

**QUESTIONS AND ANSWERS
ON THE SOP – DISAGREEMENT IN PROCEDURES – REFERRAL TO
CMDh**

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This Q&A document mainly summarises the comments from trade associations on the draft SOP on disagreements in procedure – referral to CMDh. Many of the comments resulted in amendments to the SOP and are therefore not necessarily covered by this Q & A-document.

Applicants/MAHs are advised to discuss the consequences for their medicinal products with the Reference Member State.

Scope of the procedure

Question 1. (March 2010)

Which type of applications should be eligible for CMDh-referral?

Answer: New applications including repeat use, extensions and renewals should go via CMDh. Also type II variations and, in case of a worksharing procedure, those variations (including groupings) according to Article 20(8) of the Commission Regulation 1234/2008 shall be within the scope of a CMDh-referral.

CMDh

Question 2. (September 2006)

If there is consensus among MSs on Day 210 of a DCP that an application is not approvable (if the RMS and the CMS(s) can agree on potential serious risk to public health) will the application then be referred to the CMDh?

Answer: ~~No, an application will only be referred to the CMDh if the MSs involved in the procedure cannot reach consensus. The applicant can appeal the decision to reject the application according to national legislation in each involved Member State.~~

If the RMS in a DCP concludes that an application is not approvable, will the application be referred to CMDh if one or more CMSs are of the opinion that the application is approvable?

Answer: No. Only a positive assessment by the RMS can be the reason for a CMS to raise a potential serious risk to public health concern. The DCP will end with a decision that the product is not

approvable. All member states concerned need to take a final decision at national level rejecting the application, unless it is withdrawn by the applicant.

Question 2a (June 2007)

If the RMS is negative but one or more CMSs are positive will the application be referred to CMDh?

~~**Answer:** Yes. There is a disagreement between the MSs and at least one MS have raised potential serious risk to public health concerns. The involved MSs should have the opportunity to discuss the matter(s) of disagreements in CMDh~~

Question 2b. (October 2007)

If there is consensus among Member States concerned by the end of a CMDh referral procedure that the DCP application is not approvable, should the application be referred to CHMP?

Answer: No, the application will not be referred to the CHMP since all Member States concerned reached consensus. The applicant can appeal the decision to refuse the application according to national legislation in each concerned Member State.

If subsequently, an appeal is successful that leads to the grant of a marketing authorisation in an individual Member State, this marketing authorisation may then be the basis of the initiation of a mutual recognition procedure.

Before start of the procedure

Question 3.

Should the RMS or the CMDh make validity test (e.g. compliance with the guideline on the definition of potential serious risks to public health) before initiation of the referral to CMDh?

Answer: It is not up to the RMS to decide if the disagreeing CMS(s) has valid reasons for a referral or not. The discussion will take place in CMDh during the 60-days procedure.

Question 4.

Are the members of CMDh the members of the former MRFG or not?

Answer: The names and background of the persons representing each Member State in CMDh are published on the CMDh website.

Question 5.

The secretariat will put the referral on the agenda of the next CMDh meeting and propose a starting date for the 60- days procedure. Will a list of planned CMDh meetings be published on a yearly basis? Could a referral be delayed because of a 'next CMDh meeting' being fully booked?

Answer: The CMDh meetings are published on the CMDh web: <http://medagencies.org/>. A referral could not be delayed because of a 'fully booked meeting'. In such a case CMDh will increase their normal meeting time.

Question 6.

As the reason for referral must be based on potential serious risk to public health, will all decisions to start the referral procedure be initiated only after a very detailed explanation supported by scientific justification provided by the MS not agreeing on the draft assessment report, draft SPC, draft package leaflet and labelling?

Answer: Yes, and it is clearly stated that there could only be scientific reasons for a referral.

Question 7.

Is it possible to begin the referral earlier than Day 90/210 in MRP/DCP?

Answer: In theory yes but in practice the Member States will try to reach agreement until day 90/210 of the procedure in order to avoid a referral.

Question 8.

Could, in certain situations, the CMDh-referral be avoided and instead a CHMP arbitration procedure be started directly?

Answer: No, this is not possible. The directive set up an obligation for CMDh to process a 60-days procedure and this could not be disregarded. The EMEA would not accept arbitration to CHMP unless CMDh discussed the health issues according to the relevant articles in the directive.

Initiating the procedure

Question 9.

Is the applicant allowed to ask for a CMDh referral?

Answer: No.

Question 10.

Who takes the decision about the referral: the chairperson and the RMS only, or is that done in collaboration with the applicant, or at least after a discussion with the applicant?

Answer: The decision to refer to CMDh is in a sense automatic because as soon as one **Concerned** Member State has potential serious risk to public health concerns the RMS must refer the issue to CMDh. The CMDh will discuss and have an opinion if the concern should be regarded as potential serious risk to public health.

Timetable

Question 11.

If the CMDh meetings take place every month, and the start date is set up at the 1st CMDh meeting after Day 90, with the recommendation to have Day 60 at least 5 days after a CMDh meeting, would the CMDh referral procedure be in length a total of 65 days (+ max 30 days before it start ?

Answer: No, counting from the start date the procedure should end 5-10 days after the second CMDh meeting at Day 60. The start date is not the date for the first CMDh meeting but rather around 20 days before the first meeting.

Question 12.

The secretariat will put the referral on the agenda of the next CMDh meeting. Is there intended to be a minimum time between Day 90/210 and Day 0 of the CMDh procedure/the initial discussion at CMDh?

Answer: No minimum time is foreseen. The timing of break out sessions makes this scenario unlikely. There will always be sufficient time between end of MRP/DCP and the CMDh meeting 1 in line with the flow chart for the procedure.

Question 13.

The CMDh procedure will start no later than 30 days after Day 90/210. Presumably this will be possible at all times of the year (e.g. August, Christmas holiday period), regardless of whether CMDh meetings are scheduled. Clarification on this would be appreciated.

Answer: In theory this is possible at any time of the year, although the Christmas holiday period should if possible be avoided.

Question 14.

It is assumed that the second CMDh meeting will take place 30 days after the initial CMDh meeting. It would be helpful to specifically state this.

Answer: The CMDh meeting dates are already decided, see <http://medagencies.org/>.

List of questions

Question 15.

On request by the CMS(s), other relevant information can be provided by the RMS. Clarification is requested on the kind of information that could be requested by the CMS(s) and provided by the RMS.

Answer: The intention of this wording is to make it possible for CMSs to ask for any information to help the understanding of the issue. No examples are given and it is difficult to foresee what kind of information could be needed in each situation.

Question 16.

Could the applicant be informed on both the information requested by the CMS(s), and the information provided by the RMS in order that the applicant views are presented in best conditions?

Answer: No, this will be taken care of in the response document later in the procedure.

Question 17.

For security reasons the use of Eudralink should be recommended for dispatch of Answers to Questions.

Answer: The applicant should check national recommendations for the sending of documents via Eudralink or contact national authorities to know requirements before sending documents via Eudralink.

Question 18.

Taking advice from one of the Committees will probably take too long. It has to be kept in mind that the CMDh procedure is a process where only Member States are involved. An involvement of the Committees is not foreseen in Art. 29 (1) - (3).

Answer: The possibility to use advice from Committees will be used only if time allows this.

Question 19.

Applicants are allowed to provide comments to CMDh in writing only or have it presented orally at a CMDh meeting. Could the decision on an oral hearing be made after receiving the list of questions? In case the applicant wants to present its points of view orally at a CMDh meeting, is it still needed to provide a written response to the list of questions?

Answer: Applicants should discuss with the RMS and will be asked by the EMEA secretariat within two weeks of receipt of the list of questions about the wish to present its points of view orally at a CMDh meeting. The RMS informs the CMDh whether it will be an oral hearing or not. A written response to the list of questions is always needed, even if the applicant decides to have an oral hearing with the CMDh.

Question 20.

What about new analyses in response to a question?

Answer: No new data are expected to be presented during the procedure. New data (e.g. results of studies never previously provided) should be distinguished from an elaboration, new presentation or clarification of data already presented. Submission of new supporting references, including published literature, will not in general be considered as new data as they provide a means of interpreting data already presented. Results of ongoing studies from which data were not available before are likely to be regarded as new data. The RMS view will be taken into account as to what additional supporting data may be accepted at this stage of the procedure.

Question 21.

Are there recommendations on the format and submission of the response document?

Answer: The applicant should send the response document in electronic format via e-mail to all national competent authorities and to the EMEA, with one paper copy to the RMS. An overview of the e-mail-addresses to be used by the applicants is available on the Heads of Medicines Agencies website.

Applicants are requested to standardise the header of the e-mail as follows: Procedure Nr. _ Name (can be shortened if too long)_Company_Response-Day 60 Referral. The following rules should be taken into account for sending the files via Eudralink:

- All files should be zipped to facilitate saving of the files
- The option that e-mail addresses of all recipients are visible should be chosen. Reference should also be made to the ‘Applicant’s response document in mutual recognition – Recommended CTD format’, published on the CMDh website. The requirements for the format are also valid for the CMD referral procedure.

Question 22.

Pursuant to Art. 29 (3) of Directive 2001/83/EC, only the RMS and CMS shall reach an agreement on the action to be taken. They (RMS and CMS) shall allow the applicant the opportunity to make his point in writing. Does this not mean: those Member States that were not part of the initial MRP / DCP process are not involved in the procedure under Art. 29 (3) and (4). Therefore the applicant is not obliged to send the response document to the Member States not involved, and these Member States should not state their view on the response document. Consensus should only be reached between RMS and CMS and not with those Member States that were not part of the MRP /DCP.

Answer: As further explained below it is necessary for the “non-involved” Member States to be a part of the discussions. However they will not be involved in the formal agreement.

Issues for discussion

Question 23.

Is it correct that the discussion shall only refer to the potential serious risk to public health as explained in detail by the disagreeing Member State(s) and no new items shall be brought up?

Answer: Yes.

Question 24.

If an issue has already been discussed in CMDh, could the same question be raised once again?

Answer: The main idea with the referral procedure is to solve problems for the future and avoid repetition of discussions. Normally it would not be appropriate to reopen issues that have previously gone through the referral procedure. The legislation does not explicitly prohibit the issue to be brought up again so in exceptional circumstances this could occur. For example if development in a scientific area could have an impact on decisions or if only a small number of Member States had been involved in a previous referral procedure. See also Notice to Applicants, Chapter 1 and 3.

Outcome of procedure

Question 25.

Could CMDh confirm that Member States should reach consensus on the remaining issues, rather than taking a majority position as in the Centralised Procedure?

Answer: Consensus means that all involved Member States will be in agreement.

Question 26.

The document states that the main conclusions of the discussions should be entered into a database by the EMEA secretariat. Further details are requested regarding this database; e.g. is this a new database? Who will have access?

Answer: The database is under development. The aim is to have a regulatory memory accessible to Member States, European Commission and EMEA, both for issues discussed in the 60- days procedure and other general discussions in CMDh.

Question 27.

Will a referral to the CHMP be decided at day 60, or will that be decided one month later?

Answer: It will be decided at Day 60 and referred immediately to the EMEA.

Question 28.

In the case of SPC disharmony, Member States should be encouraged to share the data with other Member States regarding the reference product to help resolve the issues. The time when the applicant is preparing its response to the CMDh can be used by the RMS to collect the comments from all Member States on the reference product.

Answer: At present we see no time for the proposed exercise.

Question 29.

In the case of SPC disharmony of the reference product for a generic application, if this 'mini-arbitration' fails then there should be a direct referral straight to the CHMP without all the initial delays for setting up the procedure, raising the questions etc. It should be passed directly to the CHMP to avoid unnecessary waste of time and resource.

Answer: The CMDh referral procedure has to be finalised in every case (see Q 7). If no consensus is reached during the 60-days procedure the RMS will immediately inform the EMEA who will refer the issue to CHMP.

Withdrawals

Question 30.

It should be clarified that only withdrawals that are linked to serious public health concerns should be discussed by CMDh. Applications withdrawn for other reasons (e.g. marketing reasons) should not be.

Answer: It is already made sufficiently clear, that other reasons for withdrawal are out of the scope for a CMDh referral. However if a withdrawal has been made in a Member State after that Member State has raised potential serious risk to public health concerns a referral to CMDh is unavoidable. This applies regardless of the reason for withdrawal stated from the applicant.

Question 31.

The CMDh is responsible for coordinating the discussion between the Member States where there is no agreement on the assessment report, the SPC, labelling or PL. The outcome of the procedure is either approval or refusal of the application. Therefore, why would there be any need to continue the discussion of the disagreement if the applicant decides to withdraw the application?

Answer: Because the intention of the legislation was to have a discussion on the scientific matters that is considered to be a potential serious risk to public health regardless if the applicant chooses to withdraw. This is clearly stated in the legislation and there is no room for interpretation to handle it differently.

Involvement of non-concerned Member States

Question 32.

All Member States that have raised risk to public health issues should be encouraged to participate. It is not clear why Member States should participate if they are not involved in the procedure and it is not necessary for them to have to be in agreement.

Answer: The reason for that is that the other Member States could have the same application filed in a repeat use procedure and normally the same issue cannot be brought up in CMDh more than once so this might be the only opportunity they have got to influence the discussion, see also Q number 22.

After the 60 days procedure

Question 33.

By when can a MS issue a marketing authorisation? Legally at day 1 of a recognition? Practically at the end of the referral to the CMDh?

Answer: In case of negative (non agreement) outcome in CMDh: A Member State that has approved the assessment report, SPC, labelling and package leaflet may, on request from the applicant, authorise the product when the 60 days procedure is ended and not before.

In case of a positive outcome: All Member States should approve the product within the stipulated 30 days.

Question 34.

When shall the national text for product information be submitted? Should it be during the 60-days procedure or after the finalisation of the procedure?

Answer: The national translations of the texts together with the request for MA should be submitted after finalisation of the 60-days procedure. Be aware that if the 60-days procedure results in changes to the SPC, PL or labelling this shall not result in any variations submissions.

Question 35.

Who should make the request for a MA, the applicant or a future MAH and to which MS should the request be directed, the RMS or CMS(s)?

Answer: The request according to article 29 (6) must come from the applicant and the applicant may ask the competent authority in each MS for an approval. If the MAH should be different from the applicant the request normally should come from the applicant with consent from the future MAH but companies are advised to consult each competent authority because this might differ according to national law.

Question 36. (December 2006)

Where a Member State agrees with the request from the Applicant to grant a marketing authorisation for a medicinal product according to Article 29(6), i.e. where the CMDh failed to reach an agreement within the 60-day period, what should the product information (SPC, package leaflet and labelling) to be included in the marketing authorisation be?

Answer: For Member States which have approved the assessment report, draft SPC, labelling and package leaflet, the product information submitted should be the proposed SPC, package leaflet and labelling on Day 60 of the CMDh referral procedure.

However, the authorisation granted shall be without prejudice to the outcome of the CHMP referral procedure, which will have to be implemented by all the Member States concerned in the procedure.