DECENTRALISED PROCEDURE
MEMBER STATES' STANDARD OPERATING PROCEDURE

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Abbreviations

ASMF Active Substance Master File
BOS Break-Out Session
DCP Decentralised procedure
CMD(h) Co-ordination group for Mutual Recognition and Decentralised Procedures for human medicines
CMS Concerned Member State
CTS Communication and Tracking System
DAR Draft Assessment Report
FAR Final Assessment Report
HBD Harmonised Birth Date
MRP Mutual recognition procedure
MS Member State
PL Package Leaflet
PrAR Preliminary Assessment Report
PSUR Periodic Safety Update Report
RMS Reference Member State
RSI Request for Supplementary Information
SPC Summary of Product Characteristics

Introduction

This document was produced by the CMD(h) in order to facilitate and harmonise the practical application of Article 28(3) of Directive 2001/83/EC as amended.
All time lines in this SOP are based on calendar days, i.e. days should be read as calendar days. The RMS and the applicant should be in close contact before and during the procedure in order to exchange information particularly on the time lines and how to proceed within the procedure.

Prerequisite: extracts from European legislation

1- Article 28(1) of Directive 2001/83/EC as amended
"With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10b, 10c and 11. The documents submitted shall include a list of Member States concerned by the application.
The applicant shall request one Member State to act as "reference Member State" and to prepare an assessment report on the medicinal product in accordance with paragraphs 2 or 3."

2- Article 28(3-5) of Directive 2001/83/EC as amended
"3. In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. The reference Member State shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned Member States and to the applicant."

"4. Within 90 days of receipt of the documents referred to in paragraph 2 and 3, the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the reference Member State accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly."

"5. Each Member State in which an application has been submitted in accordance with paragraph 1 shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement."

Outline of Decentralised Procedure

The Decentralised Procedure will be divided in five steps:

- Pre-procedural step, including validation phase
- Assessment step I
- Assessment step II
- Discussion at the CMD(h), if needed
- National step

Pre-procedural step, including validation phase

Consultation with RMS

It is recommended that the applicant informs the Member State (MS) chosen as Reference Member State (RMS) that an application under the Decentralised Procedure is planned, as soon as the applicant has an estimation of the intended submission date of the application.

The RMS will allocate a procedure number to this application (according to the numbering system described in Chapter 2 of the Notice to Applicants) and will inform the applicant accordingly.

The applicant should seek regulatory advice or prediscuss the application with the RMS either during a presubmission meeting or via a teleconference/e-mail at least 2 months before submission of the dossier.

The applicant has drafted the package leaflet (PL) within its development programme. The applicant has considered the need for 'user consultation' and undertaken initial testing as necessary or the applicant indicates that 'user consultation' will be done during the clock-off period.
Discussion with the RMS indicates whether 'user consultation' may be necessary or expert justification for its absence is likely to be acceptable.

In the case of possible different views among MSs on the legal basis of the application the matter can be discussed in the meeting of the Co-ordination group for Mutual Recognition and Decentralised Procedures (CMD(h)) prior to the application but also during the validation phase, to be initiated by the RMS.

The RMS creates the procedure in the CTS database as soon as the dossier is submitted, so that CMS and RMS are able to communicate on the procedure through the CTS record immediately after receipt of the dossier.

Making the application

The applicant submits an application to the National Competent Authorities of each of the MS where a marketing authorisation is to be sought**.**

The applicant is required to give assurance, usually in the cover letter accompanying the application, that the dossier submitted is identical in all MSs concerned (RMS + CMSs). The application should be made according to the legal basis applied for. Guidance on format, appropriate number of copies of the dossier, languages requirements, fees etc. can be found in Chapter 7 of the Notice to Applicants. Text proposals for SPC, PL and labelling in English only are acceptable with the submission of the dossier[1]. Sample mock-ups in an official language of the EU should be submitted for the application to be valid.
The applicant notifies the RMS of the dates of dispatch of the dossier, so that the RMS is able to update the CTS record and to complete the 'date of last dossier submission' in CTS. This date of last dossier submission is the start of the validation period. At the time of updating the CTS record, validation of the application does not have to be completed by the RMS.

Validation phase

[1] Due to national legal requirements in Poland, Polish translations of the SPC, PL and labelling are required before the start of a DCP.

The application should be checked in by all MSs concerned (RMS + CMSs). The check can be made according to the check-in procedure described in Chapter 7 of the Notice to Applicants or using any other appropriate form.

Both RMS and CMSs should promptly inform the applicant and the CMSs/RMS about any validation issues (administrative and regulatory issues). The MSs should indicate in CTS that the application is invalid when there are justified reasons to do so. An application will not automatically be set invalid if a MS has not yet received the dossier and the validation period has not started.

If, at day 7 of the validation period the CTS record is not complete with respect of valid or invalid application for each MS, the RMS will notify (initially by Eudranet email) the CMS who have not completed the CTS record that the validation period will close at the end of the next 7 day period unless notification of an invalid application is received.
The RMS will close the validation period 7 days after this notification, if the RMS has declared the application valid, and may start the procedure unless informed by a CMS that the application is not valid.
If a CMS has previously informed the RMS that the application is not valid, the procedure will not be started until that CMS confirms to the RMS that the issue has been resolved and the application is valid. The CMS has a duty to update the CTS record accordingly. The CMS must inform the RMS that the application has become valid within 7 days of the missing information being supplied.

If it is not expected that the application will become valid within an acceptable time, the applicant will be advised to withdraw the application in the MS.

If the application is withdrawn in a CMS during the validation period (before start of the procedure) the procedure should be regarded as finalised in that CMS. So this CMS should not receive any further communication/e-mails/documents related to this procedure. It is then considered that this CMS did not participate in the procedure.

The RMS confirms to CMS (via CTS) and applicant the start of the procedure and the updated timetable, if necessary.

Assessment step I

The assessment step I corresponds to the 120-day period for preparing Draft Assessment Report (DAR) and comments on draft SPC, draft PL and draft labelling.

The RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SPC, PL and labelling) on the dossier to the CMSs and the applicant within 70 days after the start of the procedure. This PrAR will include a comment on whether 'user consultation' of the PL has been performed or is foreseen, or the justification for its absence is acceptable.
The RMS will have the main responsibility for the assessment of the PL.

By Day 100 CMSs should communicate their comments to the RMS, CMS and applicant, using the template agreed upon, differentiating between potential serious risks to public health and points for clarification. Any issues should be carefully screened within national agencies. If a CMS raises a potential serious risk to public health it shall give a detailed exposition of the reasons of its position. CMSs should comment if they disagree with the RMS position on requirement for 'user consultation'.
CMSs should clearly differentiate between comments on the open and closed part of the ASMF.

When issues have been previously discussed and agreed upon by MSs either during DCPs or 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 which other products and procedures the SPC, PL and labelling are based on, and the CMS should be listed. A reference to previous discussions in the CMD(h) should be included in the assessment report, if applicable. The CMS

should also include reference to other agreed texts, when applicable. When reference is made to other products, MSs should refer to MRP or DCP numbers.

Between Day 100 and 105, the RMS may consult with the CMSs to discuss the comments raised. Similar comments raised by different MSs may be combined into one single question and if the RMS considers a CMS comment redundant, the RMS may discuss with the CMS whether the comment could be withdrawn The RMS forwards the questions remaining from this consultation to the applicant and CMSs.
Questions on the closed part of the ASMF will be sent to the ASMF holder by the RMS.
The RMS should also inform the applicant in case questions on the closed part of the ASMF have been forwarded to the ASMF holder, indicating whether these are potential serious risks to public health and/or points for consideration.

In order to achieve a common understanding of the comments and questions raised by the MSs concerned, it is recommended that the RMS and the applicant are in close contact.

If consensus is reached that the product is approvable, the RMS updates the Overview part of the PrAR to prepare the Final Assessment Report (FAR) including agreed SPC, PL and labelling. At Day 105 the RMS may close the procedure, and the procedure continues with the national step.

If consensus is reached that the product is approvable, but there are only comments that can be easily solved, the RMS stops the clock and forwards these comments at day 105 to the applicant. After receipt of the response of the applicant the RMS restarts the clock at day 106 and updates the Overview part of the PrAR to prepare the Final Assessment Report (FAR), SPC, PL and labelling and sends it as soon as possible in order to give enough time to the CMSs to send their agreement. At Day 120 the RMS may close the procedure, and the procedure continues with the national step.

If no consensus is reached that the product (including proposed SPC, PL and labelling) is approvable, the RMS stops the clock at Day 105 and forwards the questions raised by RMS and CMS remaining from the consultation, to the applicant as a Request for Supplementary Information (RSI).

During the clock-off period, the applicant supplements the dossier by responding to the questions and providing updated SPC, PL and labelling proposals. Within the clock-off time, the applicant may undertake ‘user consultation’ of PL and in such a case the applicant should take into account MS comments received, if ‘user consultation ’had not yet been done. In these cases it is not allowed to perform ‘user consultation’ during the clock-off time with the PL submitted at the start of the procedure,

The applicant may submit draft responses, including updated SPC, PL and labelling proposals to the RMS for (pre-) assessment. The RMS must always provide feedback to the applicant on this draft response in order for the applicant to know whether there is a need to complete the response document before sending it to the CMSs or whether this document can be submitted to the CMSs (without any changes). The RMS will inform the CMSs and applicant if a delay in restart of the procedure is foreseen. In any case, the RMS should agree the date of submission of the final response with the applicant.

The applicant and the ASMF holder submit the final response to the RMS and all CMS within a recommended period of 3 months, which could be extended if justified. After submission of the final response and receipt of the list of despatch dates in all CMSs the RMS restarts the procedure at Day 106.

The applicant is allowed to submit new data in reply to the questions raised by the Member States during the procedure. Between Day 106 and 120 the RMS updates the PrAR to prepare the Draft Assessment Report (DAR), draft SPC, draft PL and draft labelling.

If the application is withdrawn before the Draft Assessment Report is distributed (i.e. before assessment step II) in a CMS which raised potential serious risks to public health earlier in the procedure, then a CMD(h) referral won’t be initiated. The procedure should be regarded as finalised in that CMS, and this CMS should not receive any further communication/e-

mails/documents related to this procedure.

Assessment step II, including discussion at CMD(h), if needed

The RMS starts the 90-day period on Day 120 by sending the Draft Assessment Report (DAR), draft SPC, draft PL and draft labelling to the CMS and applicant at Day 120. Day 120 corresponds to Day 0 of the 90-day period mentioned in 28(4) of Dir. 2001/83/EC. The DAR will include assessment of the results of 'user consultation' or justification for its absence. During the assessment step II, new data cannot be submitted by the applicant or the ASMF holder. The RMS should clearly indicate in its conclusion if the product is approvable or not.

During the assessment step II period (90 day period) the procedure can be closed at **any time-points** before day 210 if consensus is reached. The RMS should circulate its conclusion that the product is approvable together with the final proposed SPC/PL and labelling to the CMSs. The RMS should clearly indicate in this message that all remaining comments have been addressed satisfactorily and that the product(s) and SPC/PL/labelling can now be approved. If necessary a short assessment report can be added to the message. Furthermore the RMS should mention in their message that if no comments have been received within one week (a specific date should be mentioned) it is assumed that the CMSs agree with the proposed texts and that the procedure will then be concluded positively. However, in the exceptional case a CMS will not be able to respond before the requested date, he will inform the RMS and other CMSs in order to extend the deadline for comments.

The RMS will update the CTS record with the date of sending of the above mentioned documents and Day 120.

Each CMS sends its final comments to the RMS, CMS and applicant, using the template agreed upon, differentiating between potential serious risks to public health and remaining points for clarification no later than Day 145 of the procedure (i.e. Day 25 of 90-day period) and updates the CTS record.

If consensus is reached the RMS prepares the Final Assessment Report (FAR) and may close the procedure at Day 150 (i.e. Day 30 of the 90-day period). The procedure continues with the national step if the MSs consider the product approvable. If there is consensus that the product is not approvable, no national step will follow.

Between Day 145 and 150, the RMS consults with the CMSs to discuss the comments raised.

If consensus is not reached by Day 150, the RMS communicates outstanding issues with the applicant.

The applicant submits additional clarification by Day 160 or earlier, including any revised proposal for SPC, PL and labelling, and the RMS prepares a short report and forwards it to the CMSs at the latest on Day 180 (i.e. Day 60 of the 90-day period). This report of the RMS will include proposals for an update of the Overview part of the DAR to derive the FAR.

The RMS should decide in agreement with the applicant the appropriate date of a Break-Out Session (BOS), if necessary.

At latest on day 195 (i.e. Day 75 of the 90-day period) a Break-Out Session (BOS) may be held at the EMEA with the involved MSs to reach consensus on the major outstanding issues. The BOS will be held according to the principles outlined in the CMD(h) Best Practice Guide on Break-out sessions. This is also an opportunity for MSs to discuss outstanding PL and labelling concerns with the applicant. If further discussion is needed in CMD(h), the RMS will give an oral report of the BOS in CMD(h). In all situations, the RMS will circulate the minutes of this meeting to the CMD(h), the CMSs and the applicant.

After the BOS the applicant may submit amended SPC, PL and labelling proposals in accordance with agreements made during the meeting.

The RMS could also use the meeting of the CMD(h) as an opportunity to discuss major issues that are raised during the procedure and seek assistance in solving the issues.

It is advised to introduce any major amendments to the SPC, PL and labelling during an early stage of the procedure in order to allow proper discussion in each MS. The CMS should make every effort to send their comments before Day 195 and resolve outstanding issues before Day 205 (i.e Day 85 of the 90-day period). Only in exceptional cases should changes to the SPC, PL and labelling be introduced after Day 205. In such cases the RMS should actively inform the CMSs about this. The RMS and CMS have the responsibility to ensure full transparency during the procedure.

On occasion it may be desirable to have a telephone or video conference around day 195-205 (i.e. Day 75-85 of the 90-day period) to reach agreement.

Between Day 195 and Day 210, the RMS consults with the CMSs and the applicant to discuss the remaining comments raised.

At Day 210 (i.e. Day 90 of the 90-day period) the RMS closes the procedure if consensus was reached with all MS on the outstanding issues. The RMS includes information in the FAR on how major outstanding issues were solved by discussions e.g. via written procedures and/or by discussion in the CMD(h) (if applicable).
The RMS sends to the CMSs and the applicant, the final agreed SPC, labelling and PL, and the final AR (including approved finished product specifications at release and end of shelf-life).
The procedure continues with the national step if the MSs consider the product approvable. If there is consensus that the product is not approvable, no national step will follow.

The RMS will inform the CMD(h) how the major outstanding issues were solved by sending the FAR in order that all MSs can benefit from the information and, if relevant, adopt common positions in future procedures.

If CMS(s) by Day 210 cannot approve the assessment report, SPC, PL and labelling on the grounds of potential serious risk to public health, the CMS(s) shall notify the RMS, CMS(s), the CMD(h) secretariat at the EMEA and the applicant at Day 210 at the latest, preferably before 16.00 CET. The notification shall include a detailed exposition of the reasons for the negative position. This also applies in case the applicant has withdrawn from Day 120 on the application in a CMS based on potential serious risk to public health raised by this CMS. Even if CMS(s) 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 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 DCP on Day 210 at 16.00 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 210. It is not advisable to have Day 210 on a Saturday or a Sunday.

If no consensus is reached at Day 210, the RMS will refer the matter to the CMD(h) by circulation of the assessment report, proposed SPC, PL and labelling and the explanation of the grounds for referral from the disagreeing CMS(s) to all CMD(h) members, CMD(h)chair, the CMD(h) secretariat at the EMEA and the applicant, within 7 days after Day 210. The 60-day procedure in CMD(h) is described in the CMD(h)-SOP-Disagreement in procedures-referral to CMD(h).

According to article 29 (1-6) of Dir. 2001/83/EC as amended, all MSs concerned shall use their best endeavours to reach agreement on the action to be taken within 60 days of the communication of the points of disagreement, at the level of the CMD(h).

- If consensus is reached, the RMS records the agreement, closes the procedure at Day 270 (at the latest) after the CMS have approved the Final Assessment Report, SPC, PL and labelling, and informs the applicant accordingly. The procedure continues with the

national step if the MSs consider the product approvable.

- If no consensus is reached at the level of CMD(h), the RMS only informs the EMEA immediately after Day 60 of the CMD(h) discussion period, with a view to the application of the procedure under Articles 32, 33 and 34 of Dir. 2001/83/EC as amended. The RMS provides the EMEA 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 EMEA.
  MSs that have approved the Final AR, the SPC, PL and labelling may, at the request of the applicant, authorise the medicinal product (i.e. continue with the national step) without waiting for the outcome of the procedure laid down in Article 32 of Dir. 2001/83/EC as amended. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

Handling of EU HBD and PSUR cycle

If an EU harmonised birth date (HBD) for the active substance of the medicinal product has been adopted and published on the HMA website (http://www.hma.eu), the applicant is strongly recommended to use the related DLP (Data Lock Point) for PSUR submission. On a case by case basis there may also be a possibility to combine the renewal with the PSUR submission. This should always be communicated to the RMS in order that the PSUR submission cycle and common renewal date are included in the closure letter.

If the applicant does not choose the EU HBD or if such an HBD does not exist, the common renewal date will be based on the date of closure of the decentralised procedure + 5 years. PSURs should be submitted according to Volume 9A of the Rules Governing Medicinal Products in the European Union.

National step

The National Competent Authority of each involved MS shall adopt a national decision within 30 days after the RMS closes the procedure.
The applicant submits high quality national translations of the SPC, PL, labelling and mock-ups (if required) no later than 5 days after the procedure is closed.
MSs may introduce linguistic changes only to the SPC, PL and labelling and must ensure their national version of 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.