EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Review of orphan designation at the time of granting/varying a marketing authorisation		
Status: **Public**		Document no.: SOP/H/3190
Lead author	Approver	Effective date: 4-OCT-17
Name: Agnieszka Wilk-Kachlicka	Name: Kristina Larsson	Review date: 4-OCT-20
Signature: On File	Signature: On File	Supersedes: SOP/H/3190 (9-FEB-16 TW 4642)
Date: 4-OCT-17	Date: 4-OCT-17	TrackWise record no.: 5355

1. Purpose

This SOP describes the procedure for reviewing the orphan designation at the time of the initial authorisation of an orphan medicinal product, or an extension of indication for a designated orphan product with a new orphan condition. The procedure runs in parallel with the adoption of the opinion by the CHMP and the granting of or variation to a marketing authorisation by the European Commission.

2. Scope

This SOP applies to:

- Scientific Committees Secretariat Service in Committees and Inspections Department in Inspections, Human Medicines Pharmacovigilance and Committees Division
- Legal Department
- Medical and Health Information Service in Communication Department in Stakeholders and Communication Division
- Orphan Medicines Office in Product Development Scientific Support Department in Human Medicines Research and Development Support Division
- Procedure Management Department in Human Medicines Evaluation Division
- Product and application Business Support Service, Business Data and Analytics Department in Information Management Division
- Regulatory Affairs Office in Regulatory Affairs Office in Regulatory, Scientific and Regulatory Management Department in Human Medicines Evaluation Division

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

3. Responsibilities

It is the responsibility of each Head of Office/Service to ensure that this procedure is adhered to within their office/service. 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

- Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03) replaces the Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (2003/C 178/02).
- Introduction of new steps for review of orphan designation at the time of extension of authorised indication within the same orphan condition.
- Replacing publication of summary of the COMP opinion with publication of an orphan maintenance assessment report.
- Sending review report in addition to the COMP opinion to the EC.
- Introduction of core documents e-flow system using DREAM labelling and versioning as per WIN/H/3047.

5. Documents needed for this SOP

- All templates are available on X:\Templates\Others\H - Orphan medicines.
- Templates for COMP co (4a and 4b) are available also in MMD: COMP/MMD/General/Templates.

Template 1a – Review of OD - advice on procedure for SOC variation

Template 1b – Review of OD - request for report on maintenance of OD

Template 1c – Review of OD - request for report on maintenance of OD for SOC variation

Template 1d - Review of OD - request for updated report on maintenance of orphan designation

Template 2a - Review of OD - report on maintenance of orphan designation - receipt confirmation

Template 2b - Review of OD - notification to sponsor - no review for SOC

Template 3a - Review of OD - EMA-COMP report

Template 3b - Review of OD - presentation

Template 3c - Review of OD - messages for sending LoQ and invitation to OE

Template 4a - Review of OD - COMP cos-experts comments

Template 4b – Review of OD - COMP co-experts reader's guidance

Template 5a - Review of OD - positive opinion

Template 5b - Review of OD - negative opinion

Template 5c - Review of OD - positive opinion after appeal

Template 5d - Review of OD - negative opinion after appeal

Template 6a - Review of OD - opinion to EC

Template 6b - Review of OD - opinion to sponsor

Template 6c - Review of OD - negative opinion to sponsor

Template 6d - Review of OD - notification to sponsor on final negative opinion

6. Related documents

- SOP/H/3049 on orphan medicinal product designation
- SOP/H/3372 on preparation of an Orphan Maintenance Assessment Report (OMAR)
- WIN/H/3047 on orphan DREAM product folders
- Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)

  http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN
- Procedural advice

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp&mid=WC0b01ac058061f019
- Sponsor's report on the maintenance of the designation criteria at the time of marketing authorisation application for a designated orphan medicinal product (template):

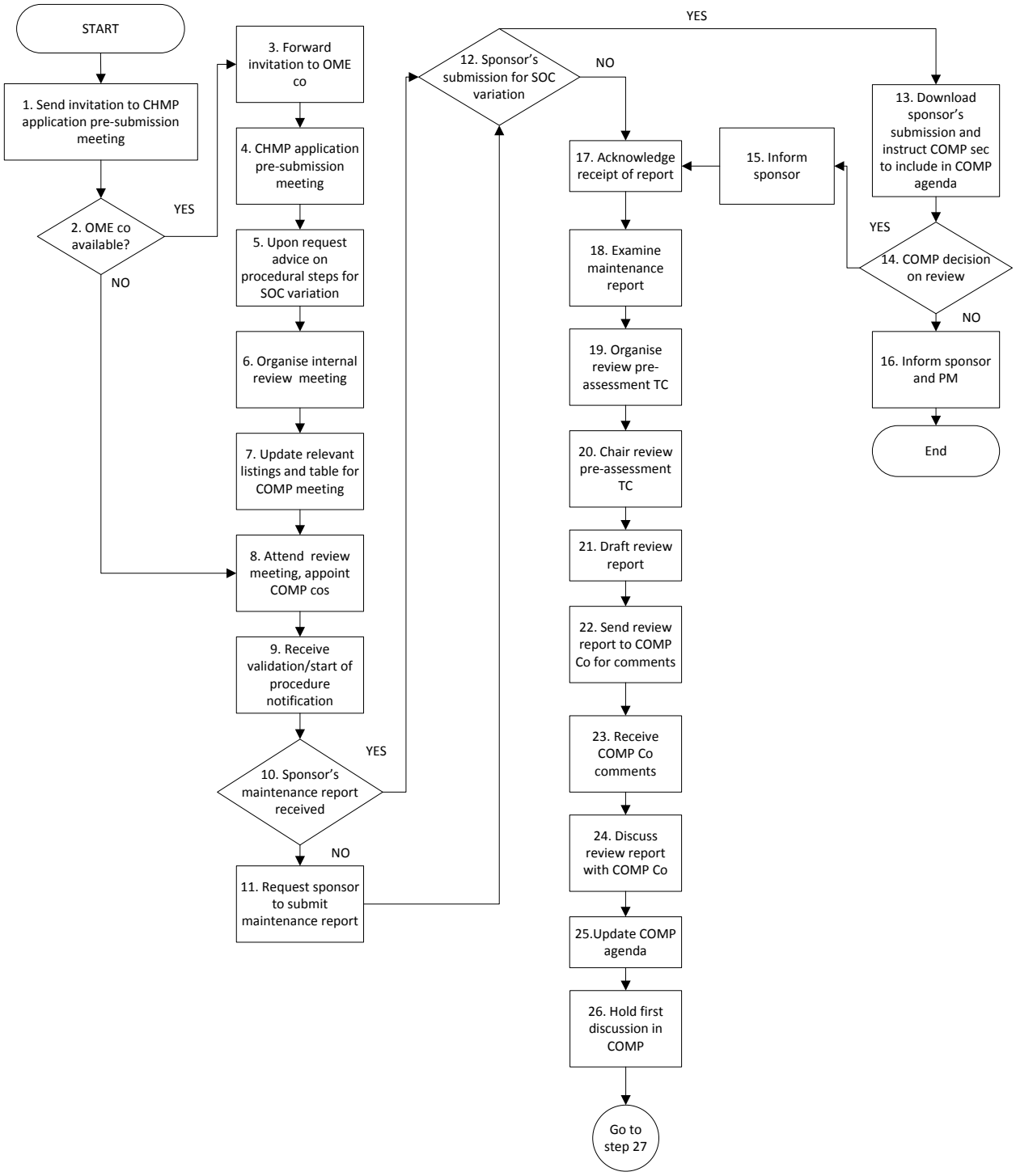
  http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500181764

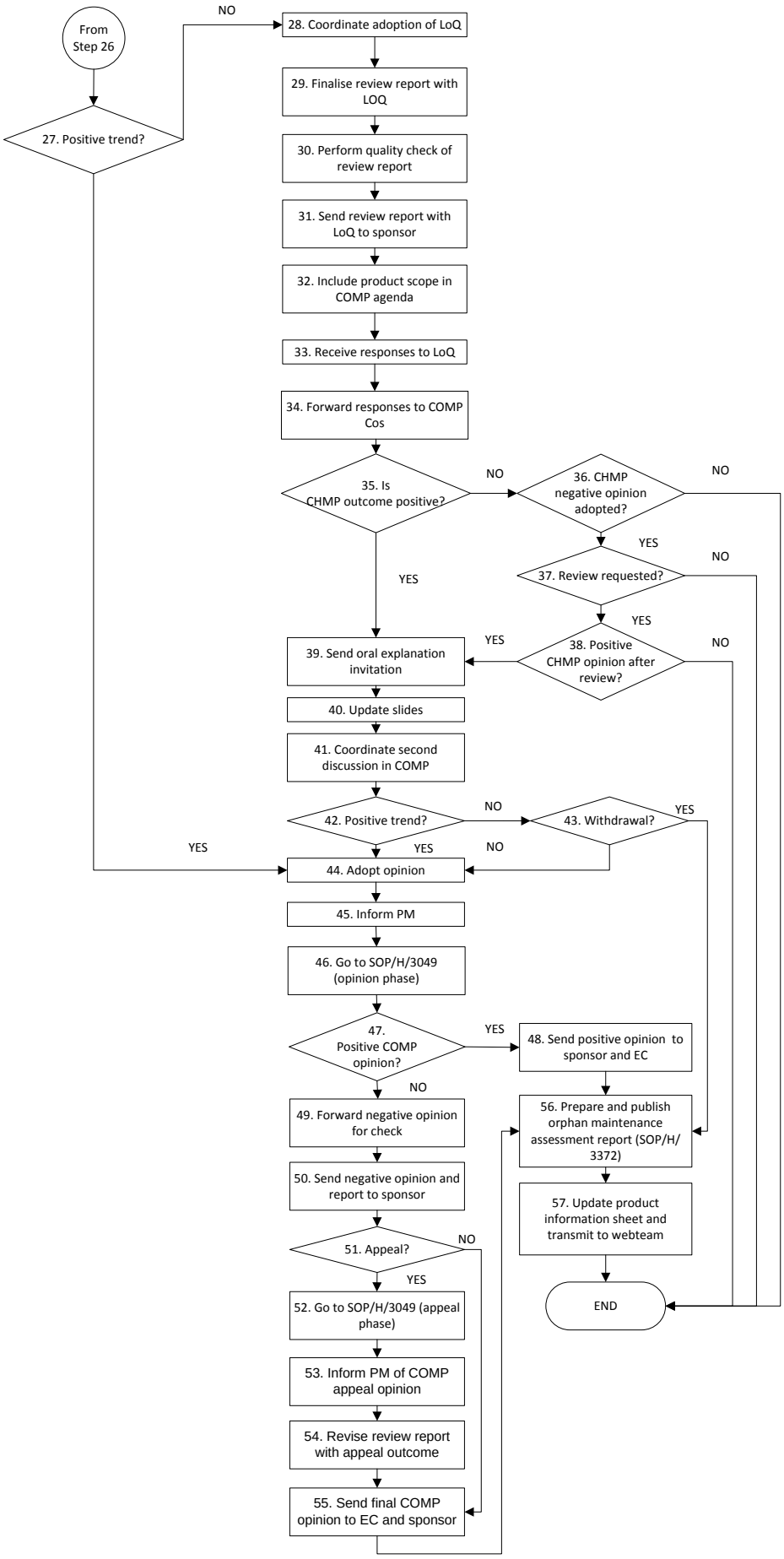
7. Definitions

AF-LD	Legal Department
CHMP	Committee for Medicinal Products for Human Use
CHMP application	In the context of this SOP, use of the term applies to the initial marketing authorisation application or to an extension of indication
COMP	Committee for Orphan Medicinal Products
COMP co	COMP co-ordinator
COMP Sec	COMP Secretariat (in P-CI-SCS)
D-DS-OME	Orphan Medicines Office in Product Development Scientific Support Department in Human Medicines Research and Development Support Division
DREAM	Document records electronic archive management
EC	European Commission
E-PM	Procedure Management Department in Human Medicines Evaluation Division
E-PM-EPB	Evaluation Procedures B service, Procedure Management Department in Human Medicines Evaluation Division

E-SR-REA	Regulatory Affairs Office in Regulatory, Scientific and Regulatory Management Department in Human Medicines Evaluation Division
EudraLink	The European medicines regulatory network's secure file-transfer system used for exchanging information for regulatory purposes
I-BD-BUS	Product and application Business Support Service, Business Data and Analytics Department in Information Management Division
LoQ	List of questions
MA	Marketing authorisation
MHI writer	Medical writer (in S-CO-MHI)
MMD	Managing meeting documents system
NOC variation	Extension of authorised indication to a new orphan condition (210 days)
OME Asst	Assistant (in D-DS-OME)
OME co	Co-ordinator (scientific officer in D-DS-OME)
OME HoO	Head of Orphan Medicines Office (in D-DS-OME)
OME line listing	Tabular information on MAA application for orphan medicines prepared by D-DS-OME updated monthly and tabled in MMD for COMP meetings
P-CI-SCS	Scientific Committees Secretariat Service in Committees and Inspections Department in Inspections, Human Medicines Pharmacovigilance and Committees Division
PM	Product manager (in E-PM)
RG	COMP co reader's guidance on response to list of questions
S-CO-MHI	Medical and Health Information Service, Communication Department in Stakeholders and Communication Division
SIAMED	Product information and application tracking system
SOC variation	Extension of authorised indication within the same orphan condition (90 days)

8. Process map/ flow chart




From Step 26
27. Positive trend?
NO
28. Coordinate adoption of LoQ
29. Finalise review report with LOQ
30. Perform quality check of review report
31. Send review report with LoQ to sponsor
32. Include product scope in COMP agenda
33. Receive responses to LoQ
34. Forward responses to COMP Cos
35. Is CHMP outcome positive?
NO
36. CHMP negative opinion adopted?
NO
YES
37. Review requested?
NO
YES
YES
38. Positive CHMP opinion after review?
YES
NO
39. Send oral explanation invitation
40. Update slides
41. Coordinate second discussion in COMP
42. Positive trend?
NO
43. Withdrawal?
YES
YES
NO
YES
NO
44. Adopt opinion
45. Inform PM
46. Go to SOP/H/3049 (opinion phase)
47. Positive COMP opinion?
YES
48. Send positive opinion to sponsor and EC
NO
49. Forward negative opinion for check
50. Send negative opinion and report to sponsor
51. Appeal?
NO
YES
52. Go to SOP/H/3049 (appeal phase)
53. Inform PM of COMP appeal opinion
54. Revise review report with appeal outcome
55. Send final COMP opinion to EC and sponsor
56. Prepare and publish orphan maintenance assessment report (SOP/H/3372)
57. Update product information sheet and transmit to webteam
END

9. Procedure

- *All messages containing confidential information must be sent via EudraLink.*
- *All procedural timelines and guidance are published on the EMA website.*
- *Unless no longer available, COMP co and OME co remain the same as per orphan designation procedure.*
- *Timelines should be adapted to the ongoing CHMP procedure.*
- *It is the responsibility of the OME co to know where the product is in the procedure and what the most recent discussions in the CHMP contain.*
- *Review report to be e-verified by HoO before sending to sponsor.*
- *Validation/start of procedure notifications should be sent by Validation Centre to OME inbox orphandrugs@ema.europa.eu*

Step	Action	Responsibility
	Presubmission phase of CHMP application as applicable	
1	Send invitation to CHMP application pre-submission meeting to OME HoO.	I-BD-BUS
2	• If OME co for orphan designation is still available, go to step 3. • If OME co is no longer available, go to step 8 and return to step 3.	OME HoO
3	Forward invitation to OME co.	OME HoO
4	Attend CHMP application pre-submission meeting and highlight to sponsor procedure for review of orphan designation and requirement to submit a maintenance of orpan designation report or a written justification (for SOC variation). Major anticipated maintenance issues may be flagged during the meeting.	OME co
5	Upon request from sponsor regarding COMP review of orphan designation for SOC variation, send advice on procedural steps (template 1a).	OME co
	After submission of CHMP application	
6	Organise monthly internal review of orphan designations meeting inviting COMP sec.	OME Asst
7	• Run SIAMED report on orphan products with on-going MA and extensions procedures. • Cross check status of procedures with the CHMP meeting documents (agenda, draft summary of outcomes and annexes). • Update relevant listings and table in MMD for forthcoming COMP meeting for nomination of COMP coordinators.	COMP Sec
8	• Attend monthly review of orphan designations meeting and	OME HoO, Asst, Co

Step	Action	Responsibility
	discuss timelines for CHMP application. • If necessary, identify experts or patient's representatives. • Discuss OME co appointment for unallocated review procedures.	/COMP sec
9	• Receive validation/start of procedure notification from E-PM-EPB Validation Centre. • Distribute review procedure to OME Asst.	OME Asst
10	• If sponsor's maintenance report is received, go to step 12. • If sponsor's maintenance report is not received, go to step 11.	OME Asst
11	Request sponsor to submit maintenance report or written justification (for SOC) to D-DS-OME (at time of submission of MA application for accelerated review or SOC variation or at day 121 of regular MA procedure or NOC variation) (template 1b).	OME Asst
12	• Receive sponsor's submission. • If it is for SOC variation, go to step 13. • If it is for MA application or NOC variation, go to step 17.	OME Asst
13	• Download sponsor's written justification or maintenance report in DREAM. • Forward relevant DREAM link to OME co. • Instruct COMP sec to include information on SOC variation in forthcoming COMP meeting agenda for discussion if review of orphan designation is required and potential appointment of COMP co. • Link sponsor's written justification or maintenance report in COMP meeting folder.	OME Asst
14	• Coordinate discussion at forthcoming COMP meeting. • If COMP decides on the need to review orphan designation, go to step 15. • If COMP decides that review of designation is not required, go to step 16.	OME Co
15	Inform sponsor about COMP decision to review orphan designation for SOC variation. If applicable, request maintenance report (template 1c), go to step 17.	OME Co
16	• Inform sponsor about COMP decision (template 2b). • Inform PM. • Save correspondence in DREAM.	OME Co

Step	Action	Responsibility
	• End of procedure.	
17	• On submission of maintenance report, acknowledge receipt (template 2a) informing about a possibility to hold pre-assessment TC. • Download sponsor's maintenance report in DREAM. • Save in DREAM review report (template 3a) and presentation (template 3b) templates and complete administrative data. • Forward relevant DREAM link to OME co.	OME Asst
18	Examine maintenance report, and notify sponsor in writing of any major issues identified.	OME co
19	Upon request from sponsor, organise pre-assesment TC to discuss these issues.	OME Asst
20	• Chair orphan designation review pre-assessment TC with sponsor. • When major issues are anticipated/identified, request from sponsor missing data. • Advise on next steps of review procedure.	OME co
	Assessment / adoption of COMP opinion on review of orphan designation	
21	• Draft the report on review of orphan designation (template 3a) following appropriate timelines assuring availability of the report at least 2 weeks before relevant discussion at the COMP meeting. • If major issues remain unaddressed request additional data from sponsor ahead of the COMP discussion and request from sponsor the updated report (template 1d).	OME co
22	• Send the review report to COMP co for comments. This should be done well before COMP pre-mailing corresponding to the COMP meeting taking place prior to the CHMP meeting where the product is scheduled for opinion (template 4a is available in MMD). • Attend the summary report meeting to internally discuss the draft review report.	OME co
23	• Download COMP co comments in DREAM and link in the review report. • Link the review report and presentation in the COMP meeting folder.	OME Asst

Step	Action	Responsibility
24	• Discuss the report and product with the COMP co. • Update the review report if necessary. • Prepare slides for the COMP plenary.	OME co
25	• Insert product expected for adoption of an opinion at forthcoming CHMP meeting in COMP agenda for first discussion at the COMP meeting. The following cases should be reviewed by the COMP one month in advance of scheduled CHMP opinion to facilitate adoption of the COMP opinion (via written procedure) immediately after the CHMP final opinion: – products without significant benefit – products under accelerated procedure – products for final CHMP opinion in July or December • Table in MMD review report linked in the meeting folder for COMP mailings. • Table relevant CHMP assessment report.	COMP Sec
26	Co-ordinate first discussion in the COMP meeting.	OME co
27	• If COMP trend is negative, go to step 28. • If COMP trend is positive, go to step 44.	OME co
28	• Co-ordinate adoption of LoQ by COMP.	OME co
29	• After the COMP meeting finalise the review report with LoQ assuring e-verification. • Make sure any text copied from the CHMP assessment report has been deleted.	OME co
30	Perform quality check of the review reports with LoQ.	OME HoO
31	Format and send the review report with LoQ to sponsor informing about deadline for written response (15 days before next COMP meeting) (template 3c).	OME Asst
32	Include product with CHMP positive opinion adopted at last CHMP meeting for a second COMP discussion and/or an oral explanation in COMP agenda for the next meeting (product with CHMP negative opinion should also be included in COMP agenda for information only).	COMP Sec
33	Receive response to LOQ and link in review reports.	OME Asst
34	Forward response to COMP co with request for comments only if sponsor didn't send responses directly to COMP co (template 4b is available in MMD).	OME Asst

Step	Action	Responsibility
35	After discussion by CHMP: • If CHMP outcome is negative, go to step 36. • If CHMP outcome is positive and a positive opinion is adopted, go to step 39.	OME co
36	• If CHMP adopts a negative opinion, go to step 37. • If the applicant withdraws the CHMP application before the CHMP adopts a negative opinion, there is no further need to review the orphan designation and the procedure ends here.	OME co
37	• If the applicant asks for a review of the CHMP negative opinion, put the second discussion by COMP on hold and go to step 38. • If the applicant does not request a review of the CHMP negative opinion, there is no further need to review the orphan designation and the procedure ends here.	OME co
38	• If the outcome of the CHMP review is positive and a positive opinion is adopted, go to step 39. • If the outcome of the CHMP review is negative and a negative opinion is adopted, there is no further need to review the orphan designation and the procedure ends here.	OME co
39	• Send to sponsor invititation to oral explanation to be held at the COMP meeting following adoption of CHMP positive opinion (template 3c). • Receive COMP co comments on sponsor's response to LOQ and link in the review report.	OME Asst
40	When necessary update slides for the plenary discussion. E.g. when the first discussion was held several months ago.	OME co
41	Coordinate oral explanation and second discussion in the COMP meeting.	OME co
42	• If COMP trend is negative, go to step 43. • If COMP trend is positive, go to step 44.	OME co
43	• Inform sponsor of negative trend, and of regulatory options and consequences (including appeal procedure, delay of marketing authorisation decision by the EC). • If sponsor does not request a withdrawal of orphan designation from EU Register, go to step 44. • If sponsor requests a withdrawal of orphan designation from EU Register, inform PM and finalise the review report (assuring e-verification), go to step 56.	OME co

Step	Action	Responsibility
44	Ensure adoption of grounds for review opinion.	OME co
45	Inform PM of COMP opinion.	OME co
46	• Go to SOP/H/3049 and follow steps in opinion phase. • Send opinion on accelerated review and/or non-significant benefit product for adoption via written procedure with 1 day adoption deadline. • Return to this SOP and go to step 47.	OME co/OME Asst
47	• If COMP opinion is positive, go to step 48. • If COMP opinion is negative, go to step 49.	OME co
48	• Following e-verification format review report and send with with COMP positive opinion (template 5a) to EC (template 6a) and to sponsor (template 6b), go to step 56.	OME Asst
49	Assure AF-LD and E-SR-REA check of review report.	OME co
50	Following e-verification send COMP negative opinion (template 5b) and review report to sponsor with information on possibility to appeal within 90 days of receipt of opinion (template 6c).	OME Asst
	Appeal	
51	• Receive response from sponsor. • If sponsor appeals, go to step 52. • If sponsor does not appeal within 90 days, go to step 55.	OME co/OME Asst
52	• Go to SOP/H/3049 and follow steps in appeal phase. • Return to this SOP and go to step 44.	OME co/OME Asst
53	Inform PM of COMP opinion.	OME co
54	Revise and finalise review report with outcome of appeal (assuring e-verification).	OME co
55	Send final opinion (template 5c or template 5d) to EC (template 6a) and to sponsor (template 6b in case of appeal or template 6d in case of no appeal).	OME Asst
	Publication	
56	Refer to SOP/H/3372 for preparation and publication of an orphan maintenance assessment report.	OME co/OME Asst
57	Update product information sheet with details of the marketing authorisation and trasmit to webteam for update for the relevant orphan webpage.	OME Asst

10. Records

Records produced from this procedure are stored in accordance with WIN/H/3047.

Review reports are versioned and labelled for tracking procedural steps and electronic verification process. Opinions are labelled for recording final version and possible correction, revisions and corrigenda as applicable. Detailed labelling and versioning instructions are available in Cabinets/14. Working areas/14.01 D-Division/02. D-DS Activities/D-DS-OME Activities/Section activities/Templates and DREAM labels.