

## CMDh STANDARD OPERATING PROCEDURE DISAGREEMENT IN PROCEDURES – REFERRAL TO CMDh

*Doc. Ref.: CMDh/103/2005/Rev5  
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### **Reference:**

- *Article 29(1) of Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code and relating to medicinal products for human use.*
- *Article 13 of Commission Regulation (EC) No 1234/2008*

### Procedure to be followed for a discussion in CMDh in case of disagreement between Member States in a particular mutual recognition or decentralised procedure

The procedure covers applications for marketing authorisations (including repeat use procedures), renewal applications, extensions, type II variations according to Article 10(4) of the Variation Regulation, and those variations (including groupings) subject to the worksharing procedure according to Article 20(8) of the Variation Regulation.

## **1. GENERAL BACKGROUND**

When an application for a marketing authorisation is submitted according to the MRP or DCP the Member States concerned shall approve the RMS draft (DCP) or updated (MRP) assessment report, the SmPC and the labelling and PL in 90 days from receipt of the relevant documents according to Article 28 (4) in the above mentioned directive.

Where one or more of the Concerned Member States cannot approve the RMS assessment report, the SmPC, labelling or PL, the points of disagreement shall be referred to the CMDh. The reasons for disagreement shall be on grounds of potential serious risk to public health and explained in detail by the disagreeing Member State(s).

A guideline on the definition of potential serious risk to public health is adopted by the Commission and published on [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/com\\_2006\\_133/com\\_2006\\_133\\_en.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf).

## **2. THE REFERRAL**

The Concerned Member State(s) that cannot approve the documents mentioned above shall notify the RMS, the Member States concerned, the CMDh Secretariat at the EMA and the applicant at Day 90/210 at the latest in the case of MRP/DCP, or at the completion of the timetabled variation or worksharing procedure. The notification shall include a detailed exposition of the reasons for the negative position. It is the duty of the RMS to refer the matter to the CMDh.

If the RMS in a DCP concludes that an application is not approvable, the DCP will end with that decision even if one or more CMSs are of the opinion that the application is approvable. Since only a positive assessment by the RMS can be the reason for a CMS to raise a potential serious risk to public health concern, there will be no matter to refer to the CMDh.

The secretariat will propose a starting date for the 60 days-procedure. The starting date should be decided by the Chair of CMDh together with the RMS (see section 4). This information should be sent by e-mail to all Members of CMDh and the applicant before the start of the 60 days procedure.

The RMS should provide the Member States not earlier concerned by the procedure with the final (latest) assessment report, proposed SmPC, labelling and PL and the explanation of the grounds for referral from disagreeing Member States. On request by the CMDh members, other relevant information can be provided by the RMS. For generic applications it may be sufficient to provide only the latest SmPC.

## **3. WITHDRAWAL**

The applicant can withdraw the application from one or more Member States at any point in time. However, depending on the procedure and/or the actual day during the procedure the question is raised, this shall not prevent that the issue of disagreement based on potential serious risk to public health will be referred to the CMDh. From the legislation it is clear that a referral to CMDh should be made if a Member State cannot approve the assessment report, SmPC, the labelling and the package leaflet *within the time period laid down in Article 28(4)*. The time period in Article 28(4) is the 90-days procedure of the mutual recognition procedure and the 90-days period following the submission of the draft documents referred to in Article 28(3), i.e. the assessment step II in the decentralised procedure. In case of MRP a withdrawal of an application will automatically be referred to the CMDh, whereas, in the case of DCP this will only be applicable if the application is withdrawn after the draft documents have been sent to the concerned Member States, normally at day 120 of the procedure. In both cases mentioned it is the duty of the RMS, if the reason of withdrawal is based on a potential serious risk to public health raised by a MS concerned, to refer the matter to the CMDh for discussion.

## **4. PROCEDURE AND TIMETABLE**

### **4.1. Parties involved**

All Members of CMDh have the right to take part of the discussions in CMDh. All Member States concerned by the application shall use their best endeavours to reach agreement on the action to be taken. The latter should include the Member States where the application has been submitted even if the application is withdrawn in MRP or after the draft documents has been sent from the RMS, normally at Day 120 (in Assessment step II) in the DCP.

The RMS will in practice lead the scientific discussions in CMDh.

## **4.2. Procedure**

The starting date should in no case be later than 30 days after Day 90/210<sup>1</sup>. It is recommended to set Day 60 of the procedure at least five to ten days after a CMDh meeting. Information from the CMDh secretariat to all CMDh Members and the applicant of the timetable for the procedure is sent out before the start of the 60 days procedure.

- On Day 0 of the procedure, the RMS distributes a proposal for the list of questions to all Member States, for agreement.
- The CMDh secretariat sends the agreed list of questions to the Applicant on Day 10, of the procedure. The Applicant is asked about his wish to make his point of view known in writing only or have it presented orally at a CMDh meeting. Applicants are advised to discuss with the RMS the need for an oral explanation for all or specific questions.
- At the CMDh meeting 1 (around Day 20 of the procedure), the list of questions is tabled for information. If needed, MS can discuss the reasons for the referral and the position from the RMS and CMS. The CMDh should also consider taking advice from the CHMP, the HMPC or their working parties and the HMPWG.
- The applicant shall prepare a response document according to the list of questions prepared by the CMDh and send it to all CMDh members no later than on Day 25 of the procedure. No new data from the applicant will be allowed since there is no time for further assessment. Guidance on the format and submission of the response document is available in the Applicant's response document in Mutual Recognition and Decentralised procedures – Recommended CTD format, published on [http://www.hma.eu/uploads/media/response\\_ctd.pdf](http://www.hma.eu/uploads/media/response_ctd.pdf)
- The RMS should circulate an updated assessment report to all CMDh members and to the Applicant around Day 35.
- All Member of CMDh should preferably state their view on the response document in writing to all CMDh members 7 days before the CMDh meeting. The comments from the CMSs on the response document will be shared by the RMS with the Applicant. Link to overview of timetables <http://www.hma.eu/26.html>
- The main scientific discussion should take place at the CMDh meeting 2 and the Members of CMDh can be accompanied by relevant national experts. Preferably the experts should be different from those taking the decisions in the Committees but it is up to the individual Member States to decide on participation. The views from the

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<sup>1</sup> The starting date should be set close to Day 90/210 in order not to prolong the procedure but the dates of the CMDh meetings have to be kept in mind. This is in line with the practice of setting of starting dates in the arbitration (centralised) procedure.

applicant, orally or in writing, should be taken into account. To ensure the efficiency of the procedure the Member of CMDh should have the proper mandate to make it possible to reach an agreement according the Article 29 of the Directive.

- Agreement on the outcome of the procedure is aimed to be reached at the CMDh meeting. However, in case no agreement could be reached at the meeting, the full 60 days, as foreseen in the legislation, should be used to get an agreement between the RMS, CMS and the Applicant. In this situation the RMS should circulate the final proposal for agreement on the procedure at latest on Day 55.
- In Article 29(1) of the Directive 2001/83/EC, as amended the time period given to CMDh to solve a disagreement is expressed as 'within 60 days'. By this wording it follows that the procedure could be ended earlier than Day 60 if agreement is reached. In these cases the RMS shall ensure that all CMSs have been provided the opportunity to state their final view until the end of the given timeline.

## **5. OUTCOME OF PROCEDURE**

There are only two possible outcomes of the procedure. Either there is a consensus<sup>2</sup>, between the Member States where the application was submitted (including those where the application was withdrawn), on approving or refusing the application or the matter should be referred to the EMA for an arbitration procedure according to Articles 32-34.

If the Member States reach an agreement within 60 days the RMS shall record the agreement, close the procedure and inform the applicant of the outcome. Subsequently the Member States shall adopt the decision in conformity with the agreed SmPC, labelling and PL within 30 days after reaching the agreement. To get an approval in the Member States where the application has been withdrawn a repeat use procedure must be started. The main conclusions of the discussions should be entered into a database by the EMA secretariat and the RMS should fill in the proper information in CTS.

If the Member States fail to reach an agreement during the 60-day period the RMS should immediately inform the EMA and the applicant and provide a detailed statement of the unresolved issues and the reasons for the disagreement. With the exception of variations and worksharing procedures, according to Article 29 (6) the Member States that have approved the assessment report, the draft SmPC and the labelling and package leaflet may, at the request of the applicant, grant an authorisation at any point of time after the end of the CMDh referral procedure without waiting for the outcome of the CHMP arbitration procedure laid down in Article 32.

## **6. TRADITIONAL HERBAL MEDICINAL PRODUCTS AND OTHER MEDICINAL PRODUCTS CONTAINING HERBAL SUBSTANCES**

For traditional herbal medicinal products as defined in Article 16a (1), that have been registered according to Art. 16 d (1)), the procedure in Articles 28 and 29 is applicable. The HMPC should be informed, without delay, of referrals to the CMDh regarding herbal

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<sup>2</sup> Consensus means that all Member States must be in agreement.

medicinal products. If CMDh fails to reach an agreement regarding traditional herbal medicinal products the matter should be referred to the HMPC. For other medicinal products containing herbal substances CMDh should refer the matter to the CHMP and inform the HMPC, accordingly.

## **7. HOMEOPATHIC MEDICINAL PRODUCTS**

For homeopathic medicinal products eligible for registration according to Article 14, Articles 28 and 29 (1) to (3) applies. However Article 29 (4), (5) and (6) shall not apply (see Article 39). That means that the same procedure as for other medicinal products should be followed except for the possible referral to CHMP. If the discussions in CMDh do not solve the disagreements the matter shall not be referred to CHMP.

## **8. DATA SUPPORT**

The procedure and outcome should be recorded in CTS.

### **Abbreviations used:**

CMDh- Co-ordination group on Mutual recognition and Decentralised procedure (human)

MRP – Mutual Recognition Procedure

DCP – Decentralised Procedure

SmPC – Summary of Products Characteristics

PL – Package Leaflet

EMA – European Medicines Agency

RMS – Reference Member State

CMS – Concerned Member State

CHMP – Committee for Human Medicinal Products

CTS – Communication and Tracking System for the mutual recognition procedure

HMPC – Committee on Herbal Medicinal Products

HMPWG – Homeopathic Medicinal Products Working Group

<b>FLOW CHART 60 DAYS PROCEDURE</b>	
<b>Day 90/210 of MRP/DCP</b>	Notification from disagreeing Concerned Member State(s), with a detailed exposition of the reasons for the negative position. This is sent to RMS, CMS(s), CMDh Secretariat and the applicant. This duty also applies to MS (s) where the application has been withdrawn in the MRP and DCP (if the withdrawal has been made after the draft documents have been sent by the RMS).
<b>Day 90/210 + max 7</b>	RMS formally initiate the referral by sending the final (latest) assessment report, proposed SmPC, labelling and package leaflet and the explanation of the grounds for referral from disagreeing Concerned Member State(s) to <u>all</u> CMDh members, CMDh chair and CMDh secretariat. CMDh Secretariat and CMDh Chair decide on starting date with agreement of RMS
<b>Day 0 (not longer than 30 days from Day 90/210)</b>	RMS starts the procedure and distributes a proposal for the list of questions to all Member States.
<b>Day 5</b>	CMSs comment on list of Questions
<b>Day 8</b>	RMS circulates final agreed list of Questions
<b>At latest Day 10</b>	CMDh secretariat sends List of Questions to Applicant
<b>Around Day 20</b>	CMDh meeting 1 – List of Questions tabled for information. If needed, MSs can discuss the reasons for referral and the positions from RMS and CMS.
<b>Until Day 25</b>	The applicant to send a response document on the list of questions to all CMDh members.
<b>Around Day 35</b>	RMS circulates an updated assessment to all CMDh members and to the Applicant.
<b>7 days before CMD meeting</b>	Members of CMDh should preferably state their view on the response document to all members 7 days before the meeting.
<b>Around Day 50</b>	CMDh meeting 2 – scientific discussion, possible hearing and decision.
<b>At latest Day 55</b>	RMS circulates final proposal for agreement on the procedure
<b>By Day 60</b>	CMDh members of the Concerned Member States should confirm agreement or disagreement with the final proposal of the RMS. If agreement, the RMS should record the agreement, close the procedure and inform the applicant. If no agreement, the RMS should immediately inform the EMA and the applicant and provide a detailed statement of the unresolved issues and the reasons for the disagreement.

**GUIDANCE ON ORAL EXPLANATIONS TO CMDh**  
**Annex to CMDh SOP**  
**Disagreement in Procedures – Referral to CMDh**

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**Reference:** *Article 29(3) of Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code and relating to medicinal products for human use.*

## **1. BACKGROUND**

When one or more of the Concerned Member States involved in a particular Decentralised Procedure (DCP) or Mutual Recognition Procedure (MRP) cannot approve the RMS draft assessment report in DCP or assessment report in MRP, the SmPC, labelling and PL in 90 days from receipt of the relevant documents according to Article 28(4) of the above mentioned Directive, the points of disagreement shall be referred to the CMDh. Standard Operating Procedure for a referral to CMDh is published on <http://www.hma.eu/26.html>. Within this procedure Member States shall use their best endeavours to reach agreement on the action to be taken and they shall allow the applicant to make his point of view known orally or in writing.

The presented guidance should contribute to efficiency of oral explanations provided by the applicants to the CMDh.

## **2. ADVICE ON AN ORAL EXPLANATION**

In the case of disagreement in a particular procedure a list of questions (LoQ) is agreed by the CMDh and sent on Day 10 of the procedure to the Applicant by the CMDh secretariat, including the following:

- List of questions
- Request to send a written response document which addresses each question from the list, at latest by day 25
- Advice to discuss with the RMS the need for an oral explanation in addition to the written response document for all or specific questions
- Request to inform the CMDh secretariat and the RMS contact, within two weeks following the receipt of the LoQ, about the applicant's wish to present its point of view orally at the CMDh meeting.

### **3. PREPARATION FOR AN ORAL EXPLANATION**

If an oral explanation is agreed, the CMDh secretariat will confirm to the applicant, one week prior to the meeting, the time slot assigned for the oral explanation, after consultation with the RMS.

The applicant should not be represented by more than five persons in total; a list of the names of proposed attendees representing the applicant, as well as details of their affiliation and their role in the oral explanation should be sent to the RMS and the CMDh secretariat by Wednesday before the CMDh meeting. The applicant should indicate the technical support required for their presentation during the oral explanation (e.g. overhead projector, own computer, slide projector). It is recommended, whenever possible, to make a computer assisted presentation.

At the request of the applicant and upon agreement of the CMDh a teleconference may be arranged by the EMA.

The applicant should provide the RMS, CMDh members and CMDh secretariat with the presentation in electronic version at the latest by Friday before the oral explanation (not later than 3 p.m. GMT).

On the day of the oral explanation, the applicant should arrive at the EMA premises no earlier than one hour before the time scheduled for the oral explanation and provide the CMDh secretariat with 60 paper copies of the handouts and the final electronic version of the presentation.

### **4. ORAL EXPLANATION**

Oral explanation takes place in the scheduled CMDh meeting according to the timetable.

Before the arrival of the applicant the RMS should summarise:

- Outcome of the review of the response document submitted by the applicant, including advice from CHMP, HMPC, their working parties or HMPWG, if relevant
- Comments on the new SmPC, PL and labelling or commitments proposed by the applicant, if relevant
- Remaining issues of concern.

The RMS should ask the MSs which have raised potential serious risk to public, if the remaining concerns are addressed. A short presentation of the concerns can be made by any of the MSs and it is recommended to make the presentation available to all CMD (h) Members before the meeting. An agreed approach to the questioning of the applicant should be defined by the CMDh members before inviting the applicant to participate.

The oral explanation should be prepared by the applicant taking into account that the actual presentation should:

- Be maximum 20 minutes
- Focus on responses to the most relevant questions from the LoQ followed by a conclusive statement
- If appropriate, describe the impact on the SmPC and PL and/or commitments proposed by the applicant.

The actual presentation may be followed by questions and answers session. The overall duration of an oral explanation including questions and answers session should be maximum 40 minutes, taking into account the number of questions and the subject concerned.

After the applicant has left the room, the CMDh members should continue their discussions on the outstanding issues, with the objective to reach agreement on the action to be taken. In principle, final agreement on the outcome of the procedure is aimed to be reached within the CMDh meeting. In the case no agreement could be reached at the CMDh meeting, the full 60 days as foreseen in the legislation should be used to get an agreement on the subject between RMS, CMSs and the applicant.

After the oral explanation and subsequent discussion, the RMS informs the applicant about the outcome of the discussion and of any remaining issues.