EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Article 20 procedures		
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1. Purpose

To provide guidance on the procedure to be followed when dealing with referral procedures according to Article 20 of Regulation (EC) No 726/2004 for centralised authorised medicinal products for human use, to indicate with whom the responsibility lies for each step, and to ensure consistency in the handling of such procedures.

2. Scope

This SOP applies to the Patient Health Protection Unit, the Human Medicines Development and Evaluation Unit, the Office of the Executive Director and the Product Data Management Sector.

3. Responsibilities

It is the responsibility of the Head of Sector and Section Head to ensure that this procedure is adhered to within their own sector. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section **9. Procedure**.

4. Changes since last revision

Updated to reflect the new organisational structure, changes to reflect the interaction with the Clinical Trials Facilitation Group (steps 4, 18, 37, 39), to include the reference to the SOP on appointment of PTLs (step 2), to incude the Scientific Adviory Group/ Expert meetings (step 14-18, 20, 25, 29 and 37) and the new corporate identity.

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5. Documents needed for this SOP

A list of all relevant templates (such as faxes and letters, time table, and sign-off slips) can be found in Word/File/New/Referrals and the templates themselves on the X:\ drive:

(X:\Templates\Others\H – Referral\Article 20).

Templates for CHMP opinion, CHMP AR, timetable for translations and opinion related letters can be found in Word/File/New.

6. Related documents

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- "Community Referral", The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 3 (general guidance on referrals)
- Guidance on Referrals (available on the Agency's website: http://www.ema.europa.eu/htms/human/referral/q_a/index.htm)
- Guidance to applicants on CPMP oral explanations in relation to centralised procedures (http://www.ema.europa.eu/pdfs/human/regaffair/239001en.pdf)
- WIN/EMA/0070 Redaction of Documents in relation to Access to Documents
- SOP/EMA/0101 Check of conflicts of interest for Product Team Leader/Member or Project Manager for an application for a centralised initial marketing authorisation, maximum residue limit, referral or paediatric Article 29
- SOP/EMA/0111 Preparation, dissemination and publication of safety-related EMA press releases and question-and-answer documents
- SOP/H/3101 Determination of fees (medicinal products for human use)
- SOP/H/3129 Organisation of Scientific Advisory Group (SAG) meetings and reporting of SAG position to the CHMP
- WIN/H/3145 Sending out documents to Applicant/MAHs in the context of referrals (Article 6(12), 6(13), 31, 36 and Article 20 procedures)
- SOP/H/3193 Master file for referrals
- WIN/H/3205 Publication of Post-authorisation Unit Referrals
- SOP/H/3346 Early Notification System: procedure for advanced notification of emerging safety issues to EU regulatory network and international partners.
- SOP/H/3347 Preparation of 'lines-to-take' documents for use within the EU regulatory network to answer external queries in a consistent manner.

7. Definitions

Article 20 of Regulation (EC) No 726/2004

According to Article 20 the supervisory authorities or the competent authorities of any other Member State shall inform the CHMP if they are of the opinion that the manufacturer or importer established within the Community territory is no longer fulfilling the obligations laid down in Title IV (Manufacture and Importation) of Directive 2001/83/EC. The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Titles IX (Pharmacovigilance) and XI (Supervision and Sanctions) of Directive 2001/83/EC should be applied in respect of the medicinal product concerned or where the said Committee has delivered an opinion to that effect in accordance with Article 5 of this Regulation.

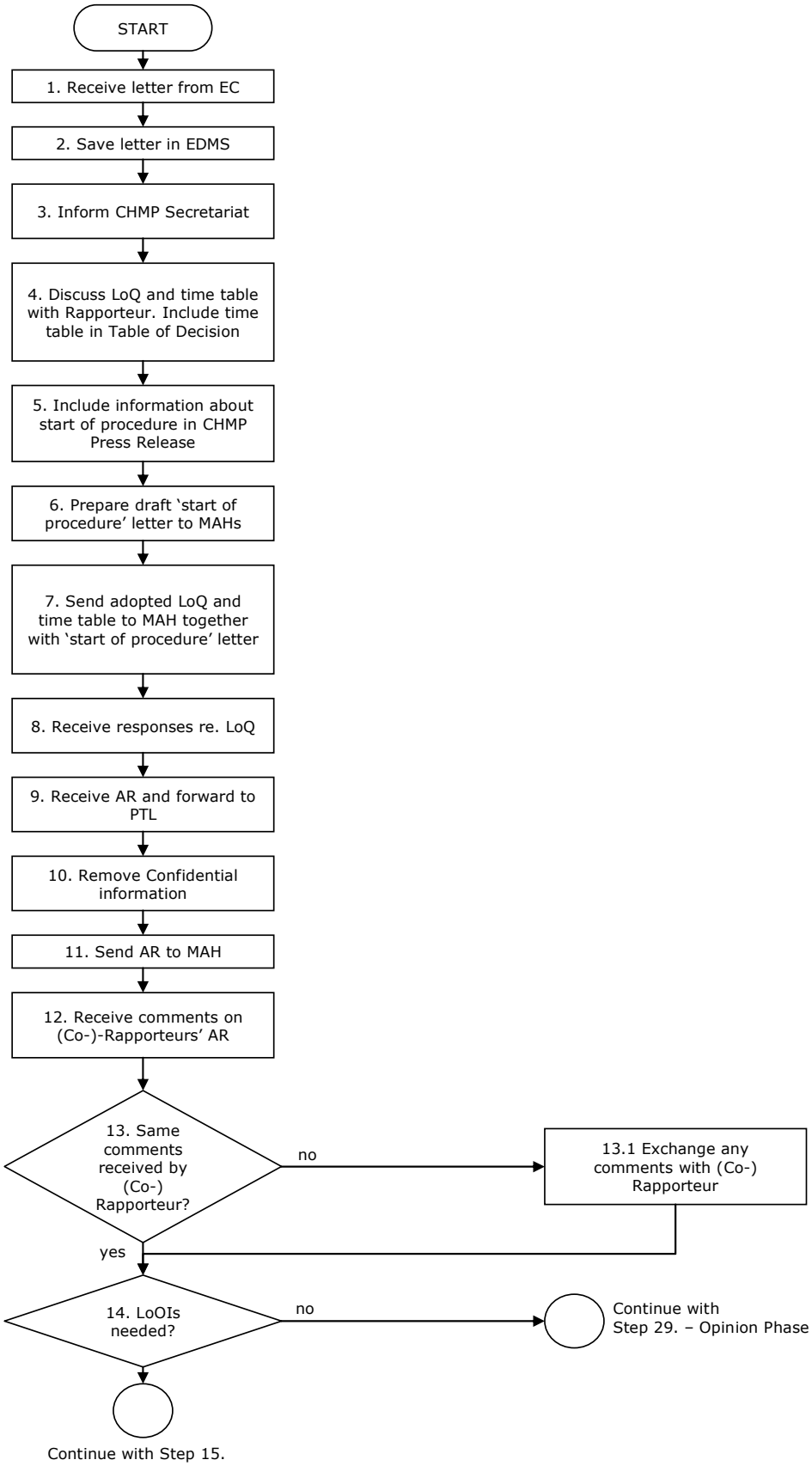
The Commission shall request the opinion of the Agency within a time-limit which it shall determine in the light of the urgency of the matter.

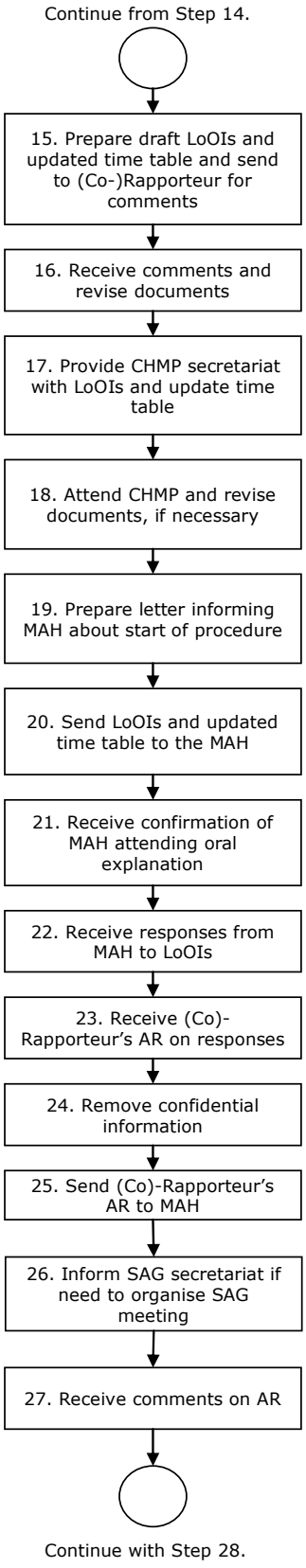
Abbreviations:

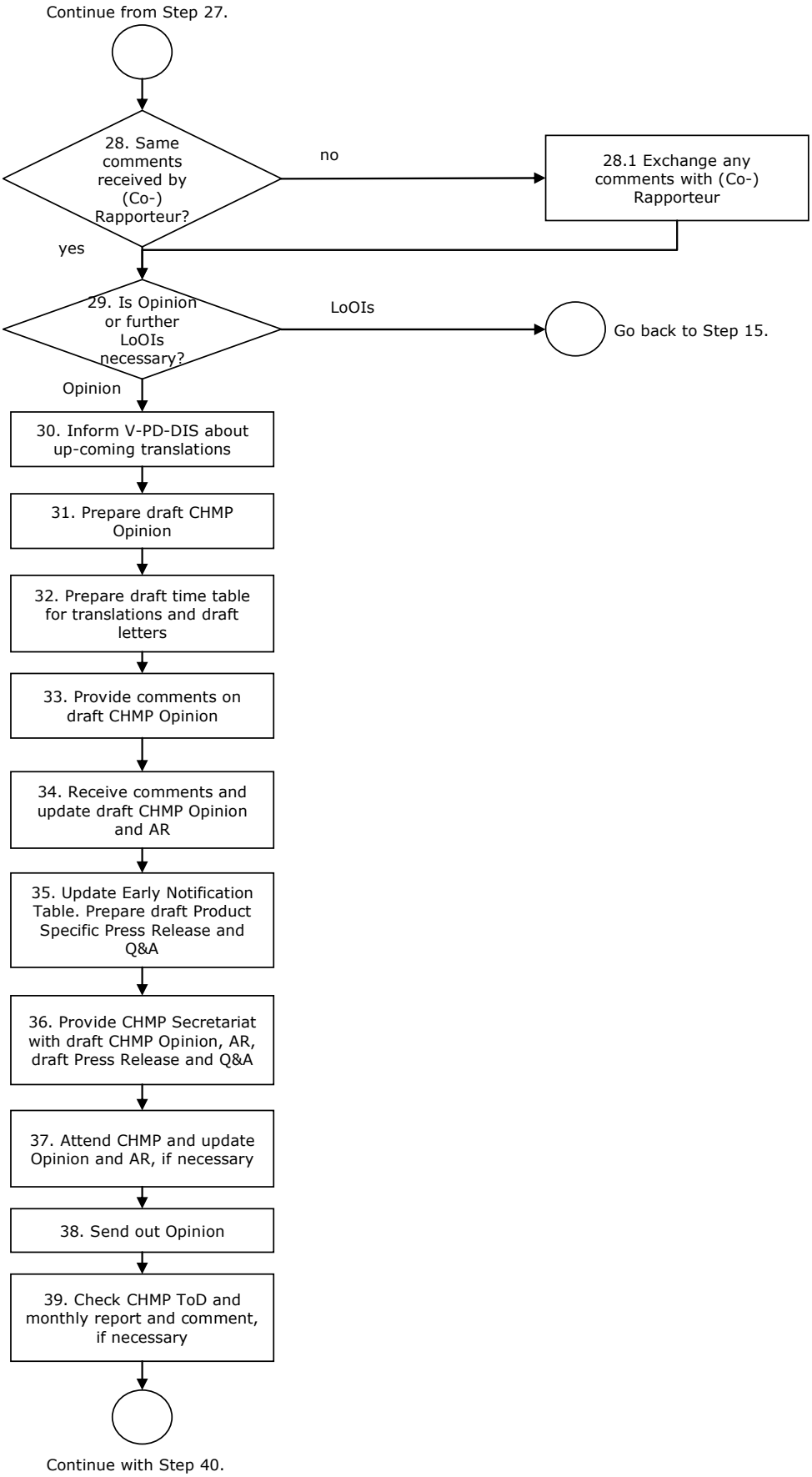
AR	Assessment Report
CHMP	Committee for Medicinal Products for Human Use
CHMP AR	Assessment Report of the Committee for Medicinal Products for Human Use
Co(Rapp)	Co-Rapporteur and Rapporteur
CTFG	Clinical Trials Falicitation Group
D-ED	Office of the Executive Director
DHPC	Direct Healthcare Professional Communication
EC	European Commission
ECD	Eudra Common Directory
EDMS	Electronic Document Management System
EPAR	European Public Assessment Report
HoS	Head of Sector
H-SE	Safety and Efficacy of Medicines Sector, Human Medicines and Development Unit
LoOIs	List of Outstanding Issues
LoQ	List of Questions
MAHs	Marketing Authorisation Holder(s)
MF	Master File
MS(s)	Member State(s)
P-CI	Compliance and Inspection Sector, Patient Health Protection Unit
PIQ	Product Information Quality
P-MI	Medical Information Sector, Patient Health Protection Unit

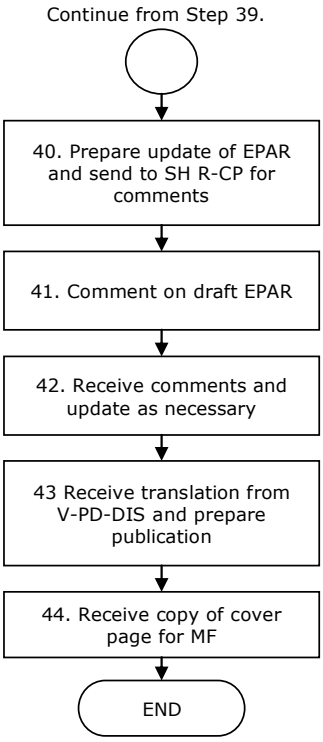
P-R	Regulatory, Procedural and Committee Support Sector, Patient Health Protection Unit
PTL	Product Team Leader for the Article 20 procedure
PTM	Product Team Member
Q&A	Questions and Answers Document
QRD	Quality Review of Documents
RA-PTM	Product Team Member from Regulatory Affairs Section,and Organisational Support Regulatory, Procedural and Committee Support Sector, Patient Health Protection Unit
SAG	Scientific Advisory CommitteeGroup
SH-CP	Section Head for Community Procedure Section
SOP	Standard Operating Procedure
V-PD-BUS	Product and Application Business Support Section, Data Management Sector, Veterinary Medicines and Product Data Management Unit
V-PD-DIS	Document and Information Services Sector, Product Data Management Sector, Veterinary Medicines and Product Data Management Unit
WIN	Work Instruction

8. Process map(s)/ flow chart(s)




Continue from Step 14.
15. Prepare draft LoOIs and updated time table and send to (Co-)Rapporteur for comments
16. Receive comments and revise documents
17. Provide CHMP secretariat with LoOIs and update time table
18. Attend CHMP and revise documents, if necessary
19. Prepare letter informing MAH about start of procedure
20. Send LoOIs and updated time table to the MAH
21. Receive confirmation of MAH attending oral explanation
22. Receive responses from MAH to LoOIs
23. Receive (Co)-Rapporteur's AR on responses
24. Remove confidential information
25. Send (Co)-Rapporteur's AR to MAH
26. Inform SAG secretariat if need to organise SAG meeting
27. Receive comments on AR
Continue with Step 28.


Continue from Step 27.
28. Same comments received by (Co-) Rapporteur?
no
28.1 Exchange any comments with (Co-) Rapporteur
yes
29. Is Opinion or further LoOIs necessary?
LoOIs
Go back to Step 15.
Opinion
30. Inform V-PD-DIS about up-coming translations
31. Prepare draft CHMP Opinion
32. Prepare draft time table for translations and draft letters
33. Provide comments on draft CHMP Opinion
34. Receive comments and update draft CHMP Opinion and AR
35. Update Early Notification Table. Prepare draft Product Specific Press Release and Q&A
36. Provide CHMP Secretariat with draft CHMP Opinion, AR, draft Press Release and Q&A
37. Attend CHMP and update Opinion and AR, if necessary
38. Send out Opinion
39. Check CHMP ToD and monthly report and comment, if necessary
Continue with Step 40.


Continue from Step 39.
40. Prepare update of EPAR and send to SH R-CP for comments
41. Comment on draft EPAR
42. Receive comments and update as necessary
43 Receive translation from V-PD-DIS and prepare publication
44. Receive copy of cover page for MF
END

9. Procedure

Step	Action	Responsibility
Before the start of procedure		
1	Receive letter from EC to the CHMP requesting an opinion according to Article 20 of Regulation (EC) No. 726/2004. Forward other documents received electronically (fax, e-mail, Eudralink) to the HoS P-R, SH R-CP PTL in H-SE and PTM-RA. Create subfolders in EDMS and save all documents received on CD-ROM in EDMS (see SOP/H/3193 Master Files for referrals and WIN/H/3107 Management of EDMS folders). Enter the procedure into SIAMED.	V-PD-BUS
2	Identify a Scientific Administrator to act as PTL and check possible conflicts of interest according to SOP/EMA/0101. Inform the PTL about the appointment and forward the documents received. Save letter in EDMS in the procedure subfolder (see SOP/H/3193 Master file for referrals). Inform the PTL for the product in HMDE. Inform the H-QM PTM, P-CI PTM, P-PV-RM PTM as appropriate.	SH-CP PTL
3	Inform the CHMP secretariat that the letter from EC needs to be added to the agenda of the CHMP meeting following the receipt of the letter. Provide CHMP secretariat with a copy of the letter from EC.	PTL
Start of procedure		
4	Attend the first CHMP discussion on the procedure. Discuss the draft LoQ and time table for the procedure with the Rapporteur and Co-Rapporteur. Liaise with PTM P-PV-RM in case the draft LoQ refers to risk management of safety concerns or if documentation submitted by MAH contains a RMP. Send draft LoQ (see template) to the CHMP secretariat for discussion at the CHMP. Following agreement with the (Co-) Rapporteur, send the time table to the CHMP secretariat for inclusion in the Table of Decision of the CHMP meeting. Liaise with the Compliance and Inspection (P-CI) Sector in case the Clinical Trials Falicitation Group (CTFG) needs to be contacted. Liaise with Medical Information on the preparation of "lines to take", if needed, in accordance with SOP/H/3347.	PTL
5	Include information about the start of procedure in the CHMP Press	D-ED

Step	Action	Responsibility
	Release.	
6	Prepare draft letter informing the MAH of the start of procedure (see template).	PTL secretary
7	After adoption by the CHMP send the LoQ and time table for the procedure to the MAH together with the letter informing the MAH of the start of procedure. Send the documents by Eudralink and check receipt of the documents by the MAH.	PTL
Receipt of responses to List of Questions		
8	Receive responses from the MAH to the LoQ. Inform the P-PV-RM about the receipt of responses, if applicable.	PTL
9	Receive (Co-)Rapporteur's assessment report(s) on the responses. Forward the report(s) to the PTL. Inform the P-PV-RM about the receipt of ARs if applicable.	V-PD-BUS PTL
10	Remove any confidential information (e.g. information on products not included in the procedure or unpublished data from the (Co-) Rapporteur(s) AR. Redact any confidential information (see WIN/EMA/0070 Redaction of Documents in relation to Access to Documents).	PTL
11	Send the (Co-)Rapporteur(s)' AR(s) to the contact person of the MAH by Eudralink and check receipt of documents by the MAH.	PTL
12	Receive comments on the (Co-)Rapporteur(s)' AR(s) from other CHMP members. Forward the comments to the PTL. Inform the P-PV-RM about the receipt of comments, if applicable.	V-PD-BUS PTL
13	Check with the (Co-)Rapporteur(s) whether they have received comments and if the comments received are the same. If yes to both, go to 14. If no to either, go to 13.1.	PTL
13.1	Send the (Co-)Rapporteur(s) any comments that they have not received and/or ask them to send any comments that have not yet been provided to the Agency. Continue with Step 14.	PTL
14	Discuss with the (Co-)Rapporteur(s) if a LoOIs will be needed and inform the CHMP secretariat accordingly.	PTL

Step	Action	Responsibility
	Discuss with the (Co-)Rapporteur(s) whether a Scientific Advisory Group (SAG) or an ad hoc Expert Meeting needs to be convened, and inform the CHMP secretariat accordingly. If no to both, go to 29. If yes to either, go to 15.	
List of Outstanding Issues		
15	Prepare/discuss with the (Co-)Rapporteur(s) the draft List of Outstanding Issues (LoOIs) and update the time table (including the number of active days). Discuss with the (Co-)Rapporteur whether there is a need for an oral explanation to the CHMP and incorporate if necessary the specific issues to be addressed at an oral explanation in the LoOIs. Liaise with PTM P-PV-RM in case the draft LoOIs refers to risk management of safety concerns or if documentation submitted by MAH contains a RMP. Send the draft LoOIs and time table to the (Co-)Rapporteur(s) for comments.	PTL
16	Receive comments from the (Co-)Rapporteur(s) on the draft LoOIs, the draft list of questions for the SAG/ ad hoc Expert Meeting if relevant and updated time table. Amend the documents accordingly.	PTL
17	Provide the CHMP secretariat with the draft LoOIs, list of questions for the SAG/ ad hoc Expert Meeting if relevant, and updated time table for discussion at the CHMP.	PTL
18	Attend the CHMP meeting and adoption of the list of attendees for the SAG/ ad hoc Expert meeting if relevant. Update the CTFG on the status of the procedure in liaison with the P-CI Sector, if applicable. Revise the draft LoOIs, list of questions for the SAG/ ad hoc Expert Meeting if relevant, and time table if necessary and send the revised documents to the CHMP secretariat for inclusion in the Table of Decision of the CHMP meeting.	PTL
19	Prepare the letter informing the MAH about the LoOIs and in case of an oral explanation to the CHMP was deemed necessary, include the part of the template letter which gives information on the oral explanation (see template). Inform the CHMP secretariat about the need for an oral explanation.	PTL secretary
20	Send LoOIs to the MAH together with the updated time table for the procedure. Inform the MAH about the adoption of a list of	PTL

Step	Action	Responsibility
	questions for a SAG/ ad hoc Expert Meeting if relevant. Send the documents by Eudralink and check receipt of documents by the MAH.	
21	Receive information whether or not the MAH will attend the oral explanation, if applicable. Inform the CHMP secretariat accordingly.	PTL
22	Receive responses from MAH to the LoOIs. Inform the P-PV-RM about the receipt of responses, if applicable.	PTL
23	Receive (Co-)Rapporteur's assessment report(s) on the responses. Forward the report(s) to the PTL. Inform the P-PV-RM about the receipt of assessment reports, if applicable.	V-PD-BUS PTL
24	Remove any confidential information (e.g. information on products not included in the procedure or unpublished data) from the Rapporteur(s)' AR(s). Redact any confidential information (see WIN/EMA/0070 Redaction of Documents in relation to Access to Documents).	
25	Send the (Co-)Rapporteur(s)' AR(s) to the contact person of the MAH by Eudralink and check receipt of documents by the MAH.	PTL
26	If applicable, inform the SAG secretariat about the need to organise a SAG meeting according to SOP/H/3129. Forward the (Co-)Rapporteur(s)' AR(s) to the SAG/ ad hoc Expert Meeting Members if applicable in preparation of the meeting, if applicable.	PTL
27	Receive comments on the (Co-)Rapporteur(s)' AR(s) from other CHMP members. Forward the comments to the PTL. Send comments on the Rapporteur(s)' AR in relation to the risk management plan to the PTL. Inform the P-PV-RM about the receipt of comments on the Rapporteur(s)' AR from other CHMP members, if applicable.	V-PD-BUS PTM-RM PTL
28	Check with the (Co-)Rapporteur(s) whether they have received comments and if the comments received are the same . If yes to both, go to 29. If no to either, go to 28.1.	PTL

Step	Action	Responsibility
28.1	Send the (Co-)Rapporteur(s) any comments that they have not received and/or ask them to send any comments that have not yet been provided to the Agency.	PTL
29	Ensure that comments are received prior to discussion at CHMP i.e. PTL will contact at the latest by the Wednesday prior to the CHMP week all CHMP Members who did not yet reply by the agreed deadline in order to obtain their feedback. Adress the status of the comments to the CHMP Chairman and Vice -Chairman during the pre-meeting teleconference. Send the minutes of the SAG/ ad hoc Expert meeting to the (Co-) Rapporteur(s). Liaise with the (Co-)Rapporteur(s) to discuss whether the procedure is going for an opinion (and if appropriate clarify the grounds for subsequent lifting of the suspension)or for a further LoOIs. If applicable discuss whether the (Co-)Rapporteur(s) will circulate updated (Co) Rapporteur's assessment report(s) to consider the SAG/ ad hoc Expert meeting outcomes. If a further LoOIs is necessary, go back to 15. If an opinion is foreseen, go to 30.	PTL
30	Inform V-PD-DIS about up-coming translations (Annex II and IV).	PTL secretaries
Opinion		
31	Prepare draft CHMP opinion including the scientific grounds and the revised product information and grounds for lifting the suspension, if applicable, and assessment report. Provide the RA-PTM, SH R-CP, the product PTL from H-SE and as applicable the PTM from H-QM, P-CI or P-PV-RM with the draft documents for review at the latest by the Wednesday the week before the CHMP.	PTL
32	Prepare draft time table for translations and draft letters for sending out the opinion (see templates and Action list for product secretaries).	PTL secretary
33	Provide comments on the draft CHMP opinion and assessment report at the latest by Friday the week before CHMP. Provide comments on the draft CHMP opinion and assessment report at the latest by Friday the week before CHMP if applicable.	RA-PTM, HS R-CP, product PTL H-SE PTM H-QM, PTM P-CI, PTM P-PV-RM
34	Receive comments from PTM-RA and SH R-CP.	PTL

Step	Action	Responsibility
	Update draft CHMP opinion and assessment report as necessary.	
35	Update the Early Notification table (see SOP/H/3346) and attend the Product Oversight Meeting.	PTL
	Prepare draft product specific press release (according to SOP/EMA/0111).	D-ED
	Prepare draft Q&A document (according to SOP/EMA/0111).	P-MI
36	Provide CHMP secretariat with draft CHMP opinion and AR.	PTL
	Provide CHMP secretariat with the draft product specific press release and Q&A for discussion at the CHMP.	
37	Attend the CHMP during which the Chairman of the SAG/ ad hoc Expert meeting will present the outcomes of the SAG/ ad hoc Expert meeting (if applicable). Attend oral explanation(s) if applicable.	PTL
	Attend the discussion of the Direct Healthcare Professional Communication (DHPC) at the PhVWP and adoption at the PhVWP followed by adoption at the CHMP.	
	Update Opinion and AR as needed to reflect the discussion and the oral explanation if applicable, the voting and any divergent positions.	
	Update the CTFG on the status of the procedure in liaison with the P-CI Sector, if applicable.	
	Send revised documents to the CHMP secretariat for adoption at the CHMP.	
Post opinion and decision making phase		
38	Send out the opinion to the MAH and EC and check receipt of documents by the MAH (see WIN/H/3145 Sending out document to Applicant - MAHs in the context of referrals).	PTL secretaries
39	Check the CHMP Table of Decision and Monthly report and provide comments if necessary.	PTL
	Update the CTFG on the practical aspects of the outcome of the procedure in liaison with the P-CI Sector, if applicable.	
40	Prepare update of EPAR including preparation for publication of the scientific conclusions (Annex IV of the opinion).	PTL
	Send it to SH R-CP for comments.	
41	Comment on the draft EPAR update.	SH R-CP
42	Receive comments on the draft EPAR update and revise as necessary.	PTL

Step	Action	Responsibility
43	Receive translations from the V-PD-DIS. Prepare documents for publication (see WIN/H/3205 Publication of Post-authorisation Unit Referrals). Liaise with product PTL in H-SE regarding the publication. If the EPAR needs to be updated following other procedures than the Article 20 the document are sent to the PTL. In case no other procedures need to be included in the update the documents are sent for publication and the product PTL is included on the sign-off slip. Prepare folder and sign off slip.	PTL secretary
44	Receive copy of cover page for the master file from V-PD-BUS (see SOP/H/3193 Master file for referrals). Check that the relevant documents have been included in the MF as indicated in the table of contents. In case documents are missing, forward these for filing to V-PD-BUS. Sign off the copy of the table of contents and return it to V-PD-BUS.	PTL

10. Records

The PTL is to forward the documents in hard copy to V-PD-BUS as set out in SOP/H/3193. V-PD-BUS will file the documents in the Master File.

MFs for ongoing procedures are stored in the V-PD-BUS office or the secured V-PD-BUS storage room. Archived MF are stored off-site. Working Files (WF) for ongoing procedures are stored in or near the office of the PTL.

Hard paper copies are filed in the MF and/or WF. Original documents are stored in the MF and not in the WF.

Electronic files are stored in the concerned procedure folder in EDMS or on an EMA server. Both attachments and the Eudralink/email cover notes must be saved. When saving Eudralink messages the type "Webpage, html only" must be chosen when saving as the message will otherwise not be readable after expiry of the period of time in which the package can be collected.