Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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Best Practise Guide for Decentralised and Mutual Recognition Procedures

Introduction

1. Competent authorities should ensure that their assessment reports are written according to the CMDh Best Practice Guide on the assessment report for Mutual Recognition and Decentralised Procedures and the agreed templates. For mutual recognition procedures (MRP) they should ensure that their assessment report is updated, if necessary, to be consistent with the dossier whenever possible.

2. For MRP and DCP, competent authorities should ensure that assessment reports are released on time in accordance with the MRP/DCP timetables. This will be facilitated by good communication between the applicants and the Reference Member State (RMS).

3. Competent authorities should do their best endeavour to avoid delay in the start of the procedure.

4. In accordance with Directive 2001/83/EC as amended, not only the SmPC but also the package leaflet (PL) and labelling are part of the MRP and DCP agreement. The applicant should also have considered the need for 'user consultation' and undertaken testing as necessary. The RMS should in their assessment report include a comment on which form of 'user consultation' of the PL has been performed (a full test or a bridging report) and the acceptability of the level of testing carried out.

5. When issues have been previously discussed and agreed upon by Member States (MSs) either during DCPs or during MRPs, they should not be reopened for discussion during other DCPs or MRPs including the same MSs, unless new information has become available. The RMS should indicate in the Assessment Report (AR) which other products and procedures the SmPC, PL and labelling are based on, and the CMS (Concerned Member State) should be listed. A reference to previous discussions in CMDh should be included in the AR, if applicable. The CMS should also include reference to other agreed MRP/DCP texts in their comments, when applicable. When reference is made to other products, MSs should refer to MRP/DCP numbers.

6. In case of multiple MRP/DCP applications submitted at the same time the RMS should inform the CMS about any differences of the ARs, SmPCs and PLs. The RMS should harmonise, whenever

possible, the SmPCs and PLs of different parallel applications before the start of the MRP or in the Day 70 Preliminary ARs in case of a DCP, in order to achieve harmonisation.

7. For a clear overview of the timelines for the MRP/RUP procedure and DCP procedure see the 'Flow chart of the Mutual Recognition Procedure (MRP) and Repeat Use Procedures (RUP)' (https://www.hma.eu/93.html) and the 'Flow chart of the Decentralised Procedure' (https://www.hma.eu/92.html), respectively.

Pre-procedural phase

8. The applicant has to follow the rules adopted by the MS chosen as the RMS for allocating a timeslot. It is recommended to use the common request form in order to ask a MS to be the RMS in a DCP (http://www.hma.eu/219.html).

9. It is strongly advised that the applicant discusses a timetable with the RMS before submission of the dossier in the RMS/CMS. For guidance on submission dates, reference is made to the CMDh document 'Recommendations on submission dates for Applicants of the Decentralised Procedure (DCP)' (https://www.hma.eu/93.html).

10. All incoming MRP applications should be registered and validated within 14 calendar days by CMSs and in case of DCP applications by CMSs and RMS, in accordance with the CMDh document 'Procedural advice on Validation of MR/Repeat-use/DC Procedures' (see http://www.hma.eu/91.html).

11. All competent authorities should commit to maintain the CTS database and ensure that the information from each competent authority is updated daily. In general positive validation and Clock Starts/ should be communicated via CTS only in order to avoid unnecessary mails. (see also: "Decentralised Procedure: Member States' Standard Operating Procedure", http://www.hma.eu/92.html). However, for MRP/RUP start of procedure notifications should also be communicated via email.

During the procedure

12. Emerging potential serious public health issues should be communicated to the RMS and applicant as soon as possible. CMSs should send their position to the RMS and the applicant ultimately by Day 30 in MRP, and Day 100 and Day 145 in DCP; delays should be an exception. The CMSs should clearly indicate whether their comment should be regarded as a 'other concern' or as a 'potential serious risk to public health'. If the CMSs have no comment, this should only be communicated via CTS. The CMSs do not necessarily have to send an e-mail to the applicant in such cases. The RMS should inform the applicant on all comments (also in case a CMS has no comments) raised.

    CMSs should notify the RMS and the applicant, by e-mail, in case they are not able to send their position on these deadlines. Comments should be sent after the deadlines only in exceptional circumstances. All comments should be sent in a single e-mail. If this is not possible, the CMS should mention in the first e-mail that more comments will follow. All CMSs should give details of their 'point of contact' that is available on the crucial days of the procedure.

13. In principle, CMSs should rely on the assessment of the RMS. Potential serious risks to public health and other concerns should be carefully screened within the national agencies. It is recommended that this screening system should be part of the quality system within the national agencies. If a MS raises a potential serious risk to public health, it shall give a detailed exposition of the reasons for this position. The RMS should actively co-ordinate the dialogue between the applicant and the National Competent Authority (NCA) and all efforts should be made to resolve

any divergence. All points, with the exception of potential serious risks to public health, which have not been agreed, are to be dropped before Day 90 in MRP, Day 55 in RUP and Day 210 in DCP. All unsolved potential serious risks to public health should be referred to the CMDh in accordance with Article 29 of Directive 2001/83/EC as amended.

14. Before submitting the application and also during the entire procedure, the applicant should check potential similarity with authorised orphan medicinal product(s) under market exclusivity for the proposed indication(s). In case a marketing authorisation is granted for an orphan medicinal product for the proposed indication(s), the applicant should submit or update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2). Note: in case the market exclusivity of an orphan indication expires during the procedure it is not allowed to include this indication during the procedure, it has to be added via the appropriate variation once the procedure is completed.The applicant should circulate their response document so that it reaches all CMSs by day 40 in MRP, and by Day 106 and Day 160 in DCP, in accordance with the CMDh document Applicant's Response Document in Mutual Recognition and Decentralised Procedure for Marketing Authorisation Applications (see https://www.hma.eu/98.html).

15. The RMS should, in all situations, evaluate the response given by the applicant (to the issues raised by the MSs) and circulate a report on the applicant's response to all CMSs before any break-out session or discussion in CMDh takes place. The RMS should indicate in their report the date that the comments from the CMSs are expected. Even in cases when no break-out session or discussion in CMDh is planned, comments from CMSs on the applicant´s response should preferably be given within reasonable time, e.g. around day 75 of the MRP and day 145/day 195 of the DCP.

16. When the application concerns a new isomer/mixture of isomer/complex/salt of an active substance already approved in the EU and the MA applicant claims this as a new active substance, the RMS day 70 Preliminary assessment report should be circulated to CMDh for information before day 105 in the procedure. It is also recommended that in event of a similar claim in a purely national application, the CMDh should be informed of the application before a designation of new active substance is concluded.

Break-out sessions, teleconferences and discussion at CMDh

17. If potential serious risks to public health are identified, a break- out session or hearing may be arranged. The occasion, format and the timing of this should be determined by the RMS (current experience has shown that this is often best around day 75/Day 195 of the procedure). The RMS could also use the meeting of the CMDh as an opportunity to discuss major issues that are raised during the procedure and seek assistance in solving the issues.

18. If the RMS is of the opinion that a break-out session / hearing connected to a CMDh meeting should take place, the RMS makes a proposal for the timing to be communicated to the CMSs, Chairman of the CMDh and CMDh Secretariat at the EMA, in accordance with the Best Practice Guide on Break-out sessions / hearings for MRP and DCP (see http://www.hma.eu/91.html). The Chairman and the CMDh Secretariat co-ordinate the proper timing in case several break-out sessions have to take place. Parallel meetings should not be excluded. If further discussion is needed in CMDh, the RMS will give an oral report of the break-out session in CMDh.

19. If the RMS is of the opinion that a discussion / hearing in the CMDh meeting should take place, the RMS should liaise with the CMDh Secretariat to place it on the agenda and should inform all CMDh members in advance of the meeting on the issues to be discussed.

20. It may be desirable to have a virtual or telephone conference around day 75-85/day 195-205 to reach agreement. To allow for this, it is recommended that CMSs inform the RMS and applicant about any outstanding issues before the date indicated by the RMS.

Finalisation of the procedure

21. It is advised to introduce any major amendments to the SmPC, PL and labelling during an early stage of the procedure in order to allow proper discussion in each MS. The CMSs should make every effort to send their comments on time and resolve outstanding issues before day 85 in MRP and day 205 in DCP. Only in exceptional cases should changes to the SmPC, PL and labelling be introduced after day 85 and day 205 in MRP and DCP, respectively. In such cases the RMS should actively inform the CMSs about this. The RMS and CMSs have the responsibility to ensure full transparency during the procedure.

22. No post day 90/210 commitments that can hinder the granting of a national marketing authorisation should be requested by MSs (see CMDh Questions and Answers on Applications for Marketing Authorisation, http://www.hma.eu/20.html). Any post-authorisation requirements should be exceptional and full justification should be given by the requesting MS.

23. In exceptional cases, if the RMS changes its recommendation in the assessment report from non-approvable to approvable after Day 205 (i.e. considers their previous major objection(s) resolved) the following applies: the RMS will circulate their (positive) assessment report and state in the cover e-mail that the RMS refers the procedure to the CMDh as an automated referral. This e-mail and assessment report should be circulated by the RMS to the mrna email addresses of the CMS(s) involved in the procedure with a copy to the CMD-referrals mailbox and the CMDh secretariat. This e-mail should also state that the CMSs will be given 7 more calendar days, after day 210, to confirm agreement with the RMS position or to mention their PSRPH(s) and ground(s) for referral. If agreement from all CMSs is received, the referral procedure will be withdrawn by the RMS and the procedure can be closed positively. In case of receipt of CMS objections/grounds for referral (using the referral request template), the procedure under point 26 below applies and the RMS will circulate the referral notification.

24. If consensus is reached with all MSs or if at Day 210 in DCP the RMS concludes that the product is not approvable, the RMS closes the procedure.

    If consensus is reached that the product is approvable, the RMS sends the final agreed SmPC, PL and labelling and, in case of DCP, the final day 210 Overview AR to the CMSs and the applicant.

    The RMS should also complete the risk assessment template to identify risk factors and provide test recommendations for post-marketing surveillance analysis by Official Medicines Control Laboratories. The template does not need to be completed for products that are subject to Official Control Authority Batch Release (OCABR) testing.

    If the RMS concludes that the product is not approvable, the RMS includes information in the FAR on the remaining outstanding issues at the end of the procedure. No referral to CMDh will follow. The procedure continues with the national step. No further discussion on the content of the dossier is possible after day 90/day 210.

CMDh referral

25. If a CMSs by Day 90/210 cannot approve the AR, SmPC, labelling or PL on the grounds of potential serious risk to public health, the CMSs shall notify the RMS, CMSs, the CMDh Secretariat at the EMA and the applicant at Day 90/Day 210 at the latest, preferably before 4.00 pm CET. The notification shall include a detailed exposition of the reasons for the negative position. This also applies in case the applicant has withdrawn the application in a CMS based on potential serious risk to public health raised by this CMS, unless it concerns a withdrawal of an application via DCP before the DAR is sent (day 120). Even if CMSs earlier in the procedure have informed that they are of the opinion that there are potential serious risks to public health with the application, they need to confirm their final position on Day 90/Day 210, so that it is clear to all parties involved, whether the issues have been resolved or not by the applicant's response. It is encouraged to stop a MRP or DCP on Day 90/Day 210 at 4.00 pm CET. It is recommended that the CMSs give their final position according to the timelines given above so that the procedure can be closed on day 90/day 210. A notification to the CMDh of a referral cannot be submitted later than day 90/day 210. It is not advisable to have day 90/day 210 on a Saturday or a Sunday.

26. If no consensus regarding a positive RMS AR is reached by Day 90/Day 210, the RMS will refer the matter to the CMDh by circulation of the AR, proposed SmPC, PL and labelling and the explanation of the grounds for referral from the disagreeing CMSs to all CMDh members, CMDh chair, the CMDh Secretariat at the Agency and the applicant, within 7 days after Day 90/Day 210. The procedure for the 60-day procedure in CMDh is described in the CMDh Standard Operating Procedure – Disagreement in procedures – referral to CMDh (see http://www.hma.eu/26.html).

27. At the level of CMDh, all CMSs shall use their best endeavours to reach agreement on the action to be taken within 60 days after the referral to the CMDh. If consensus is reached, the RMS records the agreement and closes the procedure at Day 150/Day 270. The RMS sends the final agreed SmPC, PL and labelling and, in case of DCP, the final day 210 Overview AR to the CMSs and the applicant.

28. If no consensus is reached at the level of CMDh, the RMS informs the EMA immediately after Day 60 of the CMDh discussion period, with a view to the application of the procedure under Articles 32, 33 and 34 of Directive 2001/83/EC as amended. The RMS provides the EMA with a detailed statement of the matters on which the MSs have been unable to reach agreement and the reasons for their disagreement. A copy shall be forwarded to the applicant and CMSs by the RMS. The procedure described in Chapter 3 of the Notice to Applicants should be followed using the appropriate form to notify the EMA. MSs that have approved the assessment report, SmPC, PL and labelling may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32 of Directive 2001/83/EC as amended. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

National implementation

29. Also, during the national step, i.e. until the national decision has been issued, the applicant (and national competent authority) should monitor the potential similarity with authorised orphan medicinal product(s) under market exclusivity for the proposed indication(s) to check if a marketing authorisation has been granted. In case a marketing authorisation is granted for an orphan medicinal product for the proposed indication(s), the applicant should submit or update their report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2). In that case, the RMS will circulate their (updated) assessment of similarity or (updated) separate similarity report to the CMSs. Note: in case the

market exclusivity of an orphan indication expires during the procedure (including national implementation step) it is not allowed to include this indication during the procedure, it has to be added via the appropriate variation once the procedure is completed.

30. The NCA of each MS shall adopt a national decision 30 days after the RMS closes the procedure, subject to submission of acceptable translations. The applicant submits high quality national translations of the SmPC, PL and labelling and mock-ups, if necessary, no later than 7 calendar days after the procedure is closed. See also CMDh Best Practice Guide on the submission of high-quality national translations (http://www.hma.eu/90.html). MSs may introduce linguistic changes only to the SmPC, PL and labelling and must ensure their national version of the product information is a faithful translation of the final harmonised position. The 'blue box concept' for adequate national information on the label and PL will be permissible.

    In case the procedure ended with a decision that the product is not approvable, all MSs need to take a final decision at national level, unless the applicant withdraws the application.