

<p>DECENTRALISED PROCEDURE MEMBER STATES' STANDARD OPERATING PROCEDURE</p>
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Abbreviations

ASMF	Active Substance Master File
BOS	Break-Out Session
DCP	Decentralised procedure
CMDh	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
PSRPH	Potential Serious Risk to Public Health
PSUR	Periodic Safety Update Report
RMS	Reference Member State
RSI	Request for Supplementary Information
SmPC	Summary of Product Characteristics

INTRODUCTION

This document was produced by the CMDh 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 is divided in five steps:

- Pre-procedural step, including validation phase
- Assessment step I
- Assessment step II
- Discussion at the CMDh, 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 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 decentralised procedure (<http://www.hma.eu/91.html>).

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

The RMS will inform the applicant when the marketing authorisation application could be submitted and will allocate a procedure number to this application (according to the numbering system described in Chapter 2 of the Notice to Applicants).

The applicant should discuss with the RMS which form of ‘user consultation’ of the package leaflet (PL) may be necessary (a full test or a bridging report) and when the results will be available (at the submission of the application or during the clock-off period).

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 (CMDh) prior to submission of the application but also during the validation phase. The discussion will 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 regarding 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). It is recommended to use the template for a cover letter as published on the CMD website (<http://www.hma.eu/219.html>). 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 and in the document “Additional Data requested for New Applications in the Mutual Recognition and Decentralised Procedures” as published on the CMD website (<http://www.hma.eu/91.html>). Text proposals for SmPC, PL and labelling in English only are acceptable with the submission of the dossier¹. 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.

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

Validation phase

The procedure described in 'Procedural Advice: Automatic validation of MR/Repeat-use/DC Procedures' applies (see <http://www.hma.eu/91.html>).

If there are different views on the validity of the legal basis, the RMS may discuss this in the CMDh meeting.

If the application is withdrawn in a CMS during the validation period (i.e. before start of the procedure) the procedure should be regarded as finalised in that CMS. Consequently 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.

It should be noted that successful passage through the initial validation phase does not preclude subsequent refusal, on grounds of non-compliance with the legislation or absence of satisfactory supporting data, at any other stage of the procedure, which become apparent on further consideration of the dossier cf. Article 26.2 of the Directive 2001/83/EC as amended.

ASSESSMENT STEP I

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

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

The RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, 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

By Day 100 CMSs should communicate their comments to the RMS, other CMS and the applicant, using the template agreed upon, differentiating between potential serious risks to public health (PSRPH) and points for clarification. Where a CMS is in agreement with the RMS, then a simple e-mail communication would suffice. Before sending comments, any issues should be carefully screened within national agencies. If a CMS raises a PSRPH it shall give a detailed exposition of the reasons of its position. 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 SmPC, PL and labelling are based on, and the CMS should be listed. A reference to previous discussions in the CMDh 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. 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 SmPC, PL and labelling. At Day 105 the RMS may close the procedure, and the procedure continues with the national step.

If no consensus is reached that the product (including proposed SmPC, PL and labelling) is approvable, the RMS stops the clock at Day 105 and forwards the questions raised by the RMS and CMS, 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 SmPC, PL and labelling proposals, if necessary. The applicant is only allowed to submit new data in reply to the questions raised by the Member States during the procedure.

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. If MS have made comments on the PL 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 a draft response, including updated SmPC, PL and labelling proposals to the RMS for (pre-) assessment, if agreed by the RMS. It should be agreed with the RMS whether the draft response may be submitted in different parts or should be submitted as a single submission. Applicants are reminded that the draft response document should be of high quality: this document should properly address all the questions raised by the Member States. The RMS will provide feedback to the applicant on whether there is a need to correct deficiencies in the response document before sending it to the CMSs or whether the document can be submitted to the CMSs (without any changes). The RMS will provide this feedback once-only and normally within 4 weeks after receipt. The RMS includes in this feedback on the draft response a proposal for the restart of the procedure (i.e. submission of final response to RMS and all CMS and restart at Day 106), unless an inspection (GMP or GCP requested by RMS or CMS) is necessary. In any case, the RMS should agree the date of submission of the final response with the applicant.

The RMS will inform the CMSs and applicant if a delay in the restart of the procedure is foreseen.

In case the applicant, in agreement with the RMS, does not submit a draft response to the RMS, he should give an advanced notice of 14 days on the proposed submission date of the final response document.

The applicant and the ASMF holder should submit the final response to the RMS and all CMS within a period of 3 months, which can be extended by a further 3 months. In exceptional circumstances, a further extension of this period could be applied for and approved by the RMS. A request for an extension will only be considered by the RMS if the applicant provides appropriate scientific justification. Any request for an extension should be submitted to the RMS at the latest one month before the end of the 3 months period or one month before the earlier agreed date. If no request for an extension is received within this time, the RMS will automatically restart the procedure and distribute a Draft Assessment Report (DAR) on the basis of the information available at that time.

If it is not expected that the response will be submitted within an acceptable time (i.e. 6 months maximum), the RMS will request the applicant to withdraw the application in all MSs. If the applicant has not

- submitted a response within 3 months, or
- submitted a response within the extended period requested and agreed by RMS, or
- withdrawn the application,

the RMS will continue the procedure, i.e. the RMS will restart the clock and distribute a Draft Assessment Report (DAR) on the basis of the information available at that time.

Applicants are reminded that data derived from new studies are not accepted during assessment step II, so it will not be possible to supplement a deficient dossier with new data once the clock has restarted.

After submission of the final response document and receipt of the list of despatch dates in all CMSs the RMS will finalise the timetable for Assessment Step II with the applicant and restarts the procedure at Day 106.

Between Day 106 and 120 the RMS updates the PrAR to prepare the Draft Assessment Report (DAR), draft SmPC, draft PL and draft labelling.

If the application is withdrawn before the Draft Assessment Report is distributed² (i.e. before assessment step II) in a CMS which raised a PSRPH earlier in the procedure, then a CMDh referral won't be initiated on the basis of this PSRPH. The procedure should be regarded as finalised in that CMS, and consequently this CMS should not receive any further communication/e-mails/documents related to this procedure.

ASSESSMENT STEP II, INCLUDING DISCUSSION AT CMDH, IF NEEDED

The RMS starts the the assessment step II on Day 120 at the latest by sending the Draft Assessment Report (DAR), draft SmPC, draft PL and draft labelling to the CMS and applicant. The start of the assessment step II corresponds to Day 0 of the 90-day period mentioned in 28(4) of Dir. 2001/83/EC. During the assessment step II, new data/studies (or a delayed Day 106 response) 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.

The RMS will update the CTS record with the date of sending of the DAR, draft SmPC, draft PL and draft labelling.

During the assessment step II period the procedure can be closed at **any time-point** before Day 210 if consensus is reached that the product is approvable. The RMS should circulate its conclusion that the product is approvable together with the final AR, final proposed SmPC/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 SmPC/PL/labelling can now be approved. If necessary a short assessment report can be added to the message. Each CMS sends its comments to the RMS, CMS and applicant, using the template agreed upon, differentiating between PSRPH 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. Where a CMS is in agreement with the RMS, then a simple e-mail communication would suffice.

However, in specific situations, the RMS can propose a shorter timetable for sending comments (within one week). If no comments have been received within one week, it is assumed that the CMSs agree with the proposed texts and that the procedure will then be concluded positively. However, in the absence of agreement on this proposed shorter deadline for comments, the normal timetable will be followed (i.e. comments to be sent no later than Day 145)

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

If consensus is reached that the product is approvable, the RMS prepares the Final Assessment Report (FAR) and closes the procedure. The procedure continues with the national step.

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 SmPC, PL and labelling if necessary. The RMS prepares a short report on the complete applicant's response submitted at Day 160 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 discuss with the CMS and applicant³ whether a Break-Out Session or Hearing³ would be suitable, and what would be the appropriate date.

² If the DAR is distributed earlier than day 120, then Assessment Step II starts at the actual day of distribution of the DAR.

³ See article 12 of the Rules of Procedure of the CMDh

At latest on day 195 (i.e. Day 75 of the 90-day period) a Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues. In order to facilitate the participation from MSs, the RMS may also decide to organise a BOS using Vitero or telephone conference. The BOS will be held according to the principles outlined in the CMDh Best Practice Guide on Break-out sessions. If further discussion is needed in CMDh, the RMS will give an oral report of the BOS in CMDh. In all situations, the RMS will circulate the minutes of this meeting to the CMDh, the CMSs and the applicant.

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

During any time 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.

Scientific discussion in the CMDh is recommended to discuss potential problems in the assessment of complex formulations, different interpretations of the Bioequivalence Guideline, quality issues or risk minimisation measures early in a procedure. Especially in situations where several parallel procedures of the same active moiety are ongoing it will help the MSs to agree on a consistent approach in the assessment”.

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 full 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 SmPC, 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 Vitero or telephone conference between the MSs 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, or if the RMS concludes that the product is not approvable.

- If consensus is reached that the product is approvable, 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 CMDh (if applicable). The RMS sends to the CMSs and the applicant, the final agreed SmPC, 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 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.

If CMS(s) by Day 210 cannot approve the positive RMS assessment report, SmPC, PL and labelling on the grounds of PSRPH, the CMS(s) shall notify the RMS, CMS(s), the CMDh secretariat at the European Medicines Agency and the applicant at Day 210 at the latest, preferably before 16.00 CET, by using the agreed template for a referral request (<http://www.hma.eu/262.html>). 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 after distribution of the DAR in a CMS based on PSRPH 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 finalise 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 a CMS maintains a PSRPH at Day 210, the RMS will refer the matter to the CMDh by circulation of the assessment report, proposed SmPC, PL and labelling and the explanation of the grounds for referral from the disagreeing CMS(s) to all CMDh members, CMDhchair, the CMDh secretariat at the European Medicines Agency and the applicant, within 7 days after Day 210, by using the agreed template for a referral notification (<http://www.hma.eu/262.html>). The 60-day procedure in CMDh is described in the CMDh-SOP-Disagreement in procedures-referral to CMDh.

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 CMDh.

- 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, SmPC, PL and labelling, and informs the applicant accordingly. The procedure continues with the national step.
- If no consensus is reached at the level of CMDh, the RMS informs the European Medicines Agency 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 Dir. 2001/83/EC as amended. The RMS provides the European Medicines Agency 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 European Medicines Agency. MSs that have approved the Final AR, the SmPC, 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/80.html>), 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.

- In case the procedure ended with a decision that the product is approvable, the applicant submits high quality national translations of the SmPC, 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 SmPC, 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.

- 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.