EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Orphan medicinal product designation and amendment of an existing orphan medicinal product designation		
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1. Purpose

To describe the procedure for validating and evaluating applications for orphan medicinal product designation.

2. Scope

This SOP applies to the Orphan Medicines Office in the **Product Development Scientific Support Department.**

3. Responsibilities

It is the responsibility of each Service/Office Head to ensure that this procedure is adhered to within their Service/Office. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 9.

4. Changes since last revision

- Sponsors are not required to send a notification of intent to file an orphan drug application for designation, following recommendations from the Review & Reconnect exercise that took place during the course of 2014. As a result all the steps related to the notification of intent to file have been deleted.
- Co-ordinators will be nominated after the submission of an application (steps 6-7).
- Negative opinion should be sent to legal team for final review (step 47).

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- Introduction of Unique Product Identifier number (step 6).
- Title changed. Old title 'Orphan medicinal product designation'.

5. Documents needed for this SOP

Template 1a: Pre-submission meeting - invitation to sponsor (available at X:\Templates\Others\OD Pre COMP)

Template 1b: Pre-submission meeting internal meeting request (available at X:\Templates\Others\OD Pre COMP)

Template 1c: Minutes of pre-submission meeting (available at X:\Templates\Others\OD Pre COMP)

Template 2a: Applications for appointment of coordinators (available at X:\Templates\Others\OD Database)

Template 2c: Evaluation of conflict of interest of EMA coordinators appointed for OMP designation applications (available at X:\Templates\Others\OD Database)

Template 2d: Initial correspondence with Expert (available at X:\Templates\Others\OD Pre COMP)

Template 3b: Sponsors informed of change of co-ordinator (available at X:\Templates\Others\OD Pre COMP)

Template 4: OMP application receipt confirmation (available at X:\Templates\Others\OD Pre COMP)

Template 5: Validation checklist (available at X:\Templates\Others\OD Pre COMP)

Template 6a: Validation issues letter (available at X:\Templates\Others\OD Pre COMP)

Template 6b: Outcome of validation - validation issues letter cover message (available at X:\Templates\Others\OD Pre COMP)

Template 7: Follow-up on OMP designation application under validation (available at X:\Templates\Others\OD Pre COMP)

Template 8: Outcome of validation (available at X:\Templates\Others\OD Pre COMP)

Template 9a: Summary report (available at X:\Templates\Others\OD Database)

Template 9b: COMP coordinator's /expert's comments (available at X:\Templates\Others\OD Pre COMP)

Template 9c: COMP Readers' guidance (available at X:\Templates\Others\OD Pre COMP)

Template 10: LoQ to sponsor – Eudralink message (available at X:\Templates\Others\OD COMP)

Templates 11a – 11d: Opinions (available at X:\Templates\Others\OD Database)

Template 12: Positive opinion and summary report to sponsor (available at X:\Templates\Others\OD Post COMP)

Template 13: Negative opinion and summary report to sponsor (available at X:\Templates\Others\OD Post COMP)

Template 14: Final negative opinion to EC - no grounds received (available at X:\Templates\Others\OD Post COMP)

Template 15a: Opinion to EC (available at X:\Templates\Others\OD Post COMP)

Template 15b: Translations to EC (available at X:\Templates\Others\OD Post COMP)

Template 16: Opinion and summary report to sponsor after appeal (available at X:\Templates\Others\OD Post COMP)

Template 17: Opinion to EC after appeal (available at X:\Templates\Others\OD Post COMP)

Template 18: Sponsor notified of final opinion to EC (available at X:\Templates\Others\OD Post COMP)

Template 19: Opinions to Iceland and Norway – Eudralink message (available at X:\Templates\Others\OD Post COMP)

Template 20: Product information sheet (available at X:\Templates\Others\OD Post COMP)

6. Related documents

Regulation (EC) No 141/2000 of the European Parliament and of the Council of of 16 December 1999 on orphan medicinal products.

All regulatory, procedural guidance and forms are available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000268.jsp&mid=WC0b01ac058061f01c

In addition the following SOPs and WIN are consulted.

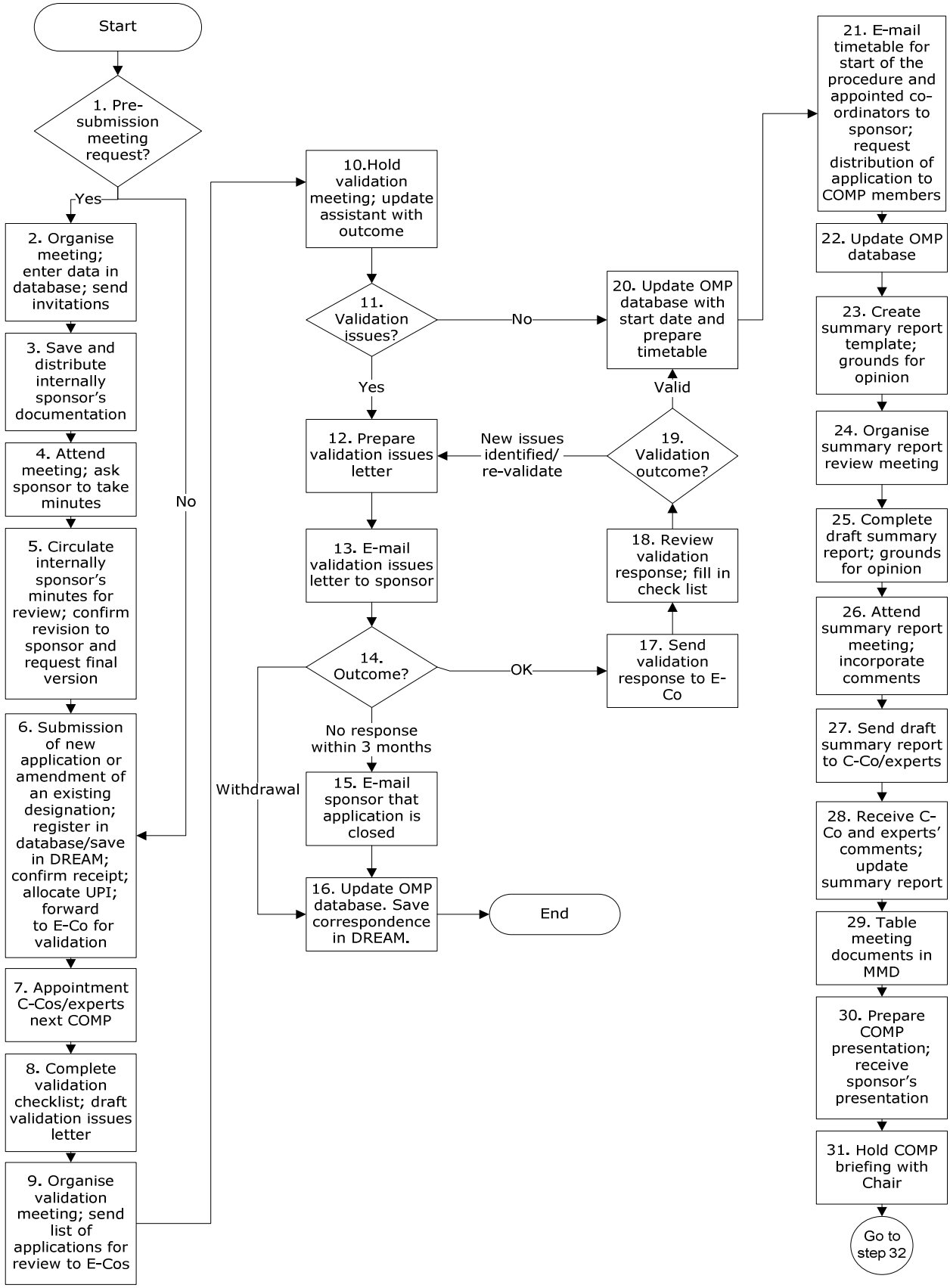
- SOP/EMA/0040: Evaluation of conflicts of interests of experts for involvement in EMA activities
- SOP/EMA/0101: Conducting checks for conflicts of interest of Agency employees assigned duties relating to medicinal products for human or veterinary use
- SOP/H/3018: Preparation and publication of COMP monthly report
- SOP/H/3046: Preparation of the public summary of opinion for orphan medicinal product designation
- WIN/H/3047: Checking-in and electronic filing of documentation for orphan medicinal product designation

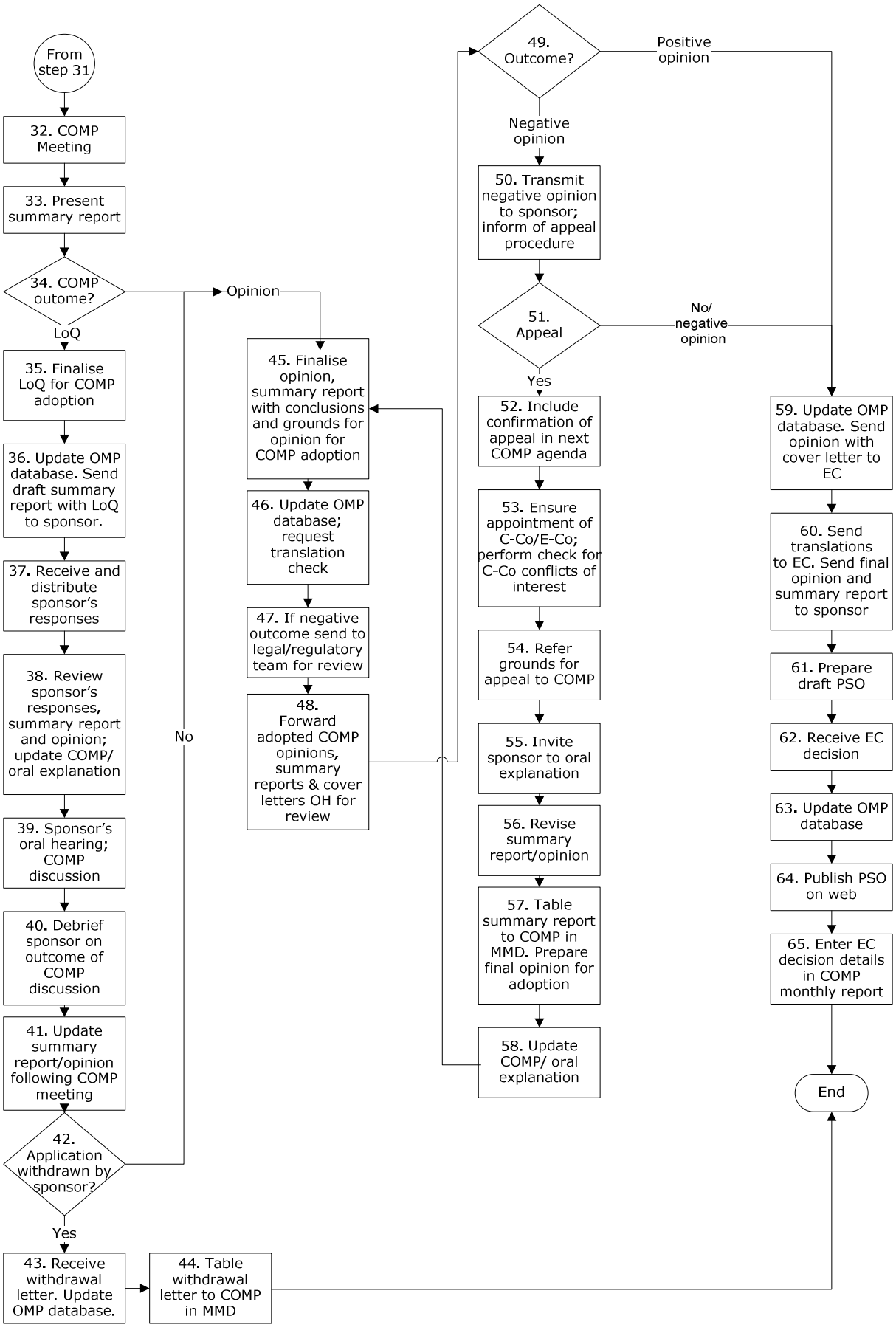
7. Definitions

C-Co:	COMP coordinator
COMP:	Committee for Orphan Medicinal Products
DREAM:	Document records electronic archive management system
E-Co:	EMA coordinator
EC:	European Commission
Eudralink:	System for secure transmission of e-mails and documents
LoQ:	List of questions
MMD:	Managing meeting documents
OMP:	Orphan medicinal product

Paed-Co:	Paediatric coordinator (scientific officer in PME)
PME:	Paediatric Medicines Section
PSO:	Public summary of opinion
OH:	Office Head
SO:	Scientific officer
UPI:	Unique product identifier

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




From step 31
32. COMP Meeting
33. Present summary report
34. COMP outome?
Opinion
LoQ
35. Finalise LoQ for COMP adoption
36. Update OMP database. Send draft summary report with LoQ to sponsor.
37. Receive and distribute sponsor's responses
38. Review sponsor's responses, summary report and opinion; update COMP/ oral explanation
39. Sponsor's oral hearing; COMP discussion
40. Debrief sponsor on outcome of COMP discussion
41. Update summary report/opinion following COMP meeting
42. Application withdrawn by sponsor?
No
Yes
43. Receive withdrawal letter. Update OMP database.
44. Table withdrawal letter to COMP in MMD
45. Finalise opinion, summary report with conclusions and grounds for opinion for COMP adoption
46. Update OMP database; request translation check
47. If negative outcome send to legal/regulatory team for review
48. Forward adopted COMP opinions, summary reports & cover letters OH for review
49. Outcome?
Positive opinion
Negative opinion
50. Transmit negative opinion to sponsor; inform of appeal procedure
51. Appeal
No/ negative opinion
Yes
52. Include confirmation of appeal in next COMP agenda
53. Ensure appointment of C-Co/E-Co; perform check for C-Co conflicts of interest
54. Refer grounds for appeal to COMP
55. Invite sponsor to oral explanation
56. Revise summary report/opinion
57. Table summary report to COMP in MMD. Prepare final opinion for adoption
58. Update COMP/ oral explanation
59. Update OMP database. Send opinion with cover letter to EC
60. Send translations to EC. Send final opinion and summary report to sponsor
61. Prepare draft PSO
62. Receive EC decision
63. Update OMP database
64. Publish PSO on web
65. Enter EC decision details in COMP monthly report
End

9. Procedure

Notes:

- Declaration of interests are checked and evaluated for all staff and experts before involvement according to SOP/EMA/0101 and SOP/EMA/0040 listed under "Related documents".
- All messages containing confidential information must be sent via EudraLink.
- All procedural timelines and application guidance are published on the EMA website.
- Orphan drugs database is updated at all different stages of the procedure and after each COMP plenary with procedural timelines including actual adoption dates.

Step	Action	Responsibility
	Pre-submission	
1	Receive request for pre-submission meeting, go to step 2. No request for pre-submission meeting, go to step 6	Assistant
2	Organise pre-submission meeting. Invite sponsor (use Template 1a with attached Template 1c) and internal participants (use Template 1b). Send invitation to SOs and paediatric team to decide if the involvement of a Paed-Co is needed. Include DREAM link in meeting invite. Enter product data on the OMP database.	Assistant
3	Receive pre-submission meeting documents from the sponsor. Save in DREAM Cabinets/01 Evaluation of Medicines H-O Orphan Drugs/Potential Applicants/Pre Submission Meetings and send link to internal participants.	Assistant
4	Participate in pre-submission meeting and take notes on issues raised. Request sponsor to take minutes of meeting and to send them (using Template 1c) to orphandrugs@ema.europa.eu for review.	Orphan SOs + Paed
5	Receive minutes from sponsor, save in DREAM and send link to relevant SOs for review. Review minutes in track changes. Save in DREAM as next version and inform Assistant. Confirm revision of minutes to sponsor and request final version if comments were made. Save final version in DREAM.	Assistant Orphan SOs + Paed Assistant
	Submission	
6	Receive submission of application for orphan medicinal product designation or amendment of an existing orphan medicinal product	Assistant

Step	Action	Responsibility
	designation.	
	Register application. Save in DREAM and send link to E-Co for validation (see WIN/H/3047).	Assistant Assistant
	Acknowledge receipt to sponsor (Template 4). Allocate UPI number and update OMP database. Verify appointment of E-Co taking into account requirements from SOP/EMA/0101.	Assistant Assistant OH
7	Prepare line listing of new applications received for the corresponding submission deadline and link to the meeting folder for appointment of C-Co, and if applicable experts, at the next COMP meeting (use Template 2a). Verify that no restrictions are applicable to the C-Co for assessment of the application in accordance with SOP/EMA/0040.	Assistant COMP Secretariat
	Validation	
8	Validate the application. Fill in the validation checklist and save in DREAM in relevant product folder (use Template 5). Prepare, if needed, a draft validation issues letter outlining specific issues to be addressed by the sponsor (use Template 6a). Save letter in DREAM in relevant folder.	E-Co
9	Organise internal validation meeting, in accordance with the procedural timetable and send list of applications to be reviewed to E-Cos. Send list of applications to Paed-Co as well.	Assistant
10	Internal review and discussion of all applications, which are under validation in accordance with the procedural timetables. Discussion of draft validation issues letters and agreement on the issues to be addressed by the sponsors. Discuss relevant applications to address potential disharmony with PIP. Inform Assistant of the validation meeting outcome for all applications.	All E-Cos
11	Where validation issues arise, go to step 12. If no validation issues are raised, go to step 20.	E-Co Assistant
12	Prepare validation issues letter (use Template 6a). Identify the issue, state what the applicant has provided and what is expected instead.	E-Co

13	Send by Eudralink validation issue letter (as PDF) to sponsor requesting response within 3 months (use Template 6b). Save Eudralink message in DREAM, in relevant product folder (Validation).	Assistant
14	If no response is received within 3 months of sending validation letter, go to step 15. If applicant withdraws application, go to step 16. If validation response is received, go to step 17.	Assistant
15	Send e-mail to applicant informing that at this stage application is considered closed (Template 7) and go to step 16.	Assistant
16	Update OMP database. File correspondence in product folder (Validation) in DREAM. End of procedure.	Assistant
17	Save validation response in DREAM and send link to E-Co (see WIN/H/3047).	Assistant
18	Review validation response. Confirm that all issues raised in the validation issues letter have been addressed. If not, prepare a follow-up validation issues letter, and save in DREAM. Fill in further validation checklist (Template 5), save in DREAM.	E-Co
	Start of Procedure	
19	Validation outcome If valid, go to step 20. If not valid, go to step 12. *Note: Validation dates (day 1, start of procedure) are fixed on an annual basis to synchronise each evaluation with COMP meetings.*	 Assistant E-Co
20	Allocate the next procedure start date and corresponding procedural timetable to application.	Assistant
21	E-mail confirmation of completion of validation and appointed co-ordinators to sponsor with timetable and requesting sponsor to send complete application to all COMP members (copy to C-Co) (use Template 8).	Assistant
22	Update OMP database.	Assistant

	Evaluation - Preparation of Summary Report	
23	Create and save summary report template 9a in relevant product folder in DREAM (Evaluation) and link to the meeting folder	Assistant
24	Organise internal meeting to review quality and consistency of draft summary reports, approximately 1 day before deadline for circulation of summary reports to COMP, in accordance with procedural timetables.	Assistant
25	Draft summary report for internal review meeting. Present a short critical review of the level of evidence and justifications presented by the sponsor to justify the criteria for designation. Draft grounds for opinion for discussion and possible adoption by COMP as needed.	E-Co
26	Participate in summary report meeting and incorporate comments in summary report (internal peer review).	All E-Co
27	Send draft summary report via Eudralink to the C-Co asking for comments (attach Template 9b) prior to the deadline for circulation to COMP. If needed also send it to expert(s) using the same template. Save Eudralink messages in relevant product folder in DREAM.	E-Co
28	Receive comments from C-Co and expert(s), save in DREAM and attach to the summary report. If appropriate revise draft summary report.	E-Co
29	Send deadline to Orphan Medicines Office for checking in all meeting documents and table them in MMD from meeting folders where documents are linked (always 14 days prior to the meeting) Inform COMP members via e-mail (first pre-mail) that documents are tabled Save message in relevant COMP meeting folder in DREAM. Repeat the step for the second pre-mail approximately 2 working days prior to the meeting and the post-mail approximately one week after the meeting.	COMP Secretariat
30	Prepare presentation to COMP and save in relevant product folder in DREAM. Receive from sponsor presentation and list of participants for the oral hearing. Saved in DREAM and link presentation to the meeting folder. Forward information to COMP Secretariat.	E-Co Assistant

	Evaluation – COMP discussion	E-Co
31	Attend COMP briefing with Chair.	Orphan Medicines Office and COMP Secretariat
32	Attend COMP meeting.	Orphan Medicines Office
33	COMP meeting presentation of summary report together with C-Co.	E-CO
34	If COMP raises formal questions for sponsor to respond to, go to step 35. If a positive opinion may be adopted directly, go to step 45.	E-Co
35	Finalise list of questions in section 3 of draft summary report following COMP discussion, in collaboration with C-Co. Present to the COMP for adoption.	E-Co
36	Update OMP database. Format draft summary report, save with version label "list of questions". Forward to relevant sponsor by Eudralink, with deadline for submission of responses approximately two weeks prior to next COMP meeting. If applicable, include invitation to an oral explanation (use Template 10) asking the sponsor to submit the oral hearing presentation and list of participants (if applicable) approximately 4 days prior to the meeting.	Assistant
37	Receive responses from sponsor and save in DREAM in relevant product folder. Send DREAM link to relevant E-Co and forward the response to COMP co-ordinator for comments (Template9c). Insert responses in the summary report, save with version label 'with response to list of questions'.	Assistant
38	Review sponsor's responses, in close liaison with C-Co and expert(s) (if applicable), summary report and opinion. Update COMP at next meeting / oral explanation by the sponsor.	E-Co
39	Participate in oral hearing with sponsor. Take part in discussion with the COMP after oral hearing. Recapitulate the main points of the COMP discussion ahead of debriefing the applicant.	E-Co
40	Debrief sponsor on the outcome of the COMP discussion.	E-Co
41	Update summary report (report dated by day of opinion adoption) and opinion in collaboration with C-Co following COMP discussion and oral explanation (if applicable).	E-Co

42	If sponsor chooses to withdraw application prior to opinion, go to step 43. If sponsor does not withdraw application, go to step 45.	Assistant
43	Receive withdrawal letter and save in product folder in DREAM insert withdrawal request in the summary report and save with label "Withdrawn" Update OMP database and inform COMP Secretariat (in order to reflect in Minutes of meeting).	Assistant
44	Table summary report for post-mail in MMD for COMP information. End of procedure.	Assistant
	Opinion	
45	Finalise opinion according to summary report (use appropriate Template 11). Finalise summary report with conclusions and grounds for opinion to be adopted at the COMP meeting. Co-ordinate adoption by COMP.	Assistant E-Co
46	Update OMP database and request check of translation of indication and active substance (use Template 15b) and grounds of negative opinion, if performed after appeal.	Assistant
47	In case of negative opinion, send to the legal and regulatory team for review.	Assistant
48	Finalise all summary reports including withdrawn applications and perform quality and consistency check. Perform final formatting of opinion and summary report and forward with cover letters to EC and sponsor to Office Head for final check.	E-Co Assistant
49	If COMP opinion is negative, go to step 50. If COMP opinion is positive notify sponsor's contact person by e-mail of COMP outcome, go to step 59.	Assistant
	Appeal	Assistant
50	Forward to sponsor negative opinion together with a copy of EMA/COMP summary report by recorded courier with delivery date/time. Inform sponsor of appeal procedure and deadline for submission of appeal documentation, i.e. 90 calendar days from receipt of opinion (use Template 13). Do not forward negative opinion to the EC pending possible appeal by sponsor.	Assistant
51	If sponsor intends to appeal, go to step 52. If sponsor confirms in writing intention not to appeal notify by e-	E-Co

	mail that the final negative opinion is being transmitted to the EC (use template 18), go to step 59.	
52	Include confirmation of intent to appeal in next COMP agenda.	Assistant
53	Ensure appointment of new C-Co by the COMP and discussion on involvement of additional experts if necessary. Verify that no restrictions are applicable to the C-Co/expert(s) for assessment of the application in accordance with SOP/EMA/0040. If appropriate, appointment of new E-Co. Verify appointment taking into account requirements from SOP/EMA/0101.	COMP Secretariat OH
54	Following receipt of grounds for appeal, inform the COMP Secretariat to include the topic in the agenda of the COMP first meeting following receipt. Save in DREAM and link to the meeting folder grounds for appeal.	Assistant COMP Secretariat
55	Invite sponsor to oral explanation at COMP meeting following receipt of grounds for appeal.	Assistant
56	Revise summary report in association with C-Co, save in DREAM with version label "appeal".	E-Co
57	Table revised summary reports in MMD for next COMP meeting. Prepare final opinion for adoption by COMP at first meeting following appeal referral (use relevant Template 11).	Assistant
58	Update COMP at meeting/ oral explanation by sponsor Repeat steps 45 to 48 for adoption and finalisation of opinion and summary report.	E-Co
	Post final opinion	
59	Update OMP database and inform the sponsor about the positive outcome by email. Send final opinion with cover letter to EC via Eudralink (Template 14, 15a or 17 after appeal).	Assistant
60	Following finalisation of translation check send translation (Template 15b) to EC via e-mail. Send final opinion (PDF) and final summary report (PDF) to sponsor via Eudralink (with version label "adopted" and dated by day of COMP opinion). (Template 12 or 16 after appeal). Send final opinions (PDF) to the COMP members of Iceland and Norway (Template 19).	Assistant
61	Collaborate with medical writers for drafting of PSO (see SOP/H/3046).	Assistant

	Post designation	
62	On receipt from EC of Eudralink message with adoption fax and link to EC decision, save both in DREAM (see WIN/H/3047).	Assistant
63	Update OMP database.	Assistant
64	Transmit PSO and Prodcut information sheet (template 20) to Webteam for publication (see SOP/H/3046).	Assistant
65	Enter details of EC decisions on designations in annex to next COMP monthly report (see SOP/H/3018).	COMP Secretariat

9. Records

- Pre-submission documentation is saved in Cabinets/14. Unit working areas/14.2 Human Medicines Development and Evaluation/03. H-HM Activities/H-HM-OM/Section activities/Potential Applicants//Pre Submission Meetings folder.
- All remaining records produced from this SOP are stored in accordance with WIN/H/3047.