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Procedural Advice to CHMP Members

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Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 2/27

INDEX

- 1. INTRODUCTION**
- 2. AIM AND SCOPE**
- 3. REFERENCES and RELATED DOCUMENTS**
- 4. GENERAL REQUIREMENTS**
- 5. PRE-PROCEDURAL PHASE**
- 6. ASSESSMENT PHASE: PRE-AUTHORISATION**
- 7. POST-AUTHORISATION ACTIVITIES FOR CENTRALLY AUTHORISED PRODUCTS**
- 8. REFERRALS AND REVIEWS**
- 9. INTERACTIONS WITH THE CHMP**
- 10. COMMUNICATIONS**

ANNEX 1 - CHMP Information Pack - List of documents – Not attached

ANNEX 2 – CHMP Members Interactions with Applicants/MAHs during the Centralised Procedure

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 3/27

1. INTRODUCTION

This Procedural Advice to CHMP Members document outlines the role, responsibilities and tasks of CHMP members and describes interactions with EMEA staff or applicants in relation to the different activities undertaken at CHMP level, irrespective of whether the members are acting as Rapporteur, Co-Rapporteur, Peer Reviewer or CHMP member.

2. AIM AND SCOPE

This document has been prepared for use by both CHMP members and EMEA staff to ensure that a consistent approach is taken with respect to all evaluations and monitoring of activities in the centralised procedure, allowing a smooth running of each procedure and CHMP plenary sessions. The document also takes into consideration the role of the CHMP in Referrals and other procedures.

3. REFERENCES AND RELATED DOCUMENTS

- Regulation (EC) No. 726/2004
- Directive 2001/83 /EC as amended
- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Rules of Procedure for the CHMP (EMEA/CHMP/111481/2004)
- Draft Explanatory Paper on the Functioning of the EMEA Secretariat (EMEA/401604/2005 Ver. 1)
- Regulatory guidance webpage
- Full list of CHMP documents related to this Procedural Advice can be found in Annex 1 and in the CHMP Information Pack

4. GENERAL REQUIREMENTS

The primary purpose of the CHMP (through its members) is to provide objective scientific opinions to the Community and to Member States (MS) on applications/questions presented to the Committee, with the support of the EMEA Secretariat which has a complementary role to that of members and alternates of the CHMP. The EMEA Secretariat provides technical, scientific, regulatory and administrative support to the Rapporteurs, Co-Rapporteurs and their experts, other members of the Committee, Working Parties, Scientific Advisory Groups (SAGs) and ad-hoc Expert Groups ensuring appropriate coordination between all parties involved. The EMEA Secretariat (through its Scientific Committees) contributes to delivering science driven and consistent regulatory opinions. The EMEA Secretariat provides high-quality support to its various Scientific Committees, their Working Parties and other scientific fora (such as ad-hoc Expert Groups) and coordinates the scientific resources available within the EU Regulatory System. As a general rule, good communication and accurate timing are at the centre of any activity undertaken by the Committee, therefore up to date communication between all parties involved (i.e. Rapporteur and Co-Rapporteur assessment teams, Peer Reviewer(s), CHMP members, EMEA staff and applicants) are of great importance. The preparation of assessment reports, their circulation and the provision of comments are crucial to the evaluation under the centralised procedure and each of these actions should be made in accordance

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 4/27

with agreed timetables. Any document requiring CHMP endorsement should be prepared using the relevant adopted template. CHMP members should not overly consider current or previous national practices or experiences when performing their assessment but preferably develop a European viewpoint when dealing with centralised procedures. In addition, all CHMP members are expected to review and comment on the Table of Decisions, Minutes and CHMP Monthly Report to ensure accurate records of each meeting. The Minutes of a given meeting will be adopted at the start of the next CHMP plenary session.

5. PRE-PROCEDURAL PHASE

5.1. Eligibility to the Centralised Procedure

The CHMP review all eligibility requests made by applicants requiring that their medicinal product be evaluated under the centralised procedure. Such eligibility requests are sent to the EMEA Secretariat, either as stand alone requests or as part of the Letter of Intent to submit if the request comes in close to the planned submission date. The CHMP review all eligibility requests mentioned on the agenda at any given CHMP plenary session and confirm whether or not the applicant meets the relevant eligibility criteria to gain access to the centralised procedure under the relevant point of legislation described in Regulation (EC) No. 726/2004.

In the event that CHMP cannot pronounce itself on the eligibility status during a given meeting, one member (at the minimum) with relevant expertise will be appointed to act as sponsor and prepare a discussion paper clarifying the issue(s) at hand. This member will report back to the Committee at the subsequent meeting. Based on this report, the CHMP will then be in a position to conclude whether or not the applicant meets the eligibility criteria to gain access to the centralised procedure. The CHMP Secretariat will report the outcome to each applicant concerned copying the EMEA Product Team Leader (PTL) appointed for any given product.

5.2. Appointment of Rapporteurs

Any scientific evaluation going through the Committee will usually require the appointment of a Rapporteur, and if relevant a Co-Rapporteur, chosen from amongst its members including co-opted members and CHMP alternates. The appointment of the Rapporteur and Co-Rapporteur for centrally authorised products is made on the basis of objective criteria, ensuring the provision of objective scientific opinions and allowing the use of the best and available expertise in the European Economic Area on the relevant scientific area.

In the pre-authorisation phase of the Marketing Authorisation Application (MAA), a Rapporteur and a Co-Rapporteur will be appointed. Appointments will take place 6-7 months prior to the intended submission date and are usually initiated following the receipt of the applicant's Letter of Intent to submit and request to assign a Rapporteur and a Co-Rapporteur for the review of the MAA. On Friday of the CHMP week, the CHMP Secretariat will send out to all CHMP members the list of products requiring appointment of Rapporteur/Co-Rapporteur at the next meeting. CHMP members wishing to act as Rapporteur/Co-Rapporteur for a given product are required to fill out a nomination form describing their proposed assessment team and send this back to the CHMP Secretariat within specified timelines. All nomination forms received will be reviewed and discussed in the presence of the CHMP Chairman prior to the subsequent CHMP meeting where the Committee will adopt the formal appointment of Rapporteurs/Co-Rapporteurs as proposed by the CHMP Chairman. The CHMP Secretariat will report the outcome to each applicant concerned copying both Rapporteurs and the EMEA PTL appointed to the product.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 5/27

5.3. Pre-submission meetings

The EMEA Secretariat strongly recommends having pre-submission meetings with applicants for MAA submissions, extensions of indication, legal status change (non-prescription switch) and renewals. Such meetings usually take place a few months prior to the intended submission date of the MAA (or the submission of an application for a Type II variation for an extension of indication or prior to a legal status change or prior to a renewal) and are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMEA. In this pre-submission phase, an applicant can also seek to meet directly with his appointed Rapporteur and Co-Rapporteur to review preparatory aspects of the MAA from both a technical and scientific viewpoint. The EMEA PTL for the product should be made aware when such meetings take place and receive a copy of the Minutes.

5.4 Requests for Accelerated Assessment

The applicant may request an accelerated review of his MAA. These requests should be supported by an appropriate justification and limited to cases where compelling public health reasons may require a quicker evaluation and management of the application. Upon receipt of such requests, the Rapporteur/Co-Rapporteur will review the justification sent by the applicant and report back to the Committee at the subsequent meeting using a pre-defined template. The EMEA PTL will inform the applicant of the outcome.

Currently such process occurs prior to submission but it is proposed that in the near future such accelerated assessment will be performed at Day 80 and a review of the applicant's arguments would be available at Day 90 of the procedure.

5.5. Validation of a Marketing Authorisation Submission, Line Extension or Renewals

The EMEA Secretariat will send to the applicant an acknowledgement of receipt of the MAA, line extension or renewal dossiers and, within 10 working days following such receipt, will complete its validation.

During the validation, the EMEA PTL may consult the Rapporteur/Co-rapporteur on the need for actions relating to specific matters (scientific, regulatory, GCP/GMP inspections etc...). For MAA, the EMEA PTL may also consult EMEA colleagues working within different scientific Committees Secretariats such as the Secretariats for the Committee for Orphan Medicinal Products and the Paediatric Committee regarding queries arising on orphan drug designation and paediatric investigation plans and waivers.

6. ASSESSMENT PHASE: PRE-AUTHORISATION

6.1. Roles and Responsibilities

The roles and responsibilities undertaken by a CHMP member will vary depending whether he/she is acting as a Rapporteur/Co-Rapporteur, Peer Reviewer or CHMP member.

6.1.1. Day 0-120 – Preparation of the consolidated List of Questions

- **Rapporteur/Co-Rapporteur**
 - The Rapporteur and Co-Rapporteur will confirm the names of their assessors (indicating if there are any changes from those appointed at the time of Rapporteurship nomination). The Rapporteur and Co-Rapporteur will ensure that all members of their assessment teams are

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 6/27

included in the EMEA Expert database with an updated declaration of interest, confidentiality undertaking form and curriculum vitae.

- The Rapporteur and Co-Rapporteur with support of their assessment teams will prepare their preliminary assessment reports using the adopted report templates. The assessment reports should be produced and circulated to the Committee within agreed timetables and meet agreed guidance.
- The Rapporteur and Co-Rapporteur or their assessment teams may contact the applicant should the need arise. Such contacts should be documented and any information provided should be copied to both the Rapporteur and Co-Rapporteur assessment teams and to the EMEA PTL in parallel.
- The Rapporteur and Co-Rapporteur will participate in the teleconference with EMEA staff and Peer Reviewer(s) to refine the proposed List of Questions (LoQ) at Day 112.
- The Rapporteur and Co-Rapporteur will update their assessment reports taking into account the outcome of the EMEA/peer review teleconference and CHMP comments received.
- The Rapporteur and Co-Rapporteur will identify whether there is a need to recommend a GxP/PMF inspection or pharmacovigilance inspection and/or product testing. If such need is foreseen the request will be adopted by the Committee and processed with the support of the Inspection Sector at the EMEA.
- Both the Rapporteur and Co-Rapporteur, with the support from the EMEA PTL, should liaise in advance of the CHMP meeting where relevant LoQ will be adopted in order to find agreement (in discussion with CHMP members) on key issues and to identify any contentious issues or areas of disagreement. Such issues should be brought out to the attention of the CHMP Chairman and CHMP members in advance of the plenary discussion, asking for specific comments.
- The Rapporteur and Co-Rapporteur should identify whether there is a need for an ad-hoc Expert Group meeting at this stage to discuss any aspect of the EU-Risk Management Plan (EU-RMP). If a meeting is needed the composition of the expert group should be discussed between both Rapporteurs and EMEA staff and presented by the Rapporteur during the CHMP discussion. Both Rapporteurs and the EMEA PTL are responsible to draft a List of Questions to be addressed by the experts identified.
- The Rapporteur with support from the Co-Rapporteur (or their nominated experts) will submit a brief Reader's Guidance summarising the stage of the procedure and the issues identified when circulating their revised assessment reports. During the relevant CHMP plenary session, the Rapporteur with support from the Co-Rapporteur (or their nominated experts) will present the proposed List of Questions. Due to time constraint, it is essential that presentations to the Committee are focused on the key issues identified in the MAA dossier and on the areas of disagreement/controversy. Redundancy and excessive background information should be avoided. Presentations should not exceed 10-12 slides at most.
- **Peer Reviewer(s)**
 - At the time of Rapporteur appointment, the Committee will decide on the scope of the peer review and the number of peer reviewers to be assigned in order to ensure quality assurance to the draft List of Questions. CHMP members wishing to act as Peer Reviewer are not required to fill out the usual nomination form sent out for Rapporteurs appointment

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 7/27

but just inform the CHMP Secretariat of their interest for a particular product (see section 5.2). The members appointed Peer Reviewer(s) are responsible to judge the quality of the assessment reports produced by both the Rapporteur and Co-Rapporteur especially in relation to potential divergences in the scientific assessment following SOPs in place and using pre-defined templates. The aim of the teleconference set up between the Rapporteur, Co-Rapporteur, Peer Reviewer(s) and EMEA staff at Day 112 is to discuss and analyse critically the different objections and concerns raised in the Rapporteur and Co-Rapporteur assessment reports and proposed draft List of Questions.

- **CHMP members**

- CHMP members are to contribute actively to the review system by providing comments on assessment reports and identifying additional major objections/questions to be addressed by the applicant using pre-defined templates. Comments on the MAA dossier and assessment reports should be provided in strict adherence to the adopted timetables. CHMP members are expected to work closely with both Rapporteurs in compiling such comments and achieving a consensus position whenever possible. Members shall prepare for each CHMP meeting, in discussion with colleagues and experts in their national agencies, in order to have a good understanding and viewpoints on the issues under discussion. To note, that CHMP members can act as Peer Reviewer and can separately provide comments – not mutually exclusive. CHMP members will also comment on the proposed wording of the Product Information.

6.1.2. Day 120-121 – Applicant responses to the List of Questions

Rapporteurs and/or their assessment teams may discuss with the applicant the broad outlines of their response strategy including any withdrawal/limitation of indications applied for as well as modified warnings regarding the precautions for use of a product etc...

6.1.3. Day 121-180 – Preparation of joint assessment report and List of Outstanding Issues as appropriate

- **Rapporteur/Co-Rapporteur**

- The Rapporteur and Co-Rapporteur will evaluate the information submitted by the applicant in response to the issues raised by the CHMP. This evaluation will then be shared with the Committee as a Day 150 joint assessment report using the appropriate template.
- The Rapporteur and Co-Rapporteur will update the Day 150 joint assessment report to take into account CHMP comments received. Both Rapporteurs in liaison with EMEA staff will identify a draft List of Outstanding Issues (if necessary) to be addressed by the applicant in writing and/or in an oral explanation.
- The Rapporteur with support from the Co-Rapporteur (or their nominated experts) will submit a brief Reader's Guidance summarising the stage of the procedure and the issues identified when circulating the Day 150 joint assessment report and present the proposed List of Outstanding Issues during the relevant CHMP plenary session and consider whether there is a need for a future oral explanation. Again presentations should be concise and limited to a small number of slides.
- The Rapporteur, Co-Rapporteur or any CHMP member may suggest to the Committee the need for a SAG/ad-hoc Expert Group meeting to be scheduled in order to clarify the issues raised. In the event that a SAG (or ad-hoc Expert Group) consultation is foreseen, both

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 8/27

Rapporteurs and the EMEA PTL (and RMTM if appropriate) are responsible to draft a List of Questions to be addressed by the experts identified. The draft List of Questions will be reviewed and adopted by the Committee. If necessary, additional expertise may be sought for such groups. The EMEA will assist the Committee by making proposals for the relevant expertise and the Committee will also review, comment and adopt the composition of the SAG/ad-hoc Expert Group and whether or not additional expertise is needed and will propose participants on request.

- The EU-RMP must be finalised before the Opinion, therefore any outstanding issues should be identified and included in the draft List of Outstanding Issues.
- In the event that no major objections remain at this stage of the procedure, both Rapporteurs should strive to finalise their assessment report and update the product information in liaison with the applicant in order to be in a position to adopt an opinion at Day 180.

- **CHMP members**

CHMP members will send their comments on the Day 150 joint assessment report within agreed timelines.

If it is likely that there will be a need for additional risk minimisation activities which will involve some form of controlled distribution or other control within each Member State, the Applicant may seek to meet with the competent authorities of each Member State (between day 121 and Day 180) to discuss how best this may be implemented. CHMP members should facilitate these meetings within his/her Member State. Feedback from Member States should be transmitted back to the Rapporteurs and the EMEA PTL.

6.1.4. Day 180-181 – Preparation of the responses to the List of Outstanding Issues and Oral Explanation

Rapporteurs and/or their assessment teams may discuss with the applicant the broad outlines of their response strategy to the List of Outstanding Issues including any regulatory advice at this stage of the procedure.

6.1.5. Day 181-210 – Opinion

- **Rapporteur/Co-Rapporteur**

- The Rapporteur and Co-Rapporteur will evaluate the information submitted by the applicant in response to the List of Outstanding Issues. This evaluation will then be shared with the Committee as a revised Day 150 joint assessment report.
- The Rapporteur and Co-Rapporteur will update the revised Day 150 joint assessment report to take into account CHMP comments received. Both Rapporteurs in liaison with EMEA staff will identify whether there is a need for an oral explanation and amendments to the List of Outstanding Issues.
 - In the event that a SAG/ad-hoc Expert Group consultation has occurred, the Chair (or a core member in his absence) will be invited to report back to the Committee on the outcome of the discussion.
 - If no oral explanation is necessary, the Committee will adopt an opinion at the relevant CHMP meeting (in line with the adopted timetable).

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 9/27

- If an oral explanation is foreseen, the applicant will be invited to discuss their position and clarify any outstanding issues the Committee may have. The Committee will adopt an opinion at the subsequent meeting if timetable allows.
- When finalising the opinion both Rapporteurs are responsible to ensure that the Package Leaflet is in line with the proposed SPC.
- **CHMP members and EMEA staff** (*section also applicable for post-authorisation variations*)

The EMEA PTL is responsible for the finalisation of the scientific CHMP assessment report ensuring that all necessary justifications on the outcome of the scientific assessment are sufficiently substantiated and accurately reflected in the final assessment report and product information. The Rapporteurs' assessment report or critique, any other relevant contributions, divergent views expressed by the Rapporteurs compared to the overall conclusion reached at CHMP level should be carefully considered. Rapporteurs are reminded of their responsibilities to provide clear justifications to the EMEA PTL for the finalisation of scientific CHMP assessment report especially when the views of the Rapporteurs may differ from the overall conclusion endorsed at Committee level. The EMEA Secretariat will provide an important input to the peer review system, in terms of quality assurance and guardian of the regulatory and scientific consistency. When finalising the opinion, the Rapporteurs, CHMP members and EMEA staff will ensure that appropriate post-marketing commitments are being set up. This will include any additional risk minimisation activities which should be included in Annex II (and IV) of the opinion as appropriate. The Committee will agree on the Letter of Undertaking provided by the applicant (if necessary). In addition the CHMP will ensure that any extra communications that have been identified as necessary are tabled and reviewed by the CHMP as appropriate (question-and-answer documents, communication action plans, lines to take etc...).

6.1.6. Re-examination procedure under Article 9(2) of Regulation EC No. 726/2004 (new applications)

In the event that the applicant appeals an opinion taken by the Committee and informs the EMEA of such course of action, the CHMP will appoint a different Rapporteur and Co-Rapporteur for the re-examination procedure. Such appointment will take place at the subsequent meeting following the receipt of the applicant written notice. The newly appointed Rapporteurs will only coordinate the evaluation for the duration of the re-examination procedure. During this stage, the Committee may also wish to discuss whether a SAG/ad-hoc Expert Group consultation is necessary and whether such groups need to be enriched with additional experts. The applicant may also at its own initiative request the consultation of a particular SAG. The original appointed Rapporteurs should keep in mind that if the re-examination procedure revises the previous opinion adopted by the Committee, responsibilities will go back to them and the product information may have to be finalised in a very short timeframe.

6.2. Other Procedures

- **Article 58 of Regulation (EC) No. 726/2004**

When the EMEA receives an application within the context of Article 58 - *CHMP Scientific Opinion in cooperation with WHO* - the Committee will appoint a Rapporteur and Co-Rapporteur who will be responsible for the procedure (see section 5.1). Both Rapporteurs will recommend to the Committee whether possible nomination of WHO Experts is foreseen for the assessment review. If agreeable, the Committee may ask WHO to propose experts for certain areas of expertise. Experts appointed will be allowed to participate in the discussion on products. In addition observers from WHO and National Competent Authorities (NCA) from developing countries may also attend relevant Working Parties

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 10/27

and CHMP plenary discussions. Participation at a plenary CHMP meeting or attending relevant Working Parties discussions will only be possible providing that the nominated experts are included in the EMEA Expert database with an updated declaration of interest, confidentiality undertaking form and curriculum vitae.

- **Article 83 of Regulation (EC) No. 726/2004**

When a Member State (MS) envisages the need to make a medicinal product available for compassionate use, the NCA of that MS must notify the EMEA. Further to the notification and request by MS(s), the CHMP will appoint a Rapporteur and a Co-Rapporteur (if necessary) to prepare an opinion on the conditions for use, the conditions for distribution and the patients targeted by the compassionate use in a given therapeutic indication. Once adopted by the Committee, opinions related to compassionate use are not binding on MSs, however MSs shall take into account any available opinion.

- **Scientific Advice**

CHMP members are encouraged to take an active role as peer reviewer of the scientific advice letters prepared by the Scientific Advice Working Party (SAWP) and comment appropriately. The SAWP Secretariat is also strongly involved in the peer review of applications as part of the quality assurance expertise. The SAWP shall transmit their conclusions for Scientific Advice and Protocol Assistance to the CHMP for formal adoption.

- **Innovation Task Force**

The Innovation Task Force Group is in charge of assessing the scientific basis of the regulatory requests from applicants to assess whether or not products being developed are considered medicinal products eligible to the centralised procedure. In cases that are not straight forward, the Committee will appoint one of its members to act as a CHMP Coordinator to review the draft report and report back to the Committee on whether the product can be considered a medicinal product or not. The Committee will adopt the relevant Regulatory Advice Report.

7. POST-AUTHORISATION ACTIVITIES FOR CENTRALLY AUTHORISED PRODUCTS

In the post-authorisation phase of the Marketing Authorisation, the Rapporteur will take the lead role along with the EMEA PTL who will be the primary contact point for the Marketing Authorisation Holder (MAH)². The Rapporteur, the Co-Rapporteur if necessary, their assessment teams respectively and the EMEA PTL will be involved in numerous activities.

7.1. Variation Type II – 90-Day - Extension of Indication

- **Pre-submission meeting**

See section 5.3.

- **Confirmation of the involvement of the Co-Rapporteur by the CHMP**

If appropriate, both the Rapporteur and Co-Rapporteur teams will be involved in the assessment of the Type II variation for an extension of indication. The MAH must send a letter of intent at least 2 months before the planned submission date. With the receipt of this letter (or at the latest at the time of

² Rapporteurs should remind applicants that planned future variations should always be discussed with the EMEA PTL prior to submission.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 11/27

the variation submission by the MAH), the EMEA PTL will confirm with the Rapporteur and Co-Rapporteur whether there is a need or not to involve the Co-Rapporteur in the assessment of the variation. The EMEA PTL will inform the CHMP Secretariat of the outcome in writing. The Committee will confirm the Co-Rapporteur's involvement at the relevant CHMP meeting.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 12/27

Preparation of the Request of Supplementary Information/Opinion

- **Rapporteur/Co-Rapporteur**

- The Rapporteur and Co-Rapporteur will ensure that all members of their assessment teams are included in the EMEA Expert database with an updated declaration of interest, confidentiality undertaking form and curriculum vitae.
- The Rapporteur and Co-Rapporteur with their assessment teams will prepare their preliminary assessment reports using the appropriate templates. The assessment reports should be produced and circulated to the Committee within the agreed timetables and meet agreed guidance.
- EU-RMP submitted as part of the variation application of the extension of indication will be forwarded by the EMEA PTL to the EMEA RMTM for comments. The EMEA RMTM's comments will be forwarded to the Rapporteur's and Co-Rapporteur's teams during the assessment. The Rapporteur and Co-Rapporteur are expected to assess and provide comments on the EU-RMP.
- The Rapporteur and Co-Rapporteur will prepare jointly the Request for Supplementary Information (RSI) (or opinion) taking into account the CHMP comments received and circulate it to the Committee prior to the CHMP meeting.
- If appropriate, the CHMP Chairman should be made aware by the EMEA PTL in liaison with the CHMP Secretariat of any controversial issues identified in the RSI in advance of the CHMP meeting
- The Rapporteur and Co-Rapporteur (or their nominated experts) will present the proposed RSI (or opinion) during the relevant CHMP meeting which will be adopted by the Committee once they, together with the EMEA PTL have finalised the CHMP RSI ((or opinion) to be sent to the MAH.
- As in the Pre-authorisation phase, any controversial issues may lead to further discussions with other Expert Groups and an Oral Explanation by the MAH may be envisaged.
- The Rapporteur, Co-Rapporteur, or any members of the Committee may suggest to the Committee whether a SAG or other ad-hoc Expert Group meeting should be convened (see section 6.1.3 - Pre-Authorisation part of the document).
- When finalising the opinion the Rapporteur (and the Co-Rapporteur if involved in the procedure) is/are responsible to ensure that the Patient Leaflet is in line with the proposed SPC.
- The Rapporteur, Co-Rapporteur and CHMP members will need to agree on the wording of the post-authorisation commitments to be performed by the MAH post opinion.

- **CHMP members**

As in the pre-authorisation phase, CHMP members are to contribute actively to the review system by providing comments on the Rapporteur and Co-Rapporteur preliminary assessment reports and proposed RSI within agreed timelines (see section 6.1.1 - Pre-Authorisation part of the document).

- **CHMP members and EMEA staff**

See section 6.1.5 in the pre-authorisation part of the document.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 13/27

7.2. Variation Type II – 60-Day

- **Rapporteur**

- The Rapporteur with support of their assessment teams will prepare their preliminary assessment reports using the adopted report templates. The assessment reports should be produced and circulated to the Committee within agreed timetables and meet agreed guidance.
- If controversial issues have arisen during the assessment, the EMEA PTL after consultation with the Rapporteur will inform the CHMP Secretariat so that the issues identified can be presented and discussed during the relevant CHMP meeting.
- In the event that the issues remained unresolved, the Rapporteur will prepare a RSI taking into account the CHMP comments received and circulate it to the Committee prior to the CHMP meeting. The proposed RSI will be presented and adopted during the relevant CHMP meeting. The Rapporteur, together with the EMEA PTL, will finalise the CHMP RSI (or opinion) to be sent to the MAH.

- **CHMP members**

CHMP members will send their comments on the preliminary assessment report of the Rapporteur within agreed timelines. CHMP members will also comment on the proposed wording of the Product Information.

7.3. Variation Type II – 30-Day

- **Exact implementation of proposed wording for the Product Information**

For the purpose of implementing the exact amendments to the Product Information (Summary of Product Characteristics (SPC) and/or Labelling and/or Package Leaflet) requested by the CHMP as a result of a previously assessed procedure (e.g FUM, PSUR, etc), an administrative 30-Day type II variation is carried out. The Rapporteur will assess the documentation provided by the MAH (mainly to ensure compliance with the CHMP request) and prepare a short assessment report for the Committee.

- **Urgent Safety Restriction Variation (USR)**

Where a USR is being considered, the Rapporteur should prepare a short assessment report for circulation to the CHMP (and PhVWP as appropriate). This report will assess relevant data, review the proposed changes to the Product Information and propose timelines. CHMP members will comment on the assessment report, the need for a USR and on the proposed wording of the Product Information. Once the wording is agreed at CHMP level, the MAH will initiate the USR.

The EMEA PTL will inform the CHMP on the start of the procedure and provide relevant timelines for comments on the Product Information wording. In parallel, the EMEA PTL will circulate to the CHMP, a Press Release, question-and-answer document, Dear Healthcare Professional Letter (DHPL) and Action Plan for comments. The Rapporteur and the EMEA PTL will review the CHMP comments and propose any revision of the wording to the MAH for agreement. If no major objections are received by the CHMP members within 24 hours after the start of the procedure, the changes in the Product Information can be implemented by the MAH.

The Rapporteur will circulate the preliminary assessment report, CHMP members will comment and the updated assessment report will be circulated by the Rapporteur within the

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 14/27

agreed timelines. A discussion during the relevant CHMP meeting will take place and the Rapporteur will present the subject to the Committee.

During a 30-Day type II variation dealing with an USR issue, the 60-Day type II variation assessment as described above (section 7.2), is followed but with shorter timelines

7.4. Renewal

Renewals follow the same timeline as the 90-Day type II variation assessment described in section 7.1.

- **Pre-submission meeting**

As for a major Type II variation planned submission, a pre-submission meeting might be scheduled (see section 5.3).

Preparation of the Opinion

- **Rapporteur/Co-Rapporteur**

- The Rapporteur with his/her assessment team will prepare the preliminary assessment report using the Renewal template. The Co-Rapporteur will comment on the Rapporteurs's assessment report before circulating the Joint Rapporteur's and Co-Rapporteur's assessment report to the Committee within the agreed timetables and meet agreed guidance.
- In case a RSI is needed, the Rapporteur and Co-Rapporteur will prepare jointly a RSI taking into account the CHMP comments received and circulate it to the Committee prior to the CHMP meeting. The proposed RSI will be presented and adopted during the relevant CHMP meeting. The Rapporteur and Co-Rapporteur together with the EMEA PTL will finalise the CHMP RSI to be sent to the MAH. Both Rapporteur will then assess the responses of the MAH and this assessment report will be circulated to the Committee for comments.
- In the preliminary assessment report, the Rapporteur and the Co-Rapporteur will make a recommendation, if applicable, on the validity of the renewed MA (unlimited validity or one further 5-year period renewal required) as well as on the future PSUR cycle. The Rapporteur will present the proposed recommendation and the Pharmacovigilance grounds for this proposal during the relevant CHMP meeting. The Committee will subsequently adopt the opinion for the renewal.

- **CHMP members**

CHMP members will send their comments on the preliminary assessment report of the Rapporteur and on the assessment of the RSI, if applicable, within agreed timelines.

7.5. Annual Re-assessment / Conditional Renewal

Annual re-assessments and conditional renewals follow the same timeline as the 60-Day type II variation assessment described in section 7.2.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 15/27

- **Rapporteur**

- The Rapporteur and his/her assessment team will prepare the preliminary assessment report within the adopted timelines and will circulate it to the Committee.
- In exceptional cases where a RSI is necessary, the Rapporteur will assess the responses of the MAH and will circulate this assessment to the Committee.
- The Rapporteur and his/her assessment team will update the preliminary assessment report with CHMP members' comments within the adopted timelines and circulate it to the Committee.
- If during the assessment there are no grounds for the MA to remain under conditional approval or exceptional circumstances, the Rapporteur will inform the Committee during the relevant CHMP meeting.

- **CHMP members**

CHMP members will send their comments on the preliminary assessment report of the Rapporteur within agreed timelines.

7.6. Extension Applications

Such applications will be treated similarly to new MA applications in the pre-authorisation phase involving the Rapporteur and if appropriate also the Co-Rapporteur. The procedure involving the Committee will be the same as described in section 6.1.

7.7. Post-authorisation Commitments (PSURs/FUMs/Specific Obligations)

The Rapporteur will circulate to the Committee the preliminary assessment report of the PSURs, FUMs or Specific Obligations within the adopted timelines. CHMP members will comment within the agreed timelines and the Rapporteur will circulate the updated Assessment Report for adoption by the Committee. If further issues are identified for discussion with the MAH a timeframe for responses to these issues should be proposed by the Rapporteur in his/her assessment report. If any controversial issues arise during the assessment, the Rapporteur with the help of the EMEA PTL may decide to bring the subject to the attention of the PhVWP and the CHMP. Where an updated Product Information is proposed, the Rapporteur should propose appropriate wording to be introduced in the SPC and Patient Leaflet, as appropriate.

7.8. Pharmacovigilance

- **Handling of safety issues** (process being currently updated, further information will be provided in the near future).
- **Signal Detection (SD)** (process being currently updated, further information will be provided in the near future).

7.9. Re-examination procedure Article 6(9) of Regulation EC No 1085/2003 (type II variations)

In the event that the applicant appeals an opinion taken by the Committee and informs the EMEA of such course of action, the CHMP will appoint a different Rapporteur and Co-Rapporteur for the re-examination procedure. Such appointment will take place at the subsequent meeting following the receipt of the applicant written notice. The newly appointed Rapporteurs will only coordinate the evaluation for the duration of the re-examination procedure. The Committee may also wish to discuss whether a SAG/ ad-hoc Expert Group consultation is necessary and whether the SAG/ ad-hoc Expert

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 16/27

Group need to be enriched with additional experts. The applicant may also at its own initiative request the consultation of a particular SAG. Original appointed Rapporteurs should keep in mind that in case the re-examination procedure revises the previous opinion adopted by the Committee, the product information may have to be finalised in a very short timeframe.

8. REFERRALS AND REVIEWS

8.1. Referrals

Whenever an arbitration mechanism is being invoked, a scientific evaluation of the matter will be undertaken by the Committee. Community arbitration mechanism may be invoked on the basis of the following articles:

1. Article 29(4) of Directive 2001/83/EC as amended (“*Mutual Recognition and Decentralised referral*”)
2. Article 30 of Directive 2001/83/EC as amended (“*Divergent decision referral*”)
3. Article 31 of Directive 2001/83/EC as amended (“*Community interest referral*”)
4. Articles 35 and 36 of Directive 2001/83/EC as amended (“*Follow-up referrals*”)
5. Articles 5(1), 6(12) and 6(13) of Regulation (EC) No. 1084/2003 (*Variations to MAA*)

Start of the referral procedure (CHMP plenary meeting) - First CHMP meeting following notification of a referral

- Rapporteur and Co-Rapporteur(s) (if applicable) will be appointed during the relevant CHMP meeting.
- A 60 days timetable will be adopted by the CHMP after agreement with Rapporteur/Co-Rapporteur(s).
- Rapporteur/Co-Rapporteur(s) in conjunction with the EMEA PTL will propose a draft LoQ to be addressed to the MAH(s).
- CHMP members will be invited to comment on the proposed LoQ* at the latest during the CHMP plenary meeting.
- The proposed timetable and List of Questions will be adopted during the CHMP meeting.

*If the referral is triggered by a MAH, it should be noted that the procedure will not start with a LoQ but with the documentation submitted by the MAH as basis for the assessment.

Day 20

- Rapporteur/Co-Rapporteur(s) will circulate their assessment reports on the MAH(s)’ written responses; if applicable the draft SPC/ Labelling/PL will be annexed to the opinion.

Day 25

- CHMP members will comment on Rapporteur/Co-Rapporteur(s) assessment reports and draft SPC/ Labelling/PL (if applicable).

Day 30 – CHMP plenary meeting

- The Rapporteur/Co-Rapporteur(s) will draft a LoOI to be answered in writing and/or in an oral explanation (the CHMP should be informed on the likelihood of a future oral explanation). If at this stage no proposal of SPC/ labelling/PL has been given, it should be requested in the LoOI.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 17/27

- Or an Opinion will be adopted by the CHMP

Between Day 30 and Day 60 (specific adopted timetable for the procedure to be followed)

- Rapporteur/Co-Rapporteur(s) will circulate their assessment reports on the MAH(s)' written responses to the LoOI with the draft SPC/ Labelling/PL. CHMP members will comment on such documents.

Day 60 – CHMP plenary meeting

- A CHMP Opinion is adopted.

It should be noted that for referrals under Articles 30 and 31 the timetable may be extended allowing a total of 150 active days (60 days with a possibility of extension for further 90 days). This extension of timetable must be done during a CHMP plenary meeting prior to reaching day 60 of the initial timetable.

At all stages, the EMEA PTL will coordinate the procedure and assist Rapporteur and Co-Rapporteur(s) making sure that appropriate regulatory guidance is provided.

8.2. Reviews

- **Article 20(1) of Regulation (EC) No. 726/2004**

The Committee may be requested to issue an opinion when a Member State is of the opinion that the manufacturer or importer established within the Community territory is no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC.

- The CHMP will discuss and appoint a Rapporteur and Co-Rapporteur(s).
- A 60 days timetable will be adopted (please refer to the timetable stated above in section 7.2).
- Rapporteur/Co-Rapporteur(s) will prepare an assessment report on the scientific matter.
- CHMP members will comment on the Rapporteur/Co-Rapporteur(s) assessment report(s).
- Further to discussion, the CHMP will adopt an Opinion.

- **Article 5(3) of Regulation (EC) No. 726/2004**

The Committee may be requested to issue an opinion on any scientific matters concerning the evaluation of medicinal products for human use following a request from the Executive Director of the Agency, the European Commission representative or a Member State. In the latter case, the request from a Member State will need to be accepted by the Committee.

- The CHMP will discuss and appoint a Rapporteur and Co-Rapporteur(s) (if necessary).
- A timetable will be prepared in accordance with the urgency.
- Rapporteur/Co-Rapporteur(s) will prepare an assessment report on the scientific matter.
- CHMP members will comment on the Rapporteur/Co-Rapporteur(s) assessment report(s).
- Further to discussion, the CHMP will adopt an Opinion, to be sent to the European Commission (if the request originated from the EC) and to be published.

At all stages, the EMEA PTL will coordinate the procedure and assist Rapporteur and Co-Rapporteur(s) making sure that appropriate regulatory guidance is provided.

- **Article 107(2) of Directive 2001/83/EC, as amended**

When a Member State is considering the suspension or revocation of the MA for a medicinal product(s) authorised in its territory as a result of the evaluation of pharmacovigilance data, a procedure under Article 107(2) is initiated and the CHMP shall prepare an opinion within a timeframe

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 18/27

to be determined depending on the urgency of the matter. In relation to variations, as a result of the evaluation of pharmacovigilance data, the procedure can be initiated by the Member State(s) which is (are) considering the variation of the concerned product(s). In principle the scope of the procedure is limited to the issues identified by the Member State(s). Given that pharmacovigilance evaluations are frequently conducted on drug substances rather than on individual medicinal products and in the interest of public health protection, a notification under Article 107(2) and the subsequent CHMP opinion(s) may relate to an individual medicinal product or a range of medicinal products containing the same active substance. This should be made clear by the Member State(s) when notifying the Agency of an Article 107(2).

- The concerned MS(s) notifies the EMEA of its intention to suspend, revoke or vary the MA and confirms the initiation of an Article 107 using the Rapid Alert system. Upon receipt of the Rapid Alert notifying of an Article 107(2) procedure the EMEA will request Member State(s) to identify all concerned products within a specified timeframe. A Rapid Alert from (a) Member State(s) notifying an Article 107(2) procedure should always be accompanied by an Assessment Report prepared by such Member State(s) and any other relevant documentation which should then be made immediately available by the EMEA to all CHMP members. The Member State(s) notifying the procedure should also make this information available to the concerned MAH(s) in its (their) own territory. Considering the urgency of the matter it can be necessary to agree on a timetable by written procedure. In exceptional cases a CHMP Extraordinary meeting can be organised. .
- Normally, in order to consider the matter the CHMP should appoint a Rapporteur and one or more Co-Rapporteur(s) (CHMP Rapporteur/Co-Rapporteur appointment – EMEA/124066/2005). However, when the timeframe does not allow for the (Co-) Rapporteur(s) to be appointed in accordance with the above procedure, the CHMP Chairman will appoint a Rapporteur and Co-Rapporteur(s) on an ad-hoc basis.
- Rapporteur/Co-Rapporteur(s) will present the issue and the assessment to the CHMP members during the relevant plenary meeting.
- Article 107(2) does not provide details on the procedures leading to the adoption of an Opinion and on the possibility for MAHs to provide written and/or oral explanations. Although all reasonable efforts should be made to hear (in writing and/or orally) the MAH(s), there could be circumstances where in order to protect public health the CHMP will decide to adopt an Opinion immediately or in a very short timeframe and therefore the CHMP may agree not to hear the MAH(s) concerned or to only hear the brand leader. This decision will be made by the CHMP on a case-by-case basis.
- In the case when the CHMP does not consider that there is a need to immediately adopt an Opinion, the MAH(s) will in principle be given the opportunity to comment on the Assessment Reports of the triggering MS(s) and/or provide answers to a CHMP List of Questions.

At all stages, the EMEA PTL will coordinate the procedure and assist Rapporteur and Co-Rapporteur(s) making sure that appropriate regulatory guidance is provided.

- **Sampling and Testing (Art. 57 (r) of the EC Regulation 726/2004)**

CHMP members will be asked to adopt/endorse a list of products to be tested during a Sampling and Testing Programme (this is usually done in February/March of the year before the programme is implemented). For those products for which the testing recommendations are not available, the Rapporteur and Co-Rapporteur for each product will be asked to provide relevant recommendations on the parameters to be tested when the product is included in a future sampling and testing programme. A template is annexed (Annex 1) in the Day 80 Assessment Report. Once the testing of a product has been completed, the Rapporteur and Co-Rapporteur for each product will receive a testing report and,

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 19/27

and if available, the comments of the MAH on the testing results. The Rapporteur and Co-Rapporteur will be asked to provide advice for follow-up actions.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 20/27

- **Dealing with Reports of Defective Medicinal Products**

In the case of significant Quality Defects to centrally authorised products, the Rapporteur together with the Inspection Sector and Supervisory Authority is expected to contribute to an assessment of the nature, extent, urgency of possible public health risk and evaluation of the seriousness of the defect

9. INTERACTIONS WITH THE CHMP

- **SAG/ad-hoc Expert Group meeting**

At any stage during the evaluation procedures (Day 120, Day 180, prior to an oral explanation, during a re-examination procedure or during a post-authorisation procedure) the Rapporteur, Co-Rapporteur or any CHMP member may suggest to the Committee the need for a SAG/ad-hoc Expert Group meeting to be scheduled in order to clarify the issues raised. In the event that a SAG (or ad-hoc Expert Group) consultation is foreseen, both Rapporteurs and the EMEA PTL (and RMTM if appropriate) are responsible to draft a List of Questions to be addressed by the experts identified. The draft List of Questions will be reviewed and adopted by the Committee. If necessary, additional expertise may be sought for such groups. The EMEA will assist the Committee by making proposals for the relevant expertise and the Committee will also review, comment and adopt the composition of the SAG/ad-hoc Expert Group and whether or not additional expertise is needed and will propose participants on request. Following the meeting of the SAG/ad-hoc Expert Group, its Chair (or a core member in his absence) will report back to the Committee on the outcome of the discussions. In case of an appeal procedure, the applicant may request the involvement of particular SAG.

- **Consultation with target groups**

In some particular cases, the Committee may suggest the need to consult a target group of patients or healthcare professionals. If such consultations are foreseen the Committee will agree to this external involvement but also define the issues that these groups/organisations should look into (i.e. patient leaflet, some aspect of the risk management plan etc...).

- **CHMP Working Parties**

- CHMP members or experts can be appointed Chair or Vice Chair of a Working Party (WP) based on individual merit and ability. Following nominations of interest, the Committee will formally vote upon these nominations and appoint a Chairperson and Vice Chairperson.
- WP Chairpersons are responsible for updating the Committee on the work of their WP, both with respect to the development of guidance documents and on the input of some WP in ongoing procedures. WPs mandates and work programme are adopted by the Committee and should be strictly adhered to by the WPs, any deviations should be brought to the attention of the Committee.
- Following experience gained in the centralised procedure or feedback from interested parties, the Committee can propose that a new guideline is needed or that existing ones are due for an update. WP members can act as Rapporteur for a particular guideline depending on his/her expertise and is then responsible for driving the process to create/update relevant guidelines. When presenting a new guideline or an update of an existing one, the Rapporteur and/or the Chairperson of the WP should make a clear presentation of the documents for adoption / release for public consultation in order to facilitate their formal adoption by the Committee.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 21/27

- During an evaluation process, the Rapporteur, Co-Rapporteur or CHMP members may suggest that a particular WP is consulted in order to help resolving the issues identified in the application. If agreeable to the Committee, such consultation will take place and the Committee will adopt a List of Questions to be answered by the relevant WP. The Committee will then adopt the report produced by the WP in response to the CHMP concerns. Consultation of the BWP is always taken on board for any biologic medicinal product.

- **Involvement of the CHMP Pharmacovigilance Working Party (PhVWP)**

This section will be updated following the finalisation of ongoing discussion with the PhVWP.

- **Consultation with the Paediatric Committee (PDCO)**

Following the Regulation on medicinal products for paediatric use coming into force in July 2007, interactions between the PDCO and the CHMP are essential in order to achieve appropriate coordination between these scientific committees. Further work on the practicality of such interactions is currently ongoing.

- **Consultation with the Committee for Orphan Medicinal Products for Human Use (COMP)**

Interactions with the COMP take place on an ad-hoc basis whenever issues are arising with regards to the orphan designation of a medicinal product and also in the context of similarity assessment.

- **Consultation with the Committee for Advanced Therapies (CAT)**

The Regulation on Advanced Therapies was adopted in October 2007 and foresees interactions between the CAT and the CHMP. Procedures/guidance on such aspect will be developed over the coming months.

- **Consultation with the Committee for Herbal Medicines (HMPC)**

Interactions with the HMPC and CHMP occur on an ad-hoc basis whenever there is a need for such consultations to take place.

- **Consultation with the Committee the Co-ordination Group for Mutual Recognition & Decentralised Procedures (CMD(h))**

Interactions with the CMD(h) and CHMP occur on an ad-hoc basis whenever there is a need for such consultations to take place, WP support, referrals, SPC harmonisation etc...

- **Involvement of the QRD**

PIQ-QRD reviews are necessary and Rapporteur might be involved in such interactions. In addition checking of translations by Members States are performed with potential liaison with CHMP members or assessors as appropriate.

- **Involvement of the Name Review Group (NRG)**

The NRG is involved in checking the proposed names for medicinal products on behalf of CHMP. The Committee then adopts the NRG proposals.

10. COMMUNICATIONS

- **Product-related announcements**

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 22/27

An Early Notification System for communication on safety related issues has been put in place. The aim of this system is to facilitate the preparation at national level of communication material on the basis of the agreed EMEA communication. The scope is limited to envisaged CHMP recommendations for regulatory action (based on identified safety concerns), accompanied by EMEA communication to the general public (e.g. Press Releases, Q&A documents). This procedure relates to both centrally authorised products and referral procedures.

During the week prior to the CHMP plenary meeting, the Heads of Medicines Agencies (HMA) and the European Commission will receive an overview of such envisaged CHMP recommendations for regulatory action. Discussions at CHMP level will be prioritised to allow finalisation of communication material by the Wednesday of the CHMP week, close of business. HMA and the European Commission will be provided on the Wednesday of the CHMP week, close of business, with the final communication material. Where feasible, an early draft can be circulated on Tuesday to further facilitate preparation at national level. On the Thursday of the CHMP week, at 16.00 hrs UK time, documents will be published on the EMEA website. Whenever the timing as outlined above cannot be adhered to, or new information arises which will affect the communication plan sent the week before the CHMP, Heads of Medicines Agencies and the European Commission will be informed without delay.

- **Communication exchange**

CHMP members are reminded that any communications on product related issues should be handled via Eudranet emails or a Eudralink account. Members should not use private email addresses when sending confidential documentation. In addition when sending documents and presentations during a CHMP plenary meeting, such communications should always be sent to the entire CHMP Secretariat team (chmpdl@emea.europa.eu).

- **External Representations**

CHMP members receive many invitations to speak at external meetings/conferences on a wide variety of topics. Whenever appearing at such events, members should make a clear announcement concerning their presence at such forum i.e. whether they are present in their capacity as CHMP member and have been requested by the Committee to speak on a given topic or whether they are present in their individual (or NCA) capacity and presenting personal views on a given subject matter. When representing the Committee it is important that the consensus or majority view on a given subject matter is presented rather than a minority or individual view.

CHMP members are also often requested to provide articles for publication within scientific/regulatory journals. In agreeing to such requests a similar analysis should be made as to the capacity in which such contributions are provided and this should be made explicit in the publication concerned.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 23/27

ANNEX 1

CHMP Information Pack – List of documents – Not attached

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 24/27

ANNEX 2

CHMP Members Interactions with Applicants/MAHs during the Centralised Procedure

Contacts with CHMP members prior to Rapporteur appointment (typically 12-18 months before submission of an MA)

Companies often request pre-submission meetings with a number of CHMP members prior to the formal appointment of Rapporteur and Co-Rapporteur by the CHMP. The motivations of such requests can range from determining a CHMP member's potential interest to take up rapporteurship to a company desire for a pre-assessment regarding the scientific adequacy of the data package to be presented and its potential approvability.

Though not obliged to accept CHMP members (in context of National Competent Authorities contacts) are free to agree to such meetings on a case-by-case basis. Where advice of a regulatory or scientific nature is discussed it is recommended that minutes of such meetings are taken, agreed and released to other CHMP members and to the EMEA PTL once the formal Rapporteur/Co-Rapporteur appointment process occurs.

Contacts with CHMP members after Rapporteur appointment (typically 4-6 months before file)

Once the Rapporteur and Co-Rapporteur have been appointed for a given product it is not considered appropriate for another CHMP member to meet with the applicant to discuss the future file. The applicant seeks to meet with his appointed Rapporteur and Co-Rapporteur in this pre-submission phase to review preparatory aspects of the MAA from both a technical and scientific viewpoint. It is considered appropriate that the Rapporteur and Co-Rapporteur agree to such meetings. These meetings are usually held at the EMEA or bilaterally at the national agencies, which may facilitate discussions with the appointed QSE assessors. It is essential however that minutes of such meetings are taken and that these are made available to the Rapporteur and Co-Rapporteur and EMEA PTL as appropriate so that all parties are informed and no conflicting information is provided.³

Companies should be made aware of limitations of such meetings and not to expect scientific pre-assessment agreements on behalf of R/cRs and their assessment teams.

Contacts with CHMP members between Day 0 and Day 120 (Consolidated List of Questions)

During the first assessment phase apart from both Rapporteurs it is not considered appropriate for CHMP members to have any contact with the applicant. It is considered appropriate that the Rapporteurs or their assessment teams at their own initiative may contact the applicant either during the initial day 80 assessment phase or during the day 80-120 phase. However this must be understood as a facility for the Rapporteurs and their assessment teams should the need arise to clarify any aspect of the review. It is recommended that such contacts are documented and that any information provided by the applicant is copied to both Rapporteur and Co-Rapporteur assessment teams and EMEA PTL in

³ This is considered necessary as once Rapporteur and Co-Rapporteur have been appointed as such discussions with the applicant become part of the audit trail of the application. In the event of a judicial review of the procedure the applicant would have the right to present this information to demonstrate the approach of CHMP members in considering its application. (Note the same could also be argued for the pre-appointment discussion if CHMP members agree to meet companies in their capacity as CHMP members and not NCA officials)

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 25/27

parallel.⁴ Applicants should be informed that they should not normally contact either of the Rapporteur and Co-Rapporteur or their assessment teams or any other CHMP members during this period.⁵

**Contacts with CHMP members between Day 120 and Day 121
(Preparation of Response to Consolidated List of Questions)**

The applicant having received the formal CHMP Consolidated List of Questions routinely seeks to have one or more meetings/contacts with the Rapporteur and Co-Rapporteur and/or their assessors to prepare an adequate response package. Such requests are considered appropriate and it is considered one of the primary roles of the Rapporteur and Co-Rapporteur to provide additional information regarding the discussions within the CHMP that led to the Consolidated List of Questions to aid understanding of the questions and facilitate an adequate response preparation. It is expected that applicants have considered/analysed the Consolidated List of Questions within their company/product team and identified relevant clarifications to be asked in advance of such meeting(s). It is also considered legitimate that the Rapporteur and Co-Rapporteur may discuss with the applicant the broad outlines of their response strategy including any withdrawal/limitation of indications applied for as well as modified warnings regarding the precautions for use of a product etc. As with the pre-submission meetings there is often a desire for applicants to have a degree of pre-approval of their response package. However this must be clearly ruled out as beyond the scope of such advisory meetings and the limitations of the Rapporteur and Co-Rapporteur in representing the future views of the plenary CHMP must be underlined. As with earlier phases of the procedure such contacts should be documented and any information provided by the applicant should be copied to both Rapporteur and Co-Rapporteur assessment teams and EMEA PTL in parallel.

During this period it should be understood by the applicant that any direct and individual contacts with CHMP members other than the appointed Rapporteur and Co-Rapporteur are considered unacceptable and CHMP members should reject such contacts and refer them to the Rapporteur and Co-Rapporteur.

Contacts with CHMP members between Day 121 and Day 180 (Preparation of Joint Assessment Report and List of Outstanding Issues as appropriate)

During the second assessment phase apart from the Rapporteur and Co-Rapporteur it is not considered appropriate for CHMP members to have any contact with the applicant except for discussions regarding the implementation of risk minimisation activities in an individual Member State (see Day 121-180 – Preparation of joint assessment report and List of Outstanding Issues as appropriate). It is considered appropriate that the Rapporteur and Co-Rapporteur or their assessment teams may contact the applicant either during the initial day 121-150 assessment phase or during the day 150-180 phase. However this must be understood as a facility for the Rapporteur and Co-Rapporteur and their assessment teams should the need arise to clarify any aspect of the review. It is recommended that such contacts are documented and that any information provided by the applicant is copied to both

⁴ Such contacts may be made either by phone, email, and fax or face-to-face as required. Although phone contact appears informal and therefore questionable as to documenting such contacts we should be aware of the long established practise within industry of documenting each and every contact with Regulatory Authority personnel even seemingly informal meetings in margins of conferences etc. Being aware of such practise it is considered important to reinforce the need to document such contacts in a more formal manner.

⁵ Due to the provision of the day 80 AR to the applicant together with a draft list of questions some applicants attempt to discuss with the R/cR or other CHMP members in advance of day 120 some of the issues identified. This practise should be halted and the Industry made aware that its persistence jeopardises the current level of transparency during this period.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 26/27

Rapporteur and Co-Rapporteur assessment teams and EMEA PTL in parallel. Applicants should be informed that they are not at liberty to contact either of the Rapporteur and Co-Rapporteur or their assessment teams or any other CHMP members during this period.⁶

Contacts with CHMP members between Day 180 and Day 181(Preparation of Response to CHMP List of Outstanding Issues and Oral explanation as appropriate)

The applicant having received the formal CHMP Consolidated List of Outstanding Issues routinely seeks to have one or more meetings / contacts with the Rapporteur and Co-Rapporteur and or their assessors to prepare an adequate response package/oral explanation. It is considered one of the primary roles of the Rapporteur and Co-Rapporteur to provide additional information regarding the discussions within the CHMP that led to the Consolidated List of Outstanding Issues to aid understanding of the questions and facilitate an adequate response preparation/oral explanation.

Although it is not appropriate to involve Rapporteurs in elements of regulatory strategy it is considered acceptable that the Rapporteur and Co-Rapporteur may discuss with the applicant the broad outlines of their scientific responses including any withdrawal/limitations of indications applied for as well as modified warnings regarding the precautions for use of a product , post approval commitments etc.. As with earlier interactions there is often a desire for applicants to have a degree of guidance on their response package/oral explanation presentation. However the scope of such advisory meetings and the limitations of the Rapporteurs in representing the future views of the plenary CHMP must be underlined once again to the applicant.

During this period it should be understood by the applicant that any direct and individual contacts with CHMP members other than the appointed Rapporteur and Co-Rapporteur are considered unacceptable and CHMP members should reject such contacts and refer them to the Rapporteur and Co-Rapporteur.

Contacts with CHMP members between Day 181 and Day 210 (Preparation of Opinion)

Following the conclusion of an oral explanation the Rapporteur and Co-Rapporteur together with the EMEA PTL hold a debriefing meeting with the applicant to communicate the results of the CHMP discussions and inform the applicant of the result of any trend vote taken with in the case of a non-consensus position an indication of the numerical divide within the Committee. In the event of a negative trend vote the applicant must be sufficiently informed via this debriefing to allow a decision to either withdraw the application or proceed to a negative opinion. In the event of a positive opinion the applicant must be aware of the final indication considered acceptable by the Committee together with labelling of major safety concerns, any conditions of use and the likely programme of follow up studies that may be required. Over the next 30 days the Rapporteur and Co-Rapporteur must interact frequently with the applicant to allow a finalised SPC /PL proposal to be made to the CHMP together with agreed timeframes for any post-authorisation commitments that may be required and or details of a risk management programme etc...

Particularly in the case of negative trend votes this is seen as the most critical stage in the evaluation procedure as it may lead to the withdrawal of the application or continuation to a public negative opinion with appeal possibilities. In the event that the rapporteur and co-rapporteur have divergent

⁶ Due to the provision of the Joint AR to the applicant together with a draft list of outstanding questions some applicants attempt to discuss with the R/cR or other CHMP members in advance of day 180 some of the issues identified. This practise should be halted and the Industry made aware that its persistence jeopardises the current level of transparency during this period.

Procedural Advice to CHMP Members	CHMP/
	Ed.: 00
	Page 27/27

views on the outcome of the evaluation or if they both diverge from the majority view of the CHMP it is recommended that the briefing be presented by the Chairman of the CHMP.

Contacts with CHMP members during a re-examination process

If a scientific opinion is re-examined a new pair of Rapporteur and Co-Rapporteur is appointed. Direct contact with the initial Rapporteur and Co-Rapporteur must cease as from this point and any individual contacts with CHMP members other than the appointed re-examination Rapporteur and Co-Rapporteur are considered unacceptable and CHMP members are directed to reject such contacts. This must be particularly emphasised as following the initial opinion if divergent the views of individual members will be known and the pressure for applicants /MAHs to lobby directly such members will be at its greatest.

Contacts with CHMP Members during the Post Authorisation Phase

The initial Rapporteurship of centrally authorised products continues post authorisation, along with the EMEA PTL, the Rapporteur is the primary contact point for the MAH when considering discussions regarding upcoming variations, safety amendments, line extensions, etc... The Co-Rapporteur can be involved in the assessment of Type II variations for an extension of indication and in Extension applications. The Co-Rapporteur is also systematically involved in Type II variation for extension of indication, the assessment of renewal applications. The CHMP usually also appoints a Co-Rapporteur(s) for Article 107 procedures and referral procedures for non-centrally authorised products. In such situations contact between the MAH and the Co-Rapporteur is appropriate. Direct contact with other CHMP members is not considered appropriate as applicable in case of pre-authorisation files with the exception of discussions on the possibility of implementing particular risk minimisation activities in the Member States (see Day 121-180 – Preparation of joint assessment report and List of Outstanding Issues as appropriate).