Legacy"[1] medicines:

		Initial Authorisation Phase	Post-authorisation Phase
"Legacy" medicines	CHMP Rapporteur	Not applicable	A
	CHMP Co-Rapporteur	Not applicable	B
	PRAC Rapporteur	Not applicable	X[2] or A
	PRAC Co-Rapporteur	Not applicable	A or X

- For CAPs, in terms of new MAAs[3]:

		Initial Authorisation Phase	Post-authorisation Phase
New MAAs as of July 2012	CHMP Rapporteur	A[4]	A[4]
	CHMP Co-Rapporteur	B[4]	B[4]
	PRAC Rapporteur	X[5]	X
	PRAC Co-Rapporteur	A	A

- Referrals (only non-CAPs involved):
  - Co-Rapporteur: Member State triggering the referral.
  - Rapporteur: open to all other Member States, and criterion of best possible and available expertise to be taken into account.

[1] "Legacy" medicines: CAPs already authorised, or products still under evaluation at the level of the CHMP, or in the process of being authorised by the European Commission.
[2] X = open to all PRAC delegates, including the MS providing the initial authorisation phase peer reviewer, the selection criteria being the best possible and available scientific expertise and, where possible, from a different MS compared to the CHMP Rapporteur (A) and CHMP Co-Rapporteur (B).
[3] New MAAs: refers to any new applications for marketing authorisation submitted to the EMA as of July 2012.
[4] Status-quo with the current situation.
[5] X = open to all PRAC delegates, including the MS providing the initial authorisation phase peer reviewer, the selection criteria being the best possible and available scientific expertise and, where possible, from a different MS compared to the CHMP Rapporteur (A) and CHMP Co-Rapporteur (B).

- Referrals (mixture of CAPs and non-CAPs):
  - Rapporteur: PRAC Rapporteur for the CAP(s).
  - Co-Rapporteur: Member State triggering the referral (whereby also the involvement of the PRAC Co-Rapporteur for the CAP(s) needs to be considered).

Implementation:

- For new MAAs:

  From September 2012 onwards and on a monthly basis, the PRAC Rapporteur will be appointed at the same time as the CHMP (Co)-Rapporteurs/ CHMP peer reviewer(s).

  For the new MAAs for which the CHMP (Co)-Rapporteurs have already been appointed but where the procedure has not yet started, the PRAC Rapporteur will be appointed as of September 2012 onwards.

- For "Legacy" medicines:

  From 4Q2012 onwards a list will be prepared for PRAC Rapporteur appointment in relation to all CAPs that are due for PSUR assessment or PASS results evaluation in 1Q2013. The preparation of such list will also follow a risk-based approach. Applying these principles, this should be rolled-out for all other CAPs throughout 2013 and 2014 on a quarterly basis to deal with all "Legacy" medicines. Whenever in the meantime a referral is made involving one or more CAP(s) or an important safety issue emerges and a PRAC Rapporteur appointment has not yet taken place as per the above process than a PRAC Rapporteur will be appointed at the moment of the start of such referral/handling of such important safety issue.

3.5. Transparency and communication

- In terms of transparency and communication the following will be undertaken:
  - Publication of agendas and minutes of PRAC meetings.
  - Publication of high-level outcomes of the PRAC's main scientific discussions.
  - Publication of the PRAC's Recommendations and Advice.
- Publication of agendas and minutes of PRAC meetings:
  - Agendas:
    - Only one agenda will be prepared, to be redacted (see below) prior to publication.
    - Topics to be included refer to the PRAC tasks (see chapter 3.2.).
    - The level of information provided in the PRAC agendas will respect the EMA policy on publication of information on ongoing evaluations[6], as well as the protection of Commercial Confidential Information (CCI) and personal data as per the EMA/HMA recommendations[7] in this field.
    - Publication of the PRAC agendas will take place around the time of the PRAC meetings but always prior to the start of the meetings.

[6] This applies to all new medicines for human use under evaluation by the CHMP. Information published relates to the INNs and therapeutic areas for all new innovative medicines under evaluation, along with information on the type of salt, ester or derivative of the active substance. For generic and biosimilar medicines, it includes the INN and therapeutic area.
[7] HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the Marketing Authorisation (MA) application – Release of information after the granting of a MA.

- Minutes:
  - Only one set of minutes will be prepared, to be redacted (see below) prior to publication.
  - Topics to be included in the published minutes will depend on the authorisation phase, but will respect the protection of CCI and personal data as per the aforementioned EMA/HMA recommendations in this area.
  - Pre-authorisation phase: the outcome of the discussions as presented in the minutes will be published once the procedure has been finalised in accordance with the EMA Access to Documents Policy[8], unless there is an overriding public health interest (IT tool to be developed first).
  - Post-authorisation phase: the outcome of the discussions as presented in the minutes will be published irrespective if the procedure is finalised or not since it is considered that there is an overriding public health interest. The aforementioned EMA Access to Documents Policy will be revised to reflect this change in policy. As regards RMPs in the context of applications for new indications and line extensions, information through the publication of minutes will be released irrespective if the procedure is finalised or not in order to maintain consistency on the release of information in the post-authorisation phase.
  - The PRAC minutes will be structured as follows: a brief background of the issue, a summary of the questions raised by the PRAC, the conclusions reached by the PRAC including actions to be taken. The outcome of any voting will be recorded in the minutes, including any divergent views with identification of the individuals. It should be noted that personal reflections/views of PRAC members will not be minuted unless specifically requested. The consequence is that such reflections/views will subsequently be published with identification of the persons concerned.
  - Publication of the PRAC minutes will take place once the minutes have been adopted at the next PRAC meeting.

- Publication of high-level outcomes of the PRAC's scientific discussions:
  - Immediately after the PRAC meeting and in any case prior to the next CHMP/CMD(h) meeting a high-level outcome of the PRAC main scientific discussions will be published on the EMA website.
  - The format will be a "PRAC Meeting Highlights". As regards the timing of publication and information/advance warning to the EU Regulatory Network, please refer to chapter 3.6. of this document.
  - "PRAC Meeting Highlights" may be complemented with a dedicated Press Release and/or a Q&A document. The existing EMA policy on communicating safety issues for medicines for human use[9] will be amended to take into account the necessary changes as a result of the PRAC establishment.

[8] European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) (EMA/110196/2006).
[9] European Medicines Agency communication on (emerging) safety related issues for medicines for human use (EMA/170165/2010).

- Publication of the PRAC's Recommendations and Advice:
  - Full scientific PRAC Recommendations and Advice will be published on the EMA website together with the final outcome of the CHMP/CMD(h) procedures once the CHMP/CMD(h) meeting has finished.
  - These transparency/communication tools may be complemented with a dedicated Press Release and/or a Q&A document. The aforementioned EMA policy on communicating safety issues will be amended to reflect this. As regards timing of publication and advance warning to the EU Regulatory Network, please refer to chapter 3.6. of this document.

3.6. PRAC-CHMP-CMD(h) interaction

- The meeting schedule of the PRAC will allow for a full one week gap between PRAC and CHMP/CMD(h) meetings. This will allow to contribute to the robustness of the outcome of the scientific review in terms of
  - Finalisation of the PRAC assessment and conclusions, hence enhancing the quality of the PRAC output.
  - Preparation of the CHMP/CMD(h) discussions in order to ensure sufficient review time at CHMP/CMD(h) level and facilitate interaction at national level between the CHMP/CMD(h) and PRAC members.
  - Facilitation of "Opinion"-making at CHMP/CMD(h) level.
- The existing Early Notification System[10] in operation for several years to inform the EU Regulatory Network (HMA, European Commission, CHMP, PhVWP) is currently being revised in order to
  - Provide advance warning to the EU Regulatory Network on
    - The scientific discussions which will be finalised at the next PRAC meeting and will result in communication immediately after the PRAC meeting and in any case prior to the next CHMP/CMD(h) meeting (including aspects such as the communication tool which will be used and the timing of the publication).
    - The planning for the subsequent discussion at CHMP/CMD(h) level including the communication aspects (both in terms of the communication tool to be used and the timing of publication).
  - Adapt the target audience of the Early Notification System to the changing environment, i.e. replacing the PhVWP by the PRAC and including the CMD(h).

3.7. Other arrangements

The following information on arrangements made for the first two PRAC meetings can be provided at this stage:

- PRAC inaugural meeting:
  - The PRAC inaugural meeting will be held on 19 and 20 July 2012 in Brussels. The meeting will be chaired by the EMA.

[10] Early Notification System for communication on safety related issues for medicines for human use, currently limited to envisaged CHMP recommendations for regulatory action (based on identified safety concerns), accompanied by communication to the general public.

  - The focus during this inaugural meeting will primarily be on providing information in the following areas: handling of conflicts of interests, key processes and deliverables of the PRAC, transparency aspects, the PhVWP legacy, the EURD list, signal management and additional monitoring, the black symbol.
  - A particular deliverable will be the adoption of the PRAC Rules of Procedure.
  - A Press Release will be issued by the EMA after the meeting.
- PRAC September 2012 meeting:
  - The PRAC September meeting is scheduled to take place from 3 until 6 September 2012 (the exact duration of the meeting will depend on the workload).
  - The first day will focus on the election of the PRAC Chair and Vice-Chair, and training given by the EMA on specific processes. The next days will deal with product related issues.
- In the event that information emerges between the July and September 2012 PRAC meetings (and acknowledging that the PhVWP will have ceased to exist by that time) which will necessitate urgent discussion by the PRAC, the EMA will organise and chair an extraordinary PRAC meeting (to be held as a virtual meeting taking into account the BCP arrangements put in place for the London Olympics). The need for an extraordinary PRAC meeting will be decided in the frame of the EU Regulatory Network Incident Management Plan for medicines for human use, and in particular the operation of the Incident Review Network (IRN). The Incident Management Plan has been revised to take into account the outcome of the pilot phase, and to incorporate as well the consequences of the new pharmacovigilance legislation, and in particular the involvement of the PRAC and the CMD(h).

4. Overview table

The aforementioned information has been summarised in the attached overview table, in terms of the PRAC output category, the relevant processes, the relevant product types, the outcome(s), and transparency and communication.

PRAC output with a direct formal decision-making phase: PRAC Recommendation			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• Pharmacovigilance referrals* • PSUR assessment • Post-authorisation safety study (PASS) results assessment	CAPs, non-CAPs and mixture of CAPs and non-CAPs	• Where at least one CAP is involved (including mixture of CAPs and non-CAPs), PRAC Recommendations lead to CHMP Opinions and one or more Commission Decisions • Where no CAP is involved, PRAC Recommendations lead to a CMD(h) consensus that the MSs shall follow, or a CMD(h) majority that leads to a Commission Decision	• Some elements (e.g. PRAC Recommendation on Referrals) to be included in the "PRAC Meeting Highlights". In certain situations characterised by a recommendation for major regulatory action, "PRAC Meeting Highlights" to be complemented with a dedicated Press Release and/or a Q&A document • Outcome of PRAC discussions to be reflected in the minutes
* Specific case that PRAC may recommend temporary measures		• For CAPs the Commission takes temporary measures immediately on the basis of the PRAC Recommendation • For non-CAPs the European Commission requests the MSs to take temporary measures immediately on the basis of the PRAC Recommendation	• Incorporation in the "PRAC Meeting Highlights", complemented with a dedicated Press Release and/or a Q&A document • For PRAC minutes: see above

PRAC output without a formal decision-making phase: directly applicable PRAC output			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• PASS protocol (initial or amendments to ongoing study)	CAPs, non-CAPs and mixture of CAPs and non-CAPs	• PRAC endorses the protocol, refuses the study outright or with proposed amendments, and the PRAC output is subsequently provided to the applicant/MAH	• PRAC output is reflected in the minutes

PRAC output without a formal decision-making phase: PRAC Recommendation			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• Signal	CAPs, non-CAPs and mixture of CAPs and non-CAPs	• For signals relating to non-CAPs the Recommendation is provided to the Reference / lead Member State (MS) in the post-meeting document pack • For signals relating to CAPs the Recommendation is provided to the CHMP • For signals relating to non-CAPs and CAPs the Recommendation is provided to the Reference /lead MS in the post-meeting document pack and to the CHMP • For signals Recommendation may include, e.g.: – Request a PSUR via an immediate request or via the EURD list – Referral from a MS or the European Commission – Request PASS (via the CHMP/European Commission for CAPs or via the Reference/lead MS for	• PRAC outcome is recorded in the PRAC minutes

PRAC output without a formal decision-making phase: PRAC Recommendation			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
		non-CAPs) – Request a type II safety variation (via the CHMP/European Commission for CAPs or via Reference/lead MS for non-CAPs) – Further evaluation by the Rapporteur (CAPs) or the Reference/lead MS (non-CAPs)	

PRAC output without a (direct) formal decision-making phase: PRAC Advice			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• RMP • Renewal • Type II safety variation • Annual reassessment • PhV inspection request or results • Pharmacovigilance audit	CAPs and non-CAPs and mixture of CAPs and non-CAPs	• For processes relating to CAPs the Advice is provided to the CHMP	• For processes relating to CAPs the Advice is included in the minutes and is made public on the EMA website; certain outcomes may be reflected in the "PRAC Meeting Highlights"
		• For processes relating to non-CAPs the Advice is provided to the Reference Member State (RMS) in the post-meeting document pack	• For processes relating to non-CAPs the Advice is included in the minutes and is made public on the EMA website; certain outcomes may be reflected in the "PRAC Meeting Highlights"
		• For processes relating to CAPs and non-CAPs the Advice is provided to the RMS in the post-meeting document pack and to the CHMP	• For processes relating to CAPs and non-CAPs the Advice is included in the minutes and is made public on the EMA website; certain outcomes may be reflected in the "PRAC Meeting Highlights"

N.B.: While all PRAC outputs are based on a scientific assessment of the issue concerned, not all processes in this category will result in a formal PRAC adoption of a PRAC assessment report (templates are under development).

PRAC output without a formal decision-making phase: PRAC Advice			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
MS safety announcement and communication	Non-CAPs only (for announcements on CAPs the EMA is in the lead)	PRAC Advice on timing and message content at the request of the EMA	Advice recorded in the minutes and final safety announcement circulated by the EMA to the EU Regulatory Network

Other PRAC Advice			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• Functionalities of EudraVigilance and PSUR databases	CAPs, non-CAPs and mixture of CAPs and non-CAPs	• Advice provided to the EMA MB (no need to go through CHMP/CMD(h))	• Advice reflected in the PRAC minutes
• Additional monitoring (black symbol)		• Advice provided to the European Commission	• Advice reflected in the PRAC minutes
• Literature ADR monitoring		• Advice provided to the EMA Executive Director	• Advice reflected in the PRAC minutes

Lists			
Relevant processes	**Relevant product types**	**Outcome(s)**	**Transparency and communication**
• Updated EURD list for PSURs	CAPs, non-CAPs and mixture of CAPs and non-CAPs	• PRAC output has to be adopted by the CHMP and the CMD(h)	• List is made public on the EMA website
• Updated list of products under additional monitoring		• PRAC output does not need to be adopted by the CHMP nor the CMD(h). In addition CHMP (for CAPs) and RMS (for non-CAPs) include the black symbol and special wording in product information for the products included on the list	• List is made public on the EMA website