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Amsterdam, <insert full date>

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<Committee for Medicinal Products for Human Use (CHMP)>

<CAT/>CHMP assessment report for <initial marketing application><EUM4All (Art 58) scientific opinion>

Rapporteurs’ Day<60\*><82>assessment report - Overview and list of questions> or <DRAFT> <CAT><CHMP> Day <90\*><120> list of questions or <DRAFT> <CHMP><CAT> Day <120\*> <180> list of outstanding issues or Final <CAT/>CHMP assessment report

\*in case of accelerated assessment

EMA to ensure the correct text is reflected above at each milestone

<Product Name>

<International non-proprietary name> or <Common name\*\*>:

[\*\*e.g. for vaccines and some ATMPs]

Procedure No.

Applicant:

|  |  |
| --- | --- |
| <CHMP><CAT> Rapporteur: | <Text> |
| <CHMP><CAT> Co-rapporteur: | <Text> |
| PRAC Rapporteur: | <Text> |
| PRAC Co-Rapporteur: | <Text> |
| <CHMP coordinator(s)>:  to be included only for CAT procedures | <Text> |
| EMA PL: | <Text> |
| EMA PA: | <Text> |
| Start of the procedure: | <DD Month YYYY> |
| Date of this report: | <DD Month YYYY> |
| <Deadline for <CHMP><CAT> comments:> | <DD Month YYYY> |
| <Deadline for PRAC comments:> | <DD Month YYYY> |

**Disclaimer:** The template for this report covers different stages of the initial marketing authorisation / EUM4All application. Hence some sections of the report might be left blank or might contain guidance text which is not applicable to the intermediate stages of the procedure. In case of withdrawal of the application, the latest intermediate report adopted by the committee will be published on the EMA website. In preparation for this, all non-applicable sections will be removed.

Instructions to Rapporteurs for the use of this template

Note – EMA is responsible for the completion of the entire section 2 (Administrative information). All other sections are to be co-authored by the Rapporteurs, including the PRAC Rapporteur (with focus on RMP and PSUR sections) and the EMA PL.

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The purpose of this template's guidance is to provide a framework for the drafting of the Assessment Report.

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At D10 of the procedure, the template with the administrative sections completed, will be placed by the EMA Procedure Assistant (PA) in SharePoint. Each Rapporteur can download a copy and work off-line on their assessment. By D80 the CHMP/CAT Rapporteur should upload (on top of the D10 version) their completed Overview. By D82 the CHMP/CAT Co-Rapporteur should add (by copy/pasting) their assessment pieces (27 boxes + questions) in the Rapporteur’s Overview already in SharePoint, thereby complementing the Rapporteur’s document. The PRAC Rapporteur can either work off-line and copy/paste their parts by D94 or work directly on the document uploaded in SharePoint by the CHMP/CAT Rapporteur at D80.

It is understood that Assessors will begin their assessment work focussing on the preparation of the stand-alone D80 quality, non‑clinical and clinical reports, hence the instructions in this template allow for easy copy/pasting from those reports, especially in the discussion and conclusion sections. The factual information in this report is expected to be much higher level than in the D80 individual reports, in order to keep this document brief but still comprehensive enough.

The document will remain a living document. It is expected that Assessors complete the first version by D80/D82/D94 and thereafter it will be updated at each milestone up to D210 of the procedure and then for the EPAR preparation. At each foreseen milestone, the EMA PA will export a copy of the document, and table the document and/or send it to the Applicant, as required.

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General Guidance

The Scientific Discussion will be built into this document sequentially, starting from the Day 60/80 AR from (Co)Rapporteurs. This document will then serve as the “Master living document” from which the DAY 90/120 Assessment Report with the List of Questions, the DAY 106/150 JAR, the D120/D150/D180 LOI and the D136/D195 JAR, as well as the D210 CHMP AR and the EPAR will be created. At each milestone a copy will be stored as a record, prior to the Master being updated again.

The conclusions from discussion during ad-hoc expert group/SAG meetings and in the CHMP plenary should be included as described in the template. In principle, the Scientific Discussion should be concise and substantiate statements made in the SmPC. Efforts should be made so that issues are described concisely and not in huge detail to avoid this document becoming too long.

The focus should be on relevant data for each main section of the assessment report. Not all submitted data needs to be reported, and the focus should be on aspects relevant to B/R and the SmPC or RMP.

If data from publications is used by the applicant or in the context of the assessment, clear references should be included to easily retrieve the publications. Consider generating a reference list if a substantial number of publications is used. If appropriate, ensure a clear description of the Committee’s position on the content of a publication and whether it serves as a basis for approval.

Where the data submitted deviates from the EU regulatory requirements, the acceptability of any justifications should be assessed and documented in this AR.

Each section should be filled with factual data that were submitted in support of the application. Evaluation and assessment text should be limited to discussions, conclusions and B/R section.

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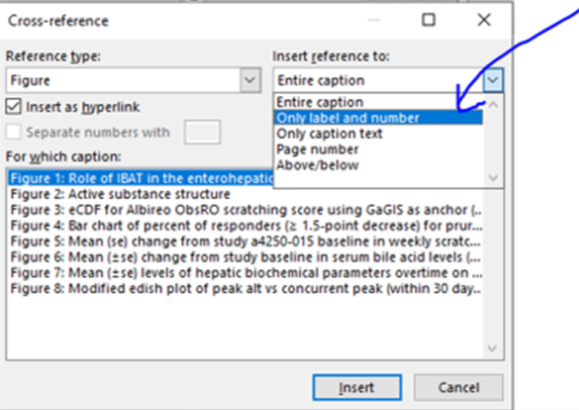
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|  |
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Table of contents

[1. Executive Summary 15](#_Toc204788236)

[2. Administrative/regulatory information and recommendations on the procedure 18](#_Toc204788237)

[2.1. Information on the product 18](#_Toc204788238)

[2.2. Scientific advice and protocol assistance 19](#_Toc204788239)

[2.3. <PRIME > 19](#_Toc204788240)

[2.4. Eligibility to the centralised procedure 20](#_Toc204788241)

[2.5. Legal basis <,><and> dossier content <and multiples> 21](#_Toc204788242)

[2.6. Information on paediatrics 23](#_Toc204788243)

[2.7. Information on orphan market exclusivity 23](#_Toc204788244)

[2.7.1. Similarity with authorised orphan medicinal products 24](#_Toc204788245)

[2.7.2. <Derogation(s) from market exclusivity applicable to similar orphan products > 24](#_Toc204788246)

[2.8. <Applicant’s request(s) for consideration > 24](#_Toc204788247)

[2.8.1. <Accelerated assessment request > 24](#_Toc204788248)

[2.8.2. <Conditional marketing authorisation (CMA) > 25](#_Toc204788249)

[2.8.3. <Marketing authorisation under exceptional circumstances> 25](#_Toc204788250)

[2.8.4. <Request for Additional data exclusivity /Marketing protection> 25](#_Toc204788251)

[2.8.5. <New active substance status> 26](#_Toc204788252)

[2.9. <Third party interventions> 28](#_Toc204788253)

[2.10. <Patient experience data> 28](#_Toc204788254)

[2.11. Steps taken for the assessment of the product 28](#_Toc204788255)

[2.12. Final CHMP outcome 31](#_Toc204788256)

[2.12.1. Considerations related to paediatrics 31](#_Toc204788257)

[2.12.2. Considerations related to orphan market exclusivity 32](#_Toc204788258)

[2.12.3. <Final opinion> to be used for positive outcome 33](#_Toc204788259)

[2.12.4. <Final opinion> to be used for positive opinion with negative similarity etc 34](#_Toc204788260)

[2.12.5. <Final opinion> to be used for negative opinion 34](#_Toc204788261)

[2.12.6. <Conclusions on biosimilarity and benefit risk balance> 35](#_Toc204788262)

[2.12.7. <Conditions or restrictions regarding supply and use> 35](#_Toc204788263)

[2.12.8. <Official batch release> 35](#_Toc204788264)

[2.12.9. Other conditions and requirements of the marketing authorisation 35](#_Toc204788265)

[2.12.10. Conditions or restrictions with regard to the safe and effective use of the medicinal product 36](#_Toc204788266)

[2.12.11. <Specific obligation to complete post-authorisation measures for the <conditional> marketing authorisation <under exceptional circumstances> 37](#_Toc204788267)

[2.12.12. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States 38](#_Toc204788268)

[2.12.13. Proposed list of recommendations 38](#_Toc204788269)

[3. Introduction 39](#_Toc204788270)

[3.1. Therapeutic Context 39](#_Toc204788271)

[3.2. Aspects of development 39](#_Toc204788272)

[3.3. Description of the product 39](#_Toc204788273)

[3.4. Inspection issues 39](#_Toc204788274)

[3.4.1. Good manufacturing practice (GMP) inspection(s) 39](#_Toc204788275)

[3.4.2. Good laboratory practice (GLP) inspection(s) 40](#_Toc204788276)

[3.4.3. Good clinical practice (GCP) inspection(s) 41](#_Toc204788277)

[4. Quality aspects 43](#_Toc204788278)

[4.1. Introduction 44](#_Toc204788279)

[4.2. Active substance 45](#_Toc204788280)

[4.2.1. General information 45](#_Toc204788281)

[4.2.2. Manufacture, process controls and process development 46](#_Toc204788282)

[4.2.3. Characterisation and impurities 51](#_Toc204788283)

[4.2.4. Control of active substance 52](#_Toc204788284)

[4.2.5. Stability 55](#_Toc204788285)

[4.3. Finished medicinal product 57](#_Toc204788286)

[4.3.1. Description of the product and pharmaceutical development 57](#_Toc204788287)

[4.3.2. Manufacture of the product and process controls 59](#_Toc204788288)

[4.3.3. Control of Finished Product 61](#_Toc204788289)

[4.3.4. Stability of the product 63](#_Toc204788290)

[4.3.5. < Biosimilarity exercise > 65](#_Toc204788291)

[4.3.6. Post approval change management protocol(s) 66](#_Toc204788292)

[4.3.7. Adventitious agents 66](#_Toc204788293)

[4.3.8. <GMO> 66](#_Toc204788294)

[4.4. Discussion and conclusions on quality aspects 66](#_Toc204788295)

[4.4.1. Recommendation(s) for future quality development 68](#_Toc204788296)

[5. Non-clinical aspects 69](#_Toc204788297)

[5.1. Introduction 69](#_Toc204788298)

[5.2. Analytical methods 69](#_Toc204788299)

[5.3. Pharmacology 69](#_Toc204788300)

[5.3.1. Pharmacodynamics 69](#_Toc204788301)

[5.3.2. Pharmacokinetics 70](#_Toc204788302)

[5.4. Toxicology 71](#_Toc204788303)

[5.4.1. <Single-dose toxicity> 71](#_Toc204788304)

[5.4.2. Repeat-dose toxicity 71](#_Toc204788305)

[5.4.3. Genotoxicity 71](#_Toc204788306)

[5.4.4. Carcinogenicity 72](#_Toc204788307)

[5.4.5. Developmental and reproductive toxicity 72](#_Toc204788308)

[5.4.6. Toxicokinetics and exposure margins 72](#_Toc204788309)

[5.4.7. Local tolerance 72](#_Toc204788310)

[5.4.8. Other toxicity studies 72](#_Toc204788311)

[5.4.9. Ecotoxicity/environmental risk assessment 73](#_Toc204788312)

[5.5. Overall discussion and conclusions on non-clinical aspects 76](#_Toc204788313)

[5.5.1. Discussion 77](#_Toc204788314)

[5.5.2. Conclusions 77](#_Toc204788315)

[6. Clinical aspects 79](#_Toc204788316)

[6.1. Introduction 79](#_Toc204788317)

[6.1.1. GCP aspects 79](#_Toc204788318)

[6.1.2. Tabular overview of clinical trials 80](#_Toc204788319)

[6.2. Clinical pharmacology 80](#_Toc204788320)

[6.2.1. Methods 80](#_Toc204788321)

[6.2.2. Pharmacokinetics 81](#_Toc204788322)

[6.2.3. Pharmacodynamics 83](#_Toc204788323)

[6.2.4. Pharmacokinetics/pharmacodynamics (PK/PD) 84](#_Toc204788324)

[6.2.5. Dose selection and therapeutic window 85](#_Toc204788325)

[6.2.6. Overall discussion and conclusions on clinical pharmacology 85](#_Toc204788326)

[6.3. Clinical efficacy 86](#_Toc204788327)

[6.3.1. Dose response study(ies) 86](#_Toc204788328)

[6.3.2. Main <study><studies> 86](#_Toc204788329)

[6.3.3. Clinical studies in special populations 92](#_Toc204788330)

[6.3.4. <In vitro biomarker test for patient selection for efficacy> 93](#_Toc204788331)

[6.3.5. <Supportive study(ies)> 94](#_Toc204788332)

[6.3.6. Analysis performed across trials (pooled analyses and meta-analysis) 94](#_Toc204788333)

[6.3.7. <Observational data><Data from registries> 94](#_Toc204788334)

[6.3.8. <Patient experience data (PED)> 94](#_Toc204788335)

[6.3.9. <Healthcare professional engagement> 95](#_Toc204788336)

[6.3.10. Overall discussion and conclusions on clinical efficacy 95](#_Toc204788337)

[6.4. Clinical safety 96](#_Toc204788338)

[6.4.1. Safety data collection 97](#_Toc204788339)

[6.4.2. Patient exposure 97](#_Toc204788340)

[6.4.3. Adverse events 98](#_Toc204788341)

[6.4.4. Adverse event of special interest, serious adverse events and deaths, other significant events 99](#_Toc204788342)

[6.4.5. Discontinuation due to adverse events 99](#_Toc204788343)

[6.4.6. Safety in special populations 99](#_Toc204788344)

[6.4.7. Immunological events 100](#_Toc204788345)

[6.4.8. Safety related to drug-drug interactions and other interactions 100](#_Toc204788346)

[6.4.9. Vital signs and laboratory findings 101](#_Toc204788347)

[6.4.10. Post marketing experience 101](#_Toc204788348)

[6.4.11. <In vitro biomarker test for patient selection for safety> 101](#_Toc204788349)

[6.4.12. Overall discussion and conclusions on clinical safety 101](#_Toc204788350)

[7. Risk management plan 105](#_Toc204788351)

[7.1. Safety specification 105](#_Toc204788352)

[7.1.1. Proposed safety specification 105](#_Toc204788353)

[7.1.2. Discussion on proposed safety specification 105](#_Toc204788354)

[7.2. Pharmacovigilance plan 106](#_Toc204788355)

[7.2.1. Proposed pharmacovigilance plan. 107](#_Toc204788356)

[7.2.2. Discussion on the Pharmacovigilance Plan 107](#_Toc204788357)

[7.3. Plans for post-authorisation efficacy studies 107](#_Toc204788358)

[7.4. Risk minimisation measures 108](#_Toc204788359)

[7.4.1. Proposed risk minimisation measures 108](#_Toc204788360)

[7.4.2. Discussion on the risk minimisation measures 108](#_Toc204788361)

[7.5. RMP Summary and RMP Annexes overall conclusion 109](#_Toc204788362)

[7.6. PRAC Outcome at <D166><D105> 109](#_Toc204788363)

[7.7. Overall conclusion on the Risk Management Plan 109](#_Toc204788364)

[8. Pharmacovigilance 111](#_Toc204788365)

[8.1. Pharmacovigilance system 111](#_Toc204788366)

[8.2. Periodic Safety Update Reports submission requirements 111](#_Toc204788367)

[9. Product information 113](#_Toc204788368)

[9.1. Summary of Product Characteristics (SmPC) 113](#_Toc204788369)

[9.1.1. SmPC section 4.1 justification 113](#_Toc204788370)

[9.1.2. <SmPC section 5.1 justification> 113](#_Toc204788371)

[9.1.3. <SmPC section X justification> 114](#_Toc204788372)

[9.2. Labelling 114](#_Toc204788373)

[9.2.1. Package leaflet (PL) 114](#_Toc204788374)

[9.2.2. User consultation 114](#_Toc204788375)

[9.2.3. <Quick Response (QR) code> 115](#_Toc204788376)

[9.2.4. <Labelling exemptions> 115](#_Toc204788377)

[9.3. <Additional monitoring> 116](#_Toc204788378)

[10. Benefit-risk assessment 117](#_Toc204788379)

[10.1. Therapeutic context 117](#_Toc204788380)

[10.1.1. Disease or condition, <proposed> therapeutic indication 117](#_Toc204788381)

[10.1.2. Available therapies and unmet medical need 117](#_Toc204788382)

[10.2. Main clinical studies 118](#_Toc204788383)

[10.3. Favourable effects 118](#_Toc204788384)

[10.3.1. Uncertainties and limitations about favourable effects 119](#_Toc204788385)

[10.4. Unfavourable effects 119](#_Toc204788386)

[10.4.1. Uncertainties and limitations about unfavourable effects 120](#_Toc204788387)

[10.5. Effects Table 121](#_Toc204788388)

[10.6. Benefit-risk assessment and discussion 124](#_Toc204788389)

[10.6.1. Importance of favourable and unfavourable effects 124](#_Toc204788390)

[10.6.2. Balance of benefits and risks 125](#_Toc204788391)

[10.6.3. <Additional considerations on the benefit-risk balance> 126](#_Toc204788392)

[10.7. Benefit-risk conclusions 134](#_Toc204788393)

[10.7.1. At <Day 60><Day 80> - individual Rapporteur conclusions 134](#_Toc204788394)

[10.7.2. At <Day 90><Day 120> - <CAT><CHMP> conclusions 134](#_Toc204788395)

[10.7.3. At Day 180 - <CAT><CHMP> conclusions 134](#_Toc204788396)

[10.7.4. At Day 210 – Final CHMP conclusions 134](#_Toc204788397)

[11. <Biosimilarity assessment> 135](#_Toc204788398)

[11.1. <Comparability exercise and indications claimed> 135](#_Toc204788399)

[11.2. <Results supporting biosimilarity> 135](#_Toc204788400)

[11.3. <Uncertainties and limitations about biosimilarity> 135](#_Toc204788401)

[11.4. <Discussion on biosimilarity> 136](#_Toc204788402)

[11.5. <Extrapolation of safety and efficacy> 136](#_Toc204788403)

[11.6. <Additional considerations> 137](#_Toc204788404)

[12. <D90\*><D120> List of Questions 138](#_Toc204788405)

[12.1. Quality Aspects 139](#_Toc204788406)

[Major Objections 139](#_Toc204788407)

[Other concerns 139](#_Toc204788408)

[12.2. Non-clinical Aspects 140](#_Toc204788409)

[Major Objections 140](#_Toc204788410)

[Other concerns 141](#_Toc204788411)

[12.3. Clinical Aspects 142](#_Toc204788412)

[Major Objections 142](#_Toc204788413)

[Other concerns 143](#_Toc204788414)

[12.4. Risk Management Plan 144](#_Toc204788415)

[Major Objections 144](#_Toc204788416)

[Other concerns 145](#_Toc204788417)

[12.5. Pharmacovigilance 145](#_Toc204788418)

[Major Objections 145](#_Toc204788419)

[Other concerns 145](#_Toc204788420)

[12.6. <Orphan similarity and derogations> 146](#_Toc204788421)

[Major Objections 146](#_Toc204788422)

[Other Concerns 146](#_Toc204788423)

[12.7. <New active substance status claim> 146](#_Toc204788424)

[Major Objections 146](#_Toc204788425)

[Other Concerns 146](#_Toc204788426)

[12.8. <Additional data exclusivity/Marketing protection> 147](#_Toc204788427)

[Major Objections 147](#_Toc204788428)

[Other Concerns 147](#_Toc204788429)

[13. <D120\*><D180> List of Outstanding Issues < to be addressed in writing <and/or in an Oral Explanation\*> 148](#_Toc204788430)

[13.1. Quality Aspects 148](#_Toc204788431)

[Major Objections 148](#_Toc204788432)

[Other concerns 149](#_Toc204788433)

[13.2. Non-clinical Aspects 149](#_Toc204788434)

[Major Objections 149](#_Toc204788435)

[Other concerns 150](#_Toc204788436)

[13.3. Clinical Aspects 151](#_Toc204788437)

[Major Objections 151](#_Toc204788438)

[Other concerns 152](#_Toc204788439)

[13.4. Risk Management Plan 152](#_Toc204788440)

[Major Objections 153](#_Toc204788441)

[Other concerns 153](#_Toc204788442)

[13.5. Pharmacovigilance 153](#_Toc204788443)

[Major Objections 153](#_Toc204788444)

[Other concerns 154](#_Toc204788445)

[13.6. <Orphan similarity and derogations> 154](#_Toc204788446)

[Major Objections 154](#_Toc204788447)

[Other Concerns 154](#_Toc204788448)

[13.7. <New active substance status> 154](#_Toc204788449)

[Major Objections 154](#_Toc204788450)

[Other Concerns 155](#_Toc204788451)

[13.8. <Additional data exclusivity/Marketing protection> 155](#_Toc204788452)

[Major Objections 155](#_Toc204788453)

[Other Concerns 155](#_Toc204788454)

[14. Re-examination 156](#_Toc204788455)

[15. Appendi<x>/<ces> 157](#_Toc204788456)

[16. QRD checklist for the review of user testing results 158](#_Toc204788457)

[16.1. Technical assessment 161](#_Toc204788458)

[16.1.1. Recruitment 161](#_Toc204788459)

[16.1.2. Questionnaire 161](#_Toc204788460)

[16.1.3. Time aspects 162](#_Toc204788461)

[16.1.4. Procedural aspects 162](#_Toc204788462)

[16.1.5. Interview aspects 163](#_Toc204788463)

[16.2. Evaluation of responses 164](#_Toc204788464)

[16.2.1. Evaluation system 164](#_Toc204788465)

[16.2.2. Question rating system 164](#_Toc204788466)

[16.3. Data processing 164](#_Toc204788467)

[16.4. Quality aspects 165](#_Toc204788468)

[16.4.1. Evaluation of diagnostic questions 165](#_Toc204788469)

[16.4.2. Evaluation of layout and design 165](#_Toc204788470)

[16.5. Diagnostic quality/evaluation 166](#_Toc204788471)

[16.6. Conclusions 167](#_Toc204788472)

List of abbreviations

Please provide a comprehensive list of all abbreviations used throughout the assessment report (quality, non-clinical, clinical).

EPAR preparation: It is important to note that this List of Abbreviations should also be included in the EPAR.

|  |  |
| --- | --- |
|  |  |
| CAT | Committee for Advanced Therapies |
|  |  |
| CHMP | Committee for Medicinal Products for Human Use |
|  |  |
| EMA | European Medicines Agency |
|  |  |
| PD | Pharmacodynamics |
|  |  |
| PK | Pharmacokinetics |
|  |  |
| PRAC | Pharmacovigilance Risk Assessment Committee |
|  |  |
| RMP | Risk management plan |
|  |  |
| SmPC | Summary of product characteristics |
|  |  |

1. Executive Summary

This section is to be completed by EMA PL (in collaboration with Rapporteurs) ahead of finalisation of the D210 (D150 for AA) final report. This executive summary is also used directly as the basis for creating the SMOP.

The text below is to be used as a guide for the creation of the executive summary. In the case that the product is so different and so specific, a different format can be used. But overall, the executive summary should not be more than half a page at most and should mirror what an abstract would look like in a peer-reviewed journal.

The text should describe the majority position, not go into details of divergent positions, if any.

Use the text below for non-biosimilar approvals:

For standard MAA:

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product {Tradename} ({INN}) intended for the <treatment of><prophylaxis against><diagnosis of> {insert high level indication}>.

For CMA:

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a conditional marketing authorisation for the medicinal product {Tradename} intended for the <treatment of><prophylaxis against><diagnosis of> {insert high level indication}>.

For MAA under exceptional circumstances:

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation under exceptional circumstances for the medicinal product {Tradename} intended for the <treatment of><prophylaxis against><diagnosis of> {insert high level indication}>.

For PUMA:

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a paediatric use marketing authorisation (PUMA) for the medicinal product {Tradename} intended for the <treatment of><prophylaxis against><diagnosis of> {insert high level indication}>.

For EU-M4all:

On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in accordance with Article 58 of Regulation (EC) No 726/2004 for the medicinal product {Tradename} intended for <the treatment of><prophylaxis against><the diagnosis of><disease>{insert high level indication}.

For all products:

{Tradename} will be available as <a> {e.g. 10 mg, 10mg/mL…} {e.g. oral, intravenous, subcutaneous…}, <film-coated><tablet, capsule, solution, suspension…>. {Tradename} {briefly describe mechanism of action}.

The full indication<s> for {Tradename} <is><are>:

{Insert approved indication(s) in full, as per SmPC section 4.1}.

<{Tradename} should be prescribed <and supervised> by a physician experienced in the treatment of {add specialty}.> The wording of this sentence should be in line with SmPC Section 4.2

The main evidence of efficacy of {Tradename} was based on <one><two><three…> Phase <II><III> clinical trials. The <improvement><non-inferiority> in {insert endpoint} was shown <against> <placebo><comparator X><in a single arm trial> in the {name of study} study ({insert outcome measure}; 95% confidence interval (CI) [{lower CI}{upper CI}]; <p = <0.XXX>>) <and in> {insert second study name} ({insert outcome measure}; 95% CI [{lower CI}{upper CI}]; p = <0.XXX>). The most relevant safety concerns were {add from the safety specification in the RMP} and the most commonly reported adverse reactions were {ADR1}{ADR2}{ADR3}.

For applications other than EU-M4All use:

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website in all official European Union languages after the marketing authorisation has been granted by the European Commission.

For EU-M4All use:

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website.

{Tradename} is intended exclusively for markets outside the European Union.

For all approvals:

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).>

Use the text below for biosimilar approvals.

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation application for the medicinal product {Tradename} ({INN}) intended for the <treatment of><prophylaxis against><diagnosis of> {insert high level indication}>.

{Tradename} will be available as <a> {e.g. 10 mg, 10mg/mL…} {e.g. oral, intravenous, subcutaneous…}, <film-coated><tablet, capsule, solution, suspension…>. {Tradename} {briefly describe mechanism of action}.

{Tradename is a biosimilar medicinal product. It is highly similar to the reference product {Tradename of ref product} ({INN of ref product}), which was authorised in the EU on {date of first authorisation}.

Data show that {Tradename} has comparable quality, safety and efficacy to {insert name of reference product ({INN of ref product}).

The main evidence of bioequivalence of {Tradename} was based on {include number and type of clinical studies; e.g. PK or efficacy/safety. If no CTs, mention the quality basis for approving bioequivalence}. If not aligned, please explain why.

The full indication<s> for {Tradename} <is><are>:

<{Tradename} should be prescribed <and supervised> by a physician experienced in the treatment of {add specialty}.> The wording of this sentence should be in line with SmPC Section 4.2

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).>

If the outcome is negative, the executive summary should very concisely describe the claims made by the applicant and the reasons underpinning the negative opinion (i.e. the grounds for refusal - GfR) but not copy/paste the GfRs word-for-word.

<On {date}, the Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion for a marketing authorisation application for {Tradename} ({INN}) for the {insert claimed indication}. {INN} is <a><an> {insert mechanism of action}.

The main claims of efficacy of {INN} were based on <one><two><three…> Phase <II><III> clinical trials. The study was a <single arm> <placebo> <active> controlled <non-><randomised> trial. The primary endpoint was {insert endpoint} <against> <placebo><comparator X><in a single arm trial>. In the {name of study} study the primary endpoint was <not> met ({insert outcome measure}; 95% confidence interval (CI) [{lower CI}{upper CI}]; <p = <0.XXX>>) <and the secondary endpoints> were <not> met {insert second study name} ({insert outcome measure}; 95% CI [{lower CI}{upper CI}]; p = <0.XXX>).

The most relevant safety concerns were {add from the safety specification} and the most commonly reported adverse reactions were {ADR1}{ADR2}{ADR3}. Having thoroughly reviewed the totality of the data provided by the applicant, the committee adopted a negative opinion, based on the rationale that {insert brief summary – not word for word of the grounds for refusal}.

This report summarizes the scientific review leading to the opinion adopted by the CHMP.>

For biosimilar negative opinion:

<On {date }, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion for a marketing authorisation application for {Tradename} ({INN}) for the {insert indication}>.

{Tradename} was submitted as a biosimilar of {insert Tradename (INN) of reference product}, which is <a><an> {insert mechanism of action}. The main evidence submitted in support of bioequivalence of {Tradename} was based on {include number and type of clinical studies; e.g. PK or efficacy/safety. If no CTs, mention the quality basis for approving bioequivalence}. <However, the CHMP concluded that biosimilarity had not been demonstrated because {insert brief rationale – not word-for-word the GfRs}.>

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).>

1. Administrative/regulatory information and recommendations on the procedure

The whole of Section 2 is to be completed by EMA.

The below information will be automatically retrieved by SIAMED/IRIS and/or completed by EMA.

Complete what possible by D10; the rest is to be completed before final CHMP opinion.

For EU-M4All, make sure to adapt the text (e.g. references to MAH should be changed to SOH and EC decision should be CHMP scientific opinion).

* 1. Information on the product

|  |  |
| --- | --- |
| Product data |  |
| Product name | <Text> |
| Active substance | <Text> |
| INN or common name | <Text> |
| Applicant | <Text> |
| EMA Product Number | EMEA/H/<C><W>/<XXXX> |
| ATC code and Pharmacotherapeutic group | <Not yet assigned>  *If initially Not yet fully assigned, check if the full ATC code has been officially adopted* <https://atcddd.fhi.no/lists_of__temporary_atc_ddds_and_alterations/new_atc_5th_levels/> *and insert in all relevant documents.*  Note: Exceptionally, products can have more than one ATC code and pharmaco-therapeutic (sub)groups, for different presentations/indications, example: Insuman, Humalog, Liprolog).  Note: if the ATC code is assigned during the procedure, it should be included at the next milestone. Please check. |
| Pharmaceutical form(s) and strength (s) | <Text> |
| Packaging | <Text> |
| Package size(s) | <Text> |
| Route of administration | <Text> |
| Device or diagnostic | <Not applicable><Text> (if applicable, include very brief info on associated device or in vitro diagnostic) |
| Orphan designation | <Yes><No> (if yes, include ODD number) |
| Orphan indication status confirmed | <Yes><No><Pending><Not applicable> |
| PRIME scheme | <Not granted><Not applied for><Granted> (if granted, include date) |
| Type of marketing authorisation granted at opinion | <Standard><Conditional><Exceptional circumstances><EU-M4All scientific opinion> |
| Legal basis | <Text> |
| Final indication | For positive opinions: insert the approved indication.  For negative opinions: insert the most recent indication proposed by the Applicant.  Leave empty for all milestones before final opinion.  <Text> |
| New active substance status | <Applied for><Granted><Not granted><Not applied for><Eligible but not applied for> |

* 1. Scientific advice and protocol assistance

Consult colleagues from the scientific advice office for their completion of this section. This section should only describe the centralised scientific advice received and not enter into discussions regarding whether it was followed or not. That is for the discussion sections later in the document.

Table 1: Scientific advice and protocol assistance

|  |  |  |  |
| --- | --- | --- | --- |
| Date | Topic (quality/ non-clinical/ clinical) | Reference number / Coordinator(s) | Brief summary of the advice |
| <Text> | <Text> | <Text> | <Text> |
|  |  |  |  |
|  |  |  |  |

<Text>

The applicant did not seek <scientific advice> <protocol assistance> from the CHMP.

* 1. <PRIME >

Delete this section, if the product is not PRIME designated. For submissions where PRIME eligibility was granted, add the following:

{«Prodname»} ({insert INN/common name }) was granted eligibility to PRIME on {date} in the following indication: <insert the indication referred to in the PRIME eligibility outcome letter/annex for publication>}.

Eligibility to PRIME was granted at the time in view of the following:

<Contact the PRIME coordinator who will insert relevant text from the PRIME eligibility outcome letter>

<Text>

Upon granting of eligibility to PRIME, the Rapporteur was appointed by the CHMP.

The applicant was recommended to address the following key issues through relevant regulatory procedures:

<Contact the PRIME coordinator who will insert key issues discussed at the kick-off meeting>

<Text>

* 1. Eligibility to the centralised procedure

For all submissions, choose one among the 7 following options. Delete those that do not apply.

Option 1: For art. 3(1) use:

The applicant {insert name of company} submitted on {insert full date} an application for Marketing Authorisation to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure falling within the Article 3(1) and point <1> <3> <4> of Annex of Regulation (EC) No 726/2004 . <The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on {insert full date}>.

*[Note: the date of acceptability by CHMP is only requested for points 3 or 4 of the Annex of Regulation].*

Option 2: For art. 3(2) use:

The applicant {insert name of company} submitted on {insert full date} an application for Marketing Authorisation to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure under Article 3 (2) <(a)> <(b)> of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on {insert full date}.

*[Note: If the eligibility to the centralised was granted under Article 3(2)(b), further details on the eligibility should be included here i.e.]*

<The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of <significant therapeutic innovation> <and> < significant scientific innovation> <and> <significant technical innovation > < interest of patients at Community level>>.

Option 3: For ‘automatic access’:

The applicant {insert name of company} submitted on {insert full date} an application for Marketing Authorisation to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure. As this application concerns active substance(s) already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on {insert full date}.

Option 4: For art. 28 use:

The applicant {insert name of company} submitted on {insert full date} an application for Marketing Authorisation to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure under Article 28 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on {insert full date}.

Option 5: For art. 30 use:

The applicant {insert name of company} submitted on {insert full date} an application for a Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on {insert full date}.

Option 6: for duplicate/multiple application:

The applicant {insert name of company} submitted on {insert full date} an application for marketing authorisation to the European Medicines Agency (EMA) for {insert name of product} ({insert INN/common name}), through the centralised procedure. This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of {Name of medicinal product} <simultaneously being under initial assessment><authorised on {insert EC Decision date}. The eligibility was granted by the CHMP on {insert full date}.

Option 7: for submissions under EU-M4All ( Art 58)

The applicant {insert name of company} submitted on {insert full date} an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organization for {insert name of product} ({insert INN/common name}).

The eligibility by the World Health Organization was agreed-upon on {insert full date}.

{insert name of product} ({insert INN/common name})will exclusively be intended for markets outside the European Union.

For all submissions:

The applicant applied for the following indication: {insert indication applied for}.

* 1. Legal basis <,><and> dossier content <and multiples>

**The legal basis for this application refers to:**

*For all submissions: Choose one among the following 8 options, delete the rest:*

<Article 8(3) of Directive 2001/83/EC, as amended - complete and independent application.>

<Article 10a of Directive 2001/83/EC, as amended – relating to applications relying on well-established medicinal use supported by bibliographic literature.>

<Article 10b of Directive 2001/83/EC, as amended – relating to applications for fixed combination products.>

<Article 10c of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product. >

<Article 10(1)> of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.

<Article 10(3)> of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

<Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.>

<Article 58 (EU-M4All) of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to <Article 8(3)> <Article 10(1)> <Article 10(3)> <Article 10(4)> <Article 10a> <Article 10b> <Article 10c> of Directive 2001/83/EC..>

<Article 58 (EU-M4All) of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to <Article 8(3)> <Article 10(1)> <Article 10(3)> <Article 10(4)> <Article 10a> <Article 10b> <Article 10c> of Directive 2001/83/EC..>

For all submissions choose one of the following options, delete the rest:

The application submitted is

<composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies <and bibliographic literature substituting/supporting certain test(s) or study(ies)>.>

<composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.>

<a fixed combination medicinal product.>

<composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH {name of the MAH} allowing the cross reference of relevant quality, non-clinical and/or clinical data.>

<composed of administrative information, complete quality data and <at least a> <justification for not submitting> bioequivalent study with the reference medicinal product {name of reference medicinal product} and literature data instead of non-clinical and clinical unless justified otherwise. >

<composed of administrative information, complete quality data, a clinical bioequivalent study with the reference medicinal product {name of reference medicinal product} and with appropriate own applicant’s non-clinical and clinical data.>

<composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.>

[The following paragraph is only to be included in case of a parallel EU-M4all and initial EU MA application. The parallel review is to be decided by EMA and CHMP before submission of both applications]

<In parallel to this EU-M4all procedure, the applicant submitted an application for marketing authorisation to the EMA for [product name][procedure number], through the centralised procedure under <Article 3(1) and point <1> or <3> or <4> of Regulation (EC) No 726/2004> <Article 3 (2) <(a)> or <(b)> of Regulation (EC) No 726/2004> <Article 28 of Regulation (EC) No 1901/2006> <Article 31 of Regulation (EC) No 1901/2006>.

The applicant applied for the following indication: <insert indication>.

[Product name] will be intended for markets in the European Union.>

In case of multiple/duplicates applications the below statement should be kept:

<This application is submitted as a multiple of {Name of medicinal product} <simultaneously being under initial assessment> <authorised on DD month YYYY> in accordance with Article 82.1 of Regulation (EC) No 726/2004.>

In case of biosimilars chose the correct statement below:

The chosen reference product is:

The standard data protection period for a new active substance is 8 years; choose 8 below for all non-orphan products. Orphan products benefit from 10 years market exclusivity; choose 10 for products with orphan designation. In rare cases, the orphan exclusivity can be reduced to six years if, at the end of the fifth year, it is established that the criteria for orphan designation are no longer met. If you need to check what applies to the product in question, the best place to check is the European Commission’s Union Register of Medicinal Products.

<Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than <6><8><10> years in the EEA:>

<Medicinal product authorised in the European Union/Members State where the application is made for European reference medicinal product:>

<Medicinal product which is or has been authorised in accordance with European Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:>

Delete table if no reference medicinal product

|  |  |
| --- | --- |
| Product name, strength, pharmaceutical form: | Also specify if the reference product is a synthetic biological.  <Text> |
| Marketing authorisation holder: | <Text> |
| Date of authorisation: | <DD Month YYY> |
| Marketing authorisation granted by: | <European Union><{Identify member State}> |
| <National Procedure> | <MRP><DCP> |
| Marketing authorisation number: | <Text> |
| <Bioavailability study(ies) number(s):> | <Text> |

* 1. Information on paediatrics

For all submissions, choose one among the following two options for Information on Paediatric requirements:

1) Paediatric requirements apply (including art 30 – PUMA only)- Note: the Decision number below has a format P/X/XX. Do not mention the date.

<Pursuant to Article <7> <8><30> of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [insert decision number(s)] on <the agreement of a paediatric investigation plan (PIP)> OR <the granting of a (product-specific) waiver> <and> <on the granting of a class waiver>.

Only if a PIP included, i.e. not if there is a waiver:

<At the time of submission of the application, the PIP [insert decision number for the PIP eligible to the reward] was <completed> <not yet completed as some measures were deferred>.>

[Note: the following sentence to be included only in case of the PIP eligible to the reward (please check the PIP reference with the paediatric coordinator) being fully completed and a PDCO Opinion on compliance is available; compliance with a PIP not fully completed (i.e. in which case the PDCO only issues a letter and compliance report) should not be indicated here:]

<The PDCO issued an opinion on compliance for the PIP [insert decision number for the PIP eligible to the reward].>

2) Paediatric requirements do not apply to all applications, e.g. biosimilars, well-established medicinal use or EU-M4All. If paediatric requirements do not apply at all to the concerned application, select the statement hereafter:

<Not applicable>

* 1. Information on orphan market exclusivity

[Not applicable for EU-M4all]

Please specify the orphan status of the product please in this paragraph:

{insert name of product}was designated as an orphan medicinal product {EU/../../...} on {insert full date} in the following condition: {insert the orphan condition that relates to the indication in the MAA}.

* + 1. Similarity with authorised orphan medicinal products

[Not applicable for EU-M4all]

For all submissions this section on orphan HAS to be included!

For all submissions, complete the following paragraph to reflect whether a similarity report was or was not submitted. If applicable, a separate AR on similarity will have to be adopted and annexed.

The conclusion should be inserted below and corresponding justification placed in the separate report on Similarity, part of the appendix, with authorised medicinal products.

In case an authorised orphan product benefiting from market exclusivity at the start of the procedure has its orphan drug designation removed from the Union Register of orphan medicinal products -under the terms of Article 5(12) or Regulation (EC) No 141/2000- prior to the adoption of the final CHMP opinion for this procedure, the similarity assessment vis a vis such orphan product should still be completed.

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did <not> submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure {add names of concerned authorised orphan products} <because there is no authorised orphan medicinal product for a condition related to the proposed indication>.

IN CASE OF ORPHAN SIMILARITY/DEROGATION, I.E., IF THIS APPLICATION IS AFFECTED BY AN AUTHORISED ORPHAN MEDICINAL PRODUCT:

* + 1. <Derogation(s) from market exclusivity applicable to similar orphan products >

[Not applicable for EU-M4all]

Delete this section if not applicable. Complete the following paragraph only for submissions where claims for derogation(s) based on Art. 8.3 was/were submitted. A separate AR on the derogation(s) will have to be adopted and annexed (except for applicant’s consent).

<Pursuant to Article 8 of Regulation (EC) No 141/2000 <and Article 3 of Commission Regulation (EC) No 847/2000>, the application contained a claim addressing the following derogation laid down in Article 8(3) of the Regulation (EC) No 141/2000; <the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant> or < the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> or <the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.>>

* 1. <Applicant’s request(s) for consideration >
     1. <Accelerated assessment request >

<The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.> <The CHMP <agreed> <did not agree> to the applicant’s request for an accelerated assessment as the product was <not> considered to be of major public health interest. This was based on {include summary of reasons for accepting or rejecting accelerated assessment}.>

If the accelerated assessment was later reverted to standard timetable:

<However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as {include summary of reasons for reverting to standard timetable}.>

* + 1. <Conditional marketing authorisation (CMA) >

[Not applicable for biosimilar]

In case the applicant submitted a request for a CMA, either at the time of initial submission or during the assessment, following concerns raised by CHMP on the comprehensiveness of data, also add the applicable text below. If not, delete:

<The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004. See section 10.6.3.3 of this document.>

* + 1. <Marketing authorisation under exceptional circumstances>

[Not applicable for biosimilar]

In case the applicant submitted a request for a MA under exceptional circumstances, either at the time of initial submission or during the assessment, following concerns raised by CHMP on the comprehensiveness of data, also add the applicable text below. If not, delete:

<The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004. See section 10.6.3.4 of this document.>

* + 1. <Request for Additional data exclusivity /Marketing protection>

*[Not applicable for biosimilars or EM-M4All – delete this section in these cases]*

Delete if no application was made.

For application including a claim from the applicant and the relevant supportive data for 1 year of data exclusivity for the specific new indication in accordance with Articles 10(5) and 74(a) of Directive 2001/83/EC, is reflected in the [GUIDANCE ON A NEW THERAPEUTIC INDICATION FOR A WELL-ESTABLISHED SUBSTANCE](https://health.ec.europa.eu/system/files/2016-11/10%252520_5_%252520guideline_11-2007_en_0.pdf) and the [GUIDELINE ON CHANGING THE CLASSIFICATION FOR THE SUPPLY OF A MEDICINAL PRODUCT FOR HUMAN USE](https://health.ec.europa.eu/system/files/2016-11/switchguide_160106_en_0.pdf), respectively. It is critical that the Rapporteur/CHMP addresses the claims of the applicant in this context in a separate report (see separate template/appendix) which will be transmitted to the Applicant/European Commission.

For application including a claim from the applicant and the relevant data for a [1 extra-year of marketing protection](https://health.ec.europa.eu/system/files/2016-11/guideline_14-11-2007_en_0.pdf) [Article 14(11) of Regulation (EC) No. 726/2004], then the Rapporteur/CHMP has to adopt an independent report (see separate template/appendix) which will be transmitted to the Applicant/European Commission and take a position on the novelty of the indication/significant clinical benefit of the medicinal product concerned in comparison with existing therapies. It is critical that the Rapporteur/CHMP addresses the claims of the applicant in this context.

<The applicant requested consideration of one year <data exclusivity> <marketing protection> in regards of its application for a <new indication> <for a change in the legal status classification> in accordance with <Article 10(5) of Directive 2001/83/EC> <Article 74a of Directive 2001/83/EC><Article 14(11) of Regulation (EC) 726/2004>.

* + - 1. <CAT/CHMP recommendation on additional data exclusivity /marketing protection >

For opinions including a new indication, for which the applicant claimed an additional year of marketing protection/data exclusivity in accordance with Art 14(11) of Regulation (EC) No 726/2004 – new indication submitted within the 8 first years of an MA, or in accordance with Art 10(5) of Directive 2001/83/EC - new indication for a well-established substance:

<The CHMP reviewed the data submitted by the applicant, taking into account the provisions of <Article 14(11) of Regulation (EC) No 726/2004> <Article 10(5) of Directive 2001/83/EC>, and <considers> <does not consider> <, by a majority of {number} out of {number} votes,> that:

<the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix on Article 14(11)0).>> [For Art 14(11)] of Regulation (EC) No 726/2004.

or

<the <non-clinical tests> <and> <clinical studies> carried out in relation to the new indication were significant>[For Art 10(5)] of Directive 2001/83/EC (see appendix on Article 10(5)).>

[For opinions including a legal status switch, for which the applicant claimed an additional year of data exclusivity:]

<The CHMP reviewed the data submitted by <the applicant> taking into account the provisions of Article 74(a) of Directive 2001/83/EC and <considers> <does not consider> <by a majority of {number} out of {number} votes,> that the <non-clinical tests> <and> <clinical trials> submitted in support of the classification of {specify medicinal product name} as ‘medicinal product not subject to medical prescription’ are significant (see appendix on Article 74a 10.3).

In case during the procedure the applicant decides to withdraw the request for addition data exclusivity or marketing protection please use:

<On <date>, the applicant withdrew their request for additional <data exclusivity> <marketing protection>.

* + 1. <New active substance status>

*[Not applicable for biosimilars or EM-M4All – delete this section in these cases]*

This section has to be filled out in case the applicant has claimed that the compound is a new active substance, either ‘in itself’ or in comparison to a substance previously authorised as a medicinal product in the European Union. If there is no claim for new active substance (NAS) the section is not required and should be deleted. In case of more than one NAS please consider including the applicable request for each of the NAS.

<The applicant requested the active substance {*active substance*} contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.>

[or]

<The applicant requested the active substance {active substance} contained in the above medicinal product to be considered as a new active substance in comparison to {active substance} previously authorised in the European Union as {name of the medicinal product authorised}, as the applicant claimed that {active substance} differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.>

[or]

<The applicant requested the radiopharmaceutical substance {active substance} to be considered as a new active substance as <it is a constituent not previously authorised in a medicinal product in the European Union> <the coupling mechanism to link {active substance}and <the radionuclide> <the ligand> has not been authorised previously in the European Union>.>

* + - 1. <CAT/CHMP recommendation on new active substance status>

[This section has to be filled out to reflect the CHMP conclusions in case of assessment of new active substance]

This section should be based on the CHMP AR on NAS (see appendix on new active substance status claim assessment report). In case of more than one NAS please consider including the outcome applicable for each of the NAS.

For opinions where the applicant claimed that the compound is a new active substance in itself:

<Based on the review of available data on the active substance, the CHMP considers that <active substance> is <not> to be qualified as a new active substance in itself as it is <not> a constituent of a medicinal product previously authorised within the European Union.

In case NAS in itself is denied, the following should be added:

<{Active substance} is contained in the marketing authorisation {invented name – authorisation number} which was authorised in the European Union on {date of authorisation}.>

For opinions where the applicant claimed that the compound is a new active substance in comparison to a known isomer/mixture of isomers/complex /derivative/salt of a chemical substance or biological previously authorised as a medicinal product in the European Union:

<Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the <CHMP><CAT> considers that <[for chemicals] <isomer/mixture of isomers/complex /derivative/salt of> {INN (+salt) applicant} in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of> {INN (salt) approved}>< [for biologicals] {active substance (biological of the applicant)} in comparison to {active substance (biological approved)} previously authorised as a medicinal product in the European Union is <not> to be qualified as a new active substance as <it differs><insufficient evidence has been provided to demonstrate that it differs> significantly in properties with regard to safety and/or efficacy from the previously authorised substance.>

[For radiopharmaceutical products]

<Based on the review of available data, it is considered that this radiopharmaceutical substance, which is <a radionuclide> <a ligand> is <not> a new active substance as <it is a constituent of a medicinal product previously authorised within the European Union> <the coupling mechanism to link {*active substance*}and <the radionuclide> has not been authorised previously in the European Union>.>

[or for cases where the same active substance is already authorised in a medicinal product or authorised in the meantime.]

<Based on the review of available data, it is considered that {active substance} is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. {Active substance} is contained in the marketing authorisation {invented name}, which was authorised in the Union on {date of authorisation}.>

Refer to the Appendix on new active substance status claim assessment report.

In case during the procedure the applicant decides to withdraw the new active substance request please use:

<On {date}, the applicant withdrew their request for new active substance.>

* 1. <Third party interventions>

If no third-party intervention is received, delete this section.

<A third party intervention has been received during the procedure. Discussion on this is reflected as relevant in the scientific report below in efficacy/safety discussions and/or Benefit/Risk.>

* 1. <Patient experience data>

The following table with tick boxes provides an overview on the type of Patient Experience Data (PED) submitted in support of this application. Please tick the option that applies and mention section where this is further referenced in the AR:

Table 2: Patient experience data relevant to the application

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient experience data submitted with this application | | | | Section where discussed (if applicable) |
|  | Patient experience data submitted by the applicant: | | |  |
|  |  | Clinical outcome assessments (COAs) such as | |  |
|  |  |  | Patient-reported outcomes (PRO) |  |
|  |  |  | Other |  |
|  |  | Patient preference studies | |  |
|  |  | Observational studies/RWD designed to capture patient experience data | |  |
|  |  | Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc) | |  |
|  |  | Other (please specify) | |  |
|  | Other patient experience data not submitted by the applicant but considered in this evaluation: | | |  |
|  |  | Input informed from participation in meetings or public hearings with patient stakeholders | |  |
|  |  | CHMP early dialogue with patient organisations | |  |
|  |  | Third party interventions from patients and patient groups | |  |
|  |  | Other (such as medical literature, summaries/analysis from patient engagement activities - please specify) | |  |

* 1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

|  |  |
| --- | --- |
| Rapporteur: | <Text> |
| Co-Rapporteur: | <Text> |

The Rapporteur and Co-Rapporteur appointed by the PRAC were:

|  |  |
| --- | --- |
| PRAC Rapporteur: | <Text> |
| PRAC Co-Rapporteur: | <Text> |

If the Rapporteur was involved in Scientific Advice or Protocol Assistance, insert the following:

<For the appointed CHMP Rapporteur it was considered exceptionally justified that the individual had previously been acting as coordinator for <Scientific Advice> <Protocol Assistance> on the development relevant for the indication subject to the present application. The justification was as follows:

[Insert the justification from the evaluation form. Exemptions could be accepted and/or justified in case that no other member or alternate with a comparable or equally adequate expertise for that product in that indication is available]

The appointed CHMP Co-Rapporteur had no such prominent role in <Scientific Advice> <Protocol Assistance> relevant for the indication subject to the present application.>

Delete any rows that are not relevant. In the case where the procedure was discussed at ETF, please add a row at the relevant time point(s).

|  |  |
| --- | --- |
| The application was received by the EMA on | <DD Month YYYY> |
| An application for accelerated assessment was filed by the applicant.  <Accelerated assessment procedure was <not> agreed-upon by CHMP on>  [if reverted to standard TT reflect at the appropriate step e.g. LOQ or later] | <DD Month YYYY> |
| The procedure started on | <DD Month YYYY> |
| The CHMP Rapporteur's first Assessment Report was received on | <DD Month YYYY> |
| The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur’s report on | <DD Month YYYY> |
| The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs’ report and circulated to all PRAC and CHMP members on | <DD Month YYYY> |
| Only in case of accelerated assessment otherwise delete the step:  <In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days> | <N/A> |
| <The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on> | <DD Month YYYY> |
| <The <Quality><Biologics> Working Party agreed on the Assessment Overview during their meeting on> | <DD Month YYYY> |
| <The Emergency Task Force (ETF) agreed on the Assessment Overview during their meeting on> | <DD Month YYYY> |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | <DD Month YYYY> |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | <DD Month YYYY> |
| In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable):  <The following <GMP> <GCP> <GLP> inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:  <A GCP inspection at <number of sites> <kind of sites> <Country of the sites> between <dates of inspection>.  The outcome of the inspection carried out was issued on.>  <A GMP inspection at <number of sites> <kind of sites> <Country of the sites> between <dates of inspection>. The outcome of the inspection carried out was issued on.>  <A GLP inspection at <number of sites> <kind of sites> <Country of the sites> between <dates of inspection>. The outcome of the inspection carried out was issued on.>> | <DD Month YYYY>  <DD Month YYYY>  <DD Month YYYY> |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP and PRAC members on | <DD Month YYYY> |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | <DD Month YYYY> |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | <DD Month YYYY> |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | <DD Month YYYY> |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP and PRAC members on | <DD Month YYYY> |
| <The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on> | <DD Month YYYY> |
| Upon request of the CHMP, the PDCO provided an opinion on the paediatric data with regard to <quality>, <safety>, <and> <efficacy> based on data collected in accordance with the agreed paediatric investigation plan. | <DD Month YYYY> |
| <SAG/Expert group/ Working Party experts (as appropriate)> were convened to address questions raised by the CHMP on  The CHMP considered the views of the <SAG/Expert group/ Working Party (as appropriate)> as presented in the minutes of this meeting. | <DD Month YYYY> |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a <conditional> marketing authorisation <under exceptional circumstances> to {product name} on | <DD Month YYYY> |
| For submissions in accordance with Art. 58 of Regulation (EC) No. 726/2004, replace the previous bullet with the following:  The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to <Product Name> on | <DD Month YYYY> |
| For submissions where ancillary claims are requested also include the following steps, as appropriate: |  |
| In case an authorised orphan product benefiting from market exclusivity from the start of the procedure has its orphan drug designation removed from the Union Register of orphan medicinal products -under the terms of Article 5(12) or Regulation (EC) No 141/2000- prior to the adoption of the final CHMP opinion for this procedure, the similarity assessment vis a vis such orphan product should still be completed.  <The CHMP adopted a report on similarity of <name of the medicinal product with name of the authorised orphan medicinal product(s) authorised from the start of the procedure on (see Appendix on similarity)> | <DD Month YYYY> |
| <The CHMP adopted a report on derogations applicable to similar orphan products for <name of the medicinal product> authorised from the start of the procedure on (see Appendix on derogations)> | <DD Month YYYY> |
| <The CHMP adopted a report on the novelty of the indication/significant clinical benefit for {product name} in comparison with existing therapies on (see Appendix on Article 14(11)) >  [in case of Article 14(11) claim] | <DD Month YYYY> |
| <Furthermore, the CHMP adopted a report on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication for {product name}, (see Appendix on Article 10(5)) on >  [in case of Article 10(5) claim] | <DD Month YYYY> |
| <Furthermore, the CHMP adopted a report on the significant non-clinical or clinical data in relation to the claimed new indication for {product name}, (see Appendix on Article 74a) on>  [in case of Article 74a claim] | <DD Month YYYY> |
| <Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)> | <DD Month YYYY> |

The (Co-) rapporteurs assessment reports have been discussed and supported by the Emergency Task Force (ETF) in the context of its public health preparedness activities.

In case the initial procedure was subject to the OPEN project, please keep and provide the necessary information in the text below:

<During the assessment of the application for the marketing authorisation of {product name}, the following non-EU authorities were allowed to participate as part of the OPEN framework and contribute to the scientific discussions of the <ETF and/or QWP/BWP and> CHMP: <OPEN partner name>. This/these authority/ies did not participate in the overall benefit/risk determination, which was decided by the CHMP.>

* 1. Final CHMP outcome

This whole section is to be completed by EMA at D210.

* + 1. Considerations related to paediatrics

*[Not applicable for biosimilars, well-established medicinal use or EM-M4All – delete this section in these cases]*

The requirements for the submitted dossier in relation to paediatrics are described in section 2.5 of this report.

The statements below regarding PIP are only needed in case the application contains paediatric data collected in accordance with a PIP.

In line with SmPC guideline, please include the relevant paediatric statements in Section 5.1 of the SmPC if the EMA has waived or deferred a paediatric development.

PIP fully or partly completed, and paediatric data included in the assessment:

<The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan [insert relevant PIP decision number(s)] and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.> [in case of (partial) waiver or deferral of paediatric development also add the following] <Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has <waived> <or> <deferred> a paediatric development have also been included>

Only in case the CHMP denies conformity with the agreed PIP.

<However, the CHMP is of the opinion that the studies are not in conformity with the agreed paediatric investigation plan [insert relevant PIP decision number(s)] as set out in Article 24 of Regulation (EC) No 1901/2006. The detailed grounds for the non-conformity conclusion are as follows:>

[In case of a negative outcome on the conformity with the agreed PIP, a detailed justification should be provided. Please liaise with the Rapporteur for the text to be included.]

<Text>

Guidance for compliance status annexed to the EC letter.

IMPORTANT NOTE REGARDING THE COMPLIANCE STATUS ANNEXED TO THE EC LETTER:

An annex to the letter to the Commission is needed in case the application contains paediatric data collected in accordance with a PIP eligible for the reward (please check the PIP reference with the paediatric coordinator), that the PIP eligible for the reward is fully completed and compliance is confirmed and the results of the studies from the PIP have been fully reflected in the SmPC. It must not be included if the CHMP denies conformity.

* + 1. Considerations related to orphan market exclusivity

[Not applicable for EU-M4all]

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 2.6 of this report.

For the preparation of the EPAR only: Use one of the following paragraphs, as appropriate, which should be deleted if the CHMP opinion is negative:

<Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of {insert name of product} as an orphan medicinal product in the approved indication. The <positive><negative> outcome of the COMP review on maintenance of the orphan designation can be found here {insert link} (note: link to be provided by COMP secretariat).>

<Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on {date of removal from Register} on request of the sponsor.>

* + - 1. Similarity with authorised orphan medicinal products

[Not applicable for EU-M4all]

This section should be completed by CHMP opinion.

This section should be based on the CHMP AR on similarity (appended) and address similarity with regard to the molecular structural feature, mechanism of action and therapeutic indication, in comparison with authorised orphan medicinal products.

The CHMP <by consensus><by majority decision> is of the opinion that {name of product} is <not> similar to {name of authorised orphan medicinal products} within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.>

* + - 1. <Derogation(s) from market exclusivity applicable to similar orphan products>

[Not applicable for EU-M4all]

This section should be based on the CHMP AR on clinical superiority (appended).

The CHMP <by consensus><by majority decision> is of the opinion that pursuant to Article 8 of Regulation (EC) No 141/2000 and <Article 3 of Commission Regulation (EC) No 847/2000> the following derogation<s> laid down in Article 8(3) of Regulation (EC) No 141/2000 <apply/ies> <do/es not apply>:

* <the holder of the marketing authorisation for {authorised orphan medicinal product name} is unable to supply sufficient quantities of the medicinal product> and/or
* <the applicant could establish in the application that the medicinal product, although similar to {authorised orphan medicinal product name}, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication> (see appendix on derogations). or
* <the holder of the marketing authorisation for {authorised orphan medicinal product name} has given his consent to the applicant.>

See the appendix on derogation(s) from market exclusivity applicable to similar orphan products.

* + 1. <Final opinion> to be used for positive outcome

For POSITIVE OPINION (POSITIVE B/R, POSITIVE ORPHAN OUTCOME) us the following:

Based on the <CAT><CHMP> review of data on quality, safety and efficacy, the CHMP considers <by consensus><by majority decision> that the benefit-risk balance of {Product Name} is favourable in the following indication(s):

{Add approved indication(s)}.

The CHMP, therefore, <endorses the CAT conclusion and> <recommends> the granting of the <conditional> marketing authorisation <under exceptional circumstances> subject to the conditions described in the following sections.

For EU-M4All use:

The CHMP, therefore, <recommends> the granting of the <conditional> scientific opinion <under exceptional circumstances> subject to the conditions described in the following sections.

* + - 1. <Divergent position(s)>

<Divergent position(s) to the majority recommendation on <Benefit/risk – Full CHMP opinion> <and> <similarity> <and> <new active substance> <and> < additional data exclusivity /marketing protection> <is><are> appended to this report.>

* + 1. <Final opinion> to be used for positive opinion with negative similarity etc

Use this section for POSITIVR OPINION IN ASSOCIATION WITH NEGATIVE SIMILARITY/CLINICAL SUPERIORITY, or for an overall NEGATIVE OPINION on B/R

<Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers <by consensus><by majority decision> that the benefit-risk balance of {Product Name} in the <treatment> <diagnosis><prophylaxis> of {claimed/approved indication} is <favourable><unfavourable>. <However><In addition>, the CHMP considers {product name} to be similar to {authorised orphan medicinal product name} for the same therapeutic indication and considers that none of the derogations regarding orphan market exclusivity apply. Therefore, the CHMP recommends the refusal of the granting of the Marketing Authorisation for the above-mentioned medicinal product.>

<Furthermore, following the review of the available data in the context of the applicant’s <claim of new active substance status>, <and> <request for an additional year of market protection/data exclusivity>, the CHMP position at the time of this report is reflected in {appendix X}.

* + - 1. <Divergent position(s)>

<Divergent position(s) to the majority recommendation on <Benefit/risk – Full CHMP opinion> <and> <similarity> <and> <new active substance> <and> < additional data exclusivity /marketing protection> <is><are> appended to this report.>

* + 1. <Final opinion> to be used for negative opinion

NEGATIVE OPINION BASED ON NEGATIVE B/R

Based on the CHMP review of data on quality, safety and efficacy for {Product Name} in the <treatment> <diagnosis><prophylaxis> of {proposed indication}, the CHMP considers <by consensus><by majority decision> that [select, as appropriate, option {a}, {b}, or {c} below]

[a] <the <quality> <safety> <efficacy> of the above-mentioned medicinal product is not sufficiently demonstrated,

[b] <particulars or documents provided in accordance with Article 6 of Regulation (EC) No 726/2004 are incorrect>

[c] <the labelling and package leaflet are not in accordance with Title V of Directive 2001/83/EC>

and, therefore, recommends the refusal of the granting of the <conditional> Marketing Authorisation <under exceptional circumstances> for the above-mentioned medicinal product. The CHMP considers that {list of grounds for refusal}.

Due to the aforementioned concerns a satisfactory <summary of product characteristics>, <labelling>, <package leaflet>, <pharmacovigilance system>, <risk management plan> and <post-authorisation measures to address other concerns as outlined in the list of outstanding issues> cannot be agreed at this stage.

<Furthermore, following the review of the available data in the context of the applicant’s <claim of new active substance status>, <and> <request for an additional year of market protection/data exclusivity>, the CHMP position at the time of this report is reflected in {appendix X}.

It is advisable not to split up the grounds for refusal into a quality chapter and an efficacy/safety chapter but to "bullet" the different grounds for refusal one after the other. The grounds for refusal should be based on the major objections.

Major objections normally form the basis for the grounds for refusal. However, there are often "other concerns" that would also need to be resolved before a marketing authorisation is granted (which, when not resolved at the time of adopting the scientific opinion in the case of a positive outcome after re-examination, could eventually be translated into follow-up measures to be taken on board in the post-marketing phase by the MAH or could, in rare cases, be "upgraded" to major concerns during the re-examination phase depending on the particularities of the product/case).

* + - 1. <Divergent position(s)>

<Divergent position(s) to the majority recommendation on <Benefit/risk – Full CHMP opinion> <and> <similarity> <and> <new active substance> <and> < additional data exclusivity /marketing protection> <is><are> appended to this report.>

* + 1. <Conclusions on biosimilarity and benefit risk balance>

Delete if not biosimilar.

Based on the review of the submitted data, {name of product} is considered <not> biosimilar to {reference product}. Therefore, a benefit/risk balance comparable to the reference product <can><cannot> be concluded.

<Divergent position(s) <is><are> appended to this report.>

The following sections should be included only in case of positive opinion

* + 1. <Conditions or restrictions regarding supply and use>

Delete in case of negative opinion

<Medicinal product subject to medical prescription.>

<Medicinal product not subject to medical prescription.>

<Medicinal product subject to special medical prescription.>

<Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).>

<Medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).>

* + 1. <Official batch release>

(only for Vaccines and Blood products)

<In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory, or a laboratory designated for that purpose.>

* + 1. Other conditions and requirements of the marketing authorisation

Delete in case of negative opinion

* + - 1. Periodic safety update reports

PRAC Rapporteur to complete this section after the D166 discussion at PRAC.

[For medicinal products authorised as a conditional marketing authorisation (CMA), please use the statement below.]

<The requirements for submission of periodic safety update reports for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder shall submit periodic safety update reports every 6 months.>

[For all medicinal products, including CMA, except Article 58 products, use the below statement. Please specify within the CHMP assessment report (section 8.2) which birth date (international or European) will form the basis of calculating the data lock point in case of a new EURD entry.]

<The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

[In addition, for initial MAA for which the 1st PSUR has a data lock point within 6 months after the Commission Decision, please select the below statement as well.]

<The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.>

[For EU-M4All products, use the following statement]

<The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on {date of initial scientific opinion}.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every {frequency} until otherwise agreed.>

* + 1. Conditions or restrictions with regard to the safe and effective use of the medicinal product

Delete in case of negative opinion

* + - 1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

* At the request of the European Medicines Agency;
* Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

[When justified on a proportional risk-based approach, the CHMP could specify the deadline for submitting the next update to the RMP. In that case, please include:]

<An updated RMP shall be submitted by {CHMP agreed time deadline}.>

* + - 1. <Additional risk minimisation measures>

[All additional risk minimisation measures and their key messages to be added here. The template for this section is included in the Guidance on the format of the risk management plan (RMP) in the EU - in integrated format - Annex 6 - Details of proposed additional risk minimisation activities on the European Medicines Agency website at <https://www.ema.europa.eu/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans>). Leave blank if no additional risk minimisation measures are proposed in the RMP.].

<Text>

* + - 1. <Obligation to conduct post-authorisation measures>

The MAH shall complete, within the stated timeframe, the below measures:

All post-authorisation measures that are imposed as a condition to the MA to be listed here.

Where appropriate, please specify whether the measure is a post-authorisation efficacy study (PAES) in accordance with the Commission Delegated Regulation (EU) No 357/2014.

For a post-authorisation safety study (PASS), please state clearly in the study description if interventional or noninterventional.

Description: please include the exact wording following the Advisory Group on Classification of Post-Authorisation Studies (CPAS) consultation and agreement by Rapporteurs.

Due date: please only include the projected time point of the final study report submission. The exact milestones regarding protocol submission/agreement and interim reports should be detailed above and in the RMP, as appropriate and included in Siamed for tracking/chasing.

Table 3: Post-authorisation measures

| Description | Due date |
| --- | --- |
| <Post-authorisation efficacy study (PAES): {insert study title or description}> | <DD Month YYYY> |
| <Non-interventional post-authorisation safety study (PASS): {insert study title or description} > | <DD Month YYYY> |
| <Other> | <DD Month YYYY> |

* + 1. <Specific obligation to complete post-authorisation measures for the <conditional> marketing authorisation <under exceptional circumstances>

[To be filled in only in case a conditional marketing authorisation or marketing authorisation under exceptional circumstances is being recommended by CHMP.]

<This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:>

<This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:>

[All specific obligations to be listed here.

For a post-authorisation safety study (PASS), please state clearly in the study description if interventional or non-interventional.

Description: please include the exact wording following CPAS consultation and agreement by Rapporteurs.

Due date: please only include the projected time point of the final study report submission. The exact milestones regarding protocol submission/agreement and interim reports should be detailed above and in the RMP, as appropriate and included in Siamed for tracking/chasing.]

Table 4: Specific obligations

| Description | Due date |
| --- | --- |
| <Post-authorisation efficacy study (PAES): {insert study title or description}> | <DD Month YYYY> |
| <Post-authorisation safety study (PASS): {insert study title or description}> | <DD Month YYYY> |
| <Other> | <DD Month YYYY> |

* + 1. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

[Any measures already described in Annex II should not be copied automatically here. Use of this section should be exceptional and limited to activities that require specific actions by the member states.]

<Not applicable.>

These conditions <fully><partly>< do not> reflect the advice received from the PRAC. <Divergences from the PRAC Advice are justified in an annex to this report.>

* + 1. Proposed list of recommendations

EMA to remove this section for the final EPAR preparation

The tables below summarise the proposed or requested post-authorisation measures that are part of the marketing authorisation as recommendations.

Table 5: Proposed list of recommendations

| Description of Recommendation(s) |
| --- |
| <Text> |
| <Text> |

1. Introduction
   1. Therapeutic Context

FACTUAL Section to be completed by Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Text for this section can be summarised from the same section in the D80 clinical report. A thorough summary of the literature is not expected in this document.

<Text>

* 1. Aspects of development

FACTUAL Section to be completed by Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Text for this section can be summarised from the same section in the D80 clinical report.

<Text>

* 1. Description of the product

FACTUAL Section to be completed by Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Text for this section can be summarised from the same section in the D80 clinical report.

<Text>

* 1. Inspection issues

State the need for an inspection (GMP, GLP, GCP). In case no inspection is required, and this is agreed, the text can be finalised as a CHMP/CAT position.

By D210, the report should capture which, if any, inspections took place and whether there was any impact on the assessment of the data in the dossier, e.g. data from certain sites could not be used in the assessment, or a manufacturing site was removed because of compliance issues. If need, can cross-refer to the quality, non-clinical and clinical sections where inspections are discussed.

* + 1. Good manufacturing practice (GMP) inspection(s)

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  <No inspection required.>  [For pre-approval inspections to verify GMP compliance]  <A request for GMP inspection <is required><has been adopted> for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>  And/or  [For pre-approval inspections to cover product or process related issues]  <A request for GMP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  <No inspection required.>  [For pre-approval inspections to verify GMP compliance]  <A request for GMP inspection <is required><has been adopted> for the following site(s) in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>  And/or  [For pre-approval inspections to cover product or process related issues]  <A request for GMP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.> |

* + 1. Good laboratory practice (GLP) inspection(s)

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  <No inspection required.>  [For pre-approval inspections to verify GLP compliance]  <A request for GLP inspection <is required><has been adopted> for the following site(s) in order to verify the GLP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>  And/or  [For pre-approval inspections to cover product or process related issues]  <A request for GLP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  <No inspection required.>  [For pre-approval inspections to verify GLP compliance]  <A request for GLP inspection <is required><has been adopted> for the following site(s) in order to verify the GLP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.>  And/or  [For pre-approval inspections to cover product or process related issues]  <A request for GLP inspection <is required><has been adopted> for the following site(s) in order to provide further product specific information. The outcome of this/these inspection(s) is required for the Committee during its examination of the application and will be needed by Day 121.> |

* + 1. Good clinical practice (GCP) inspection(s)

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  < No inspection required.>  [For routine GGP inspections]  <A request for GCP inspection <is required><has been adopted> for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>  And/or  [For triggered GCP inspections]  <A request for GCP inspection <is required><has been adopted> for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Elaborate general comments as appropriate in concordance with points made in the critical assessment report.  <Text>  For inspection request please use the following statement as necessary:  < No inspection required.>  [For routine GGP inspections]  <A request for GCP inspection <is required><has been adopted> for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>  And/or  [For triggered GCP inspections]  <A request for GCP inspection <is required><has been adopted> for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.> |

1. Quality aspects

|  |
| --- |
| **The aim of this document is to cover chemical products and biological products (e.g. recombinant proteins). For products of particular complexity, e.g. radiopharmaceuticals or ATMPs, the template and guidance may not address every critical aspect but can still be used as reference. It is not intended to be used as a checklist but rather as assistance to the assessor to critically distil the quality AR (D80 , D150 etc) into a succinct and comprehensive summary.**  **The purpose of the Overview Quality AR is to support the scientific opinion and recommendation issued by the CHMP to support the EC in its decision making. In addition the Overview develops during the procedure and evolves into the CHMP AR for Opinion and eventually the EPAR.**  **In order to achieve this, rather than a direct copy/paste, it should present in a brief, succinct way those details necessary to understand what is in the application for the MAA and sufficiently address the conclusions of the evaluation.**  **A self-standing but focused summary is expected in order to allow for the reader to have a comprehensive understanding of the relevant findings affecting the benefit-risk assessment, regulatory oversight and lifecycle management. The Overview should be a brief summary of the quality AR and should elaborate only on the significant and noteworthy findings and aspects from the critical assessments on Quality as detailed and captured in the Quality AR. The level of detail would depend on the complexity of the product and the quality of the dossier.**  **It should focus on the main conclusions and discussion/interpretation of the results giving the grounds for the benefit-risk assessment, the CHMP recommendations and/or the questions, especially the Major Objections (MO), raised to the applicant should be included in a concise and succinct manner. Some Other Concerns may be mentioned in the Overview but generally the Overview does not need to mention each and every Other Concern and the assessment text is not intended to list and describe the resolution of all other concerns raised.**  **To maintain clarity, it is strongly recommended to label unresolved outstanding issues that have led to an additional question (LOQ/LoOI), with an indicator, using (MO) for major objections or (OC) for other concerns.**  **The Overview is not intended as a history of the assessment and instead it should rather reflect the status at each milestone of the evaluation procedure. The report is expected to evolve from D80 to EPAR, arguments should be re-formulated; nevertheless the EPAR, needs to summarise the aspects that underpin the benefit/risk of the product and the claims in the product information.**  **This is particularly important in view of the need for a CHMP AR at the time of a possible withdrawal and/or access to document requests.**  **Generally for each section, consider addressing the following points:**  **1) State if the data submitted fulfil the requirements**  **2) Identify the most important findings and deficiencies described above (do not repeat results). Summarise evidence for each conclusion.**  **3) Describe the Major Objections raised and to what extent they have been/should be addressed.**  **The document should be updated at the different stages of the CHMP review (e.g. D80, D120-LOQ, D150 D180 LOI, Opinion CHMP AR, EPAR).**  **In case that a post approval measure (PAM) is agreed, it should be discussed in the respective section of the Overview (e.g. Control of finished product) so that there is a link with the recommendations (REC) for future development put forward in section 4.4.1.**  **Please note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the ‘main’ headings. Assessors may add more, or less, depending upon the complexity of the product; please also refer to the CTD guidance text for the applicant. In circumstances where there are multiple active substances or multiple pharmaceutical forms it may be considered to duplicate the “Active substance” and “Finished product” sections in order to present the information separately per active substance/pharmaceutical form. In addition, note also that the CTD terms ‘Drug Substance’ and ‘Drug Product’ are synonymous with the EU legislative terms ‘Active Substance’ and ‘Finished Product’ respectively.**  **In certain parts some proposed wording is suggested. Proposed wording is provided within angle brackets (< >). Such proposed wording is neither mandatory to use, nor is meant as the bare minimum for the Overview AR. It is meant to facilitate the drafting of the Overview and may need to be adapted by the assessor, or may not be used at all, if not appropriate. The proposed wording should be adapted by the assessor to reflect the status at a particular milestone. For example, text outlining that impurities are appropriately controlled and characterised may be adjusted to indicated that information is not yet acceptable if there are outstanding issues that the applicant must first address.**  **In the Overview, the Rapporteur is responsible for incorporating the factual data main conclusions and discussion/interpretation of the data (sections 4.1-4.3), and a comprehensive discussion, and conclusions (section 4.4) from the D80 and subsequent Quality assessment reports.**  **The Co-Rapporteur should only add to any factual sections already included by the Rapporteur if there is a major omission or mistake. In this case, the Co-Rapporteur can insert relevant boxes for Co-Rapporteur assessment as applicable.**  **The Co-Rapporteur input is essential in the conclusion and discussion section where they should add their assessment sections (directly in the boxes) especially if there are dissenting views or notable omissions requiring addressing.**  **KEY:**  **AS:** active substance  **FP:** finished product  **Boxed Text:** guidance applicable to all types of products, Chemical and Biological.  **Boxed Text with “Chem” or Bio” label:** guidance specific to Chemical or Biological products as indicated.  **<Text>** : Rapporteur should fill in this part |

* 1. Introduction

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

A brief description of the finished product pharmaceutical form, strengths, excipients and packaging would suffice in most cases.

<Text>

**Bio and Chem: The following text may be used:**

<The finished product is presented as <*pharmaceutical form(s)*> containing <*strength(s)*> of <*INN*> as active substance.

Other ingredients are: (*include the list of excipients as described in section 6.1*).

The product is available in <*primary packaging as described in section 6.5 of the SmPC*>.

**Bio and Chem:**

Mention Medical Devices, if it is part of the presentation of the medicinal product.

<Text>

* 1. Active substance
     1. General information

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

Include nomenclature: At least one sentence to mention the name of the AS. Confirm whether the name is INN, Common Name, etc.

<Text>

**Chem:**

Provide the structure, MW and chemical formula of the AS.

General Properties that are relevant to the product development (e.g. oxygen, air or light stability) or to the clinical performance (e.g., solubility, polymorphism, isomers, particle size etc.) should be mentioned.

Mention whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used.

<Text>

**Chem: The following text may be used:**

<The chemical name of <active substance> is <chemical IUPAC name(s)> corresponding to the molecular formula <CxHyNzOn>. It has a relative molecular mass of <xxx.x> and the <following structure:>

Insert active substance structure

<Figure 1: active substance structure>

**Bio:**

Consider to include key structure components such as number of amino acids and molecular size, glycosylation/post-translational modifications, “artificial” modifications (amino-acid substitutions, pegylation). For complex biologicals such as extracts, mixtures, vaccines, viruses, cells etc it may be necessary to be more descriptive e.g. include a description of the viral/cell line and whether live/inactivated etc. Highlight and discuss elements of structure important for mechanism of action or to the clinical performance.

<Text>

* + 1. Manufacture, process controls and process development

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

***Description of manufacturing process and process controls***

**Chem:**

In case a CEP is provided, summarise the manufacturing process and process controls with the following sentence:

**Chem: The following text may be used:**

<The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.>

**Chem:**

In case of ASMF procedure is used, add the following sentence:

**Chem: The following text may be used:**

<Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.>

**Chem:**

Mention the manufacturing site(s) (not testing sites) and whether satisfactory GMP documentation has been provided.

<Text>

**Chem: The following text may be used:**

<The active substance is manufactured at <name and address of site>. Satisfactory evidence of GMP compliance has been presented.>

**Chem:**

Mention the number of sources (manufacturers, ASMFs) of the active substance. If more than one source, discuss the differences in the synthetic routes and how these potentially affect or not the product.

<Text>

**Chem: The following text may be used:**

<The active substance is synthesized in <*insert number*> main steps using <commercially available,> well-defined starting materials with acceptable specification(s)>.

Insert synthetic scheme(s)

<Figure 2: active substance synthetic process >

**Chem:**

The synthetic process scheme should be included above. Discuss if the manufacturing process is sufficiently described. When relevant, summarise narratively key steps with impact on AS purity and physical properties, e.g. steps generating key /genotoxic impurities, those with CPPs, milling for inhaled/poorly soluble ASs. For chiral drugs mention the origin of stereochemical control.

State if holding times are proposed and discuss whether they are acceptable.

<Text>

**Chem: The following text may be used regarding description of manufacturing process and process controls:**

<The active substance manufacturing process has been adequately described. Main steps are <*insert name/ID of steps e.g. coupling, purification, etc*>. <The ranges of critical process parameters and the routine in-process controls along with acceptance criteria are described for each step.><The proposed <holding> <processing> times have been adequately justified.><The active substance manufacturing process is considered acceptable.>

**Bio:**

Mention the manufacturers of the active substance. In addition, include a summary (one paragraph) of the main manufacturing process steps (e.g. fermentation (fed-batch or continuous), purification (e.g. chromatography steps), virus removal/inactivation (e.g. SD (treatment (reagents/incubation time & temperature); nanofiltration (filter name/pore size)) and in-process controls with an emphasis on those related to the safety of the product, e.g. tests for adventitious agents. Include manufacturing scale., as well as definition of batch, & batch size. Highlight any re-processing. Include a statement confirming if the process has been sufficiently described and that in-process controls are adequately set to control the process.

A high-level flow chart may be considered to supplement the narrative description. Discuss if the manufacturing process is sufficiently described.

When relevant, comment on local adaptations of the process if proposed to be run at different sites and how it has been shown that the different sites deliver material of the same quality.

State if holding times are proposed and discuss whether they are acceptable.

<Text>

**Bio: The following text may be used regarding manufacturers, description of manufacturing process and process controls:**

<The active substance is manufactured at <…>. Satisfactory evidence of GMP compliance has been presented.>

<The active substance manufacturing process has been adequately described. Main steps are <e.g. fermentation, recovery and purification>. <The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, <including controls for microbial purity and endotoxin>, are described for each step.> <The active substance manufacturing process is considered acceptable.>

***Control of materials***

**Chem:**

Briefly reflect on the acceptability of the proposed starting materials or other critical materials used in the synthesis/preparation of the active substance.

<Text>

**Chem: The following text may be used regarding the control of materials**

<Sufficient information concerning the starting materials used in the active substance manufacturing process has been submitted.> <The proposed starting materials are suitably justified,> <and all other materials proposed for use are adequately described and controlled.>

**Bio:**

Provide information and assessment outcome for raw and starting materials used for the production of the active substance. Details to include depend on the product type (e.g. recombinant proteins, vaccines, plasma-derived products, ATMPs).

For recombinant products and ATMP (as appropriate) include brief description of the expression construct and producer strain/cell line (type, origin). Include statement on genetic stability.

Include brief information on establishment of the MCB/WCB and or MSB/WSB including tests performed and stability. Mention if there is a protocol for the establishment of future WCB/WSB.

For plasma-derived products include reference to PMF certificate including reference number of last certificate.

<Text>

**Bio: The following text may be used regarding the control of materials**

<Adequate information on raw materials used in the active substance manufacturing process has been submitted.> <Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including analytical procedures) for non-compendial raw materials are presented.> <No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.>

<A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs.> <Genetic stability has been demonstrated for cells at and beyond the limit of cell age.>

***Control of critical steps and intermediates***

**Chem:**

Summarise whether critical steps are defined, and if applicable, reflect the acceptability of specifications for intermediates.

<Text>

**Chem: The following text may be used regarding the control of critical steps and intermediates**

<Adequate in-process controls are applied during the synthesis> <and critical steps have been suitably defined.> <The specifications and analytical procedures for intermediate products have been presented.>

**Bio:**

Include definition of critical steps and, if applicable, of intermediates held for an extended period of time prior to further processing. For these intermediates, include specifications, storage conditions and shelf lives/maximum storage periods.

Discuss if the overall control strategy (including in process controls, testing of starting material, monitoring of process parameters etc) and the risk mitigation measures are adequate to control the process leading to an AS of intended and consistent quality. Summarize deficiencies if found.

<Text>

**Bios: The following text may be used regarding the control of critical steps and intermediates**

<A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given.> <Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.> <Actions taken if limits are exceeded are specified.>

***Process validation***

**Chem:**

Briefly summarise the approach to process validation as relevant. If the AS is supplied as a sterile material, discuss the adequacy of the process validation studies.

<Text>

**Chem: The following text may be used regarding the active substance process validation studies**

<Information concerning the validation of the active manufacturing process has not been presented; this approach is acceptable.>

<The active substance manufacturing process has been sufficiently validated.> <The process and its control (IPCs and operational process parameters) are supported by the presented information.>

**Bio:**

Include manufacturing scale and batch size, number of process verification batches and conclusion on adequacy of manufacturing process verification.

Include a short description of process verification studies as applicable and discuss if they are adequate e.g. type of studies, scale, models used and cover the proposed commercial process. Describe any proposals for ongoing process verification or concurrent validation if applicable.

<Text>

***Bio: The following text may be used regarding the active substance process validation studies***

<The active substance manufacturing process has been validated adequately.> <Consistency in production has been shown on <*number*> full scale commercial batches.> <All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the process consistently produces <*INN*> of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.>

***Manufacturing process development***

**Chem:**

Summarize the key aspects/stages of the manufacturing process development that are essential in providing reassurance with regard to the AS quality e.g. important process changes through clinical/pharmaceutical development.

<Text>

***Chem: The following text may be used regarding manufacturing process development***

<The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.> <There have been no changes with respect to the batches used in the pivotal studies and as proposed for the commercial process>

<Changes introduced have been presented in sufficient detail and have been justified.>

<Several> <important> changes have been introduced during the development of the manufacturing process, including a change in the <*describe change*>.> It has been demonstrated that the change(s) did not have a significant impact on the quality of the product.>

<The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.>

**Bio:**

Summarize the key aspects/stages of the manufacturing process development that are essential in providing reassurance with regard to the AS quality e.g. briefly describe important process changes through clinical/pharmaceutical development. Highlight any issues with the way the comparability exercise was conducted taking into account in particular differences between pivotal clinical batches and what is intended for commercial production. With respect to changes, present and discuss the outcome of critical assessment of the significance of changes and impact on comparability between batches used for clinical trials vs commercial batches. Discuss any uncertainties and provide a clear conclusion.

<Text>

***Bio: The following text may be used regarding manufacturing process development***

<The commercial active substance manufacturing process was developed in parallel with the clinical development program.> <Several important changes have been introduced during the development of the manufacturing process, including <*e.g. a change in the cell line (from Sp2/0 to CHO), the introduction of the low pH viral inactivation step and a change in virus removal filter*>. <For each change, a comparability study has been carried out demonstrating that, apart from some expected differences <*e.g. in glycosylation*>, the change did not have a significant influence on the quality of the product.>

**Bio and Chem:**

Summarise relevant studies related to the control strategy (e.g. how critical process parameters have been identified) and mention if QbD elements have been used (risk assessment, DoE, prior knowledge, etc.); provide a short summary of those and confirm if the approach is acceptable. Briefly discuss how acceptable ranges were established and if the data provided in support of the ranges is acceptable.

If design space is claimed, clearly state if it is acceptable, describe which process steps it covers, at which scale it was developed and explain whether verification of the design space is needed at commercial scale.

<Text>

***Bio and Chem: If QbD:***

<The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DOE) studies, models, <…>. >

***Bio and Chem: If design space:***

<Based on these studies, design spaces have been proposed for the following steps of the manufacturing process of the active substance: *mention the steps e.g. step 1 – crystallization of an intermediate (give the step a name if possible).*>

<The design space has been developed at <commercial scale> <lab/pilot scale>. *For lab/pilot scale:* <Since the parameters of the design space are scale independent the design space developed at lab/pilot scale is also valid at commercial scale.>

<The design space is only partly verified at commercial scale, but an appropriate verification scheme has been provided to support its validity at commercial scale.>

<The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space>.

***Bio and Chem: If PAR:***

<Based on these studies, proven acceptable ranges have been suitably defined for the manufacturing process of the active substance.> <The available development data, the proposed control strategy and batch analysis data support the proposed PARs.>

* + 1. Characterisation and impurities

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Chem:**

Briefly describe the characterisation studies of the Active Substance structure and potential impurities.

General Properties that are relevant to the product development (e.g. oxygen, air or light stability) or to the performance of the product in the clinic (e.g., solubility, polymorphism, isomers, particle size etc.) should be mentioned.

For polymorphism, state the specific polymorphic form manufactured and whether it has been shown stable upon storage (may refer to stability data). Outline whether the polymorphic form is considered relevant to the performance of the product. Mention how many polymorphs have been identified (in literature or by experimental data), which of those are relevant/possible via the proposed manufacturing process. Mention how polymorphism is controlled.

Mention physical properties relevant to route of administration (e.g. inhaled, transdermal, low solubility orals) and/or FP manufacturing issues (aqueous (non-) solubility, hygroscopicity sensitivity to light/ heat / oxidation), and the performance of the product in the clinic and give values. Mention relevant information, e.g. there is probably no particular interest/added value to state the solubility in dichloroethane for example. It would be relevant instead to refer to those properties that are considered and played a role in the pharmaceutical development.

<Text>

***Chem: The following text may be used regarding characterisation***

<The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.>

<Potential and actual impurities are well discussed with regards to their origin and characterised.>

<The chemical structure of <active substance> was elucidated by a combination of…*mention the analytical methods used e.g. NMR, IR, UV, etc.* ><The solid state properties of the active substance were measured by… *mention the analytical methods used e.g. DSC, XRPD, etc*.>

<The <active substance> is a <physical state> <solid-state properties>, <hygroscopicity>, <solubility>.>

<<INN> exhibits stereoisomerism due to the presence of <number> chiral centres.> *Refer to the sources of stereoisomerism, e.g. starting materials. Mention how it is controlled, e.g. SM specs or intermediate specs or reaction conditions. e.g.* <Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.> *Or* <<active substance> has a non - chiral molecular structure>.

<Polymorphism has <not> been observed for <active substance>.>

**Bio:**

*Include summary of physiochemical and biological studies used to characterise structural elements and or biological activities of the active substance and conclusions on results of studies.*

*Include summary of studies to identify and characterise product-related impurities (reduced/non-active product substances) and process-related impurities (e.g. raw materials used during production), and where applicable, summarise and discuss risk assessment approaches and process-related impurities clearance studies performed, and mention impurities for which routine control is foreseen.*

<Text>

***Bio: The following text may be used regarding characterisation***

<The <*INN*> active substance has been sufficiently characterised by <orthogonal> physicochemical and biological state-of-the-art methods revealing that the active substance has the <expected structure> <and><or> biological activity.><The analytical results are consistent with the proposed structure.> <Furthermore, heterogeneity of the active substance was adequately characterised by analysing <size and charge variants, cell subpopulation, glycosylation and other product-related substances.> <Biological characterisation of the active substance indicates that this antibody has the ability to bind <include target> with high affinity and to specifically bind to <Fc Receptor> as expected of an <IgG1>.>

<Product-related impurities and process-related impurities have been sufficiently identified and characterised.> <Robust clearance of raw materials is shown to below levels of concern.>

<In summary, the characterization is considered appropriate for this type of molecule.>

* + 1. Control of active substance

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

***Specifications***

**Bio and Chem:**

*Discuss whether the proposed AS specifications limits, tests and analytical procedures are acceptable.*

*Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established/ justified and if this is in accordance with ICH Q6A or Q6B as appropriate. Discuss if the acceptance criteria of stated impurities have been justified based on general ICH thresholds where applicable or qualified in non-clinical and clinical studies or clinically justified by other means as appropriate.*

*A table of the current specifications should be included.*

<Text>

***Chem: The following text may be used***

<The active substance release specification shown in Table 1 includes tests for <*mention the latest specification and the analytical methods in brackets, for example*: <appearance>,< identity (*IR, HPLC*)>, <assay (*HPLC*)>, <impurities (*HPLC*)>, <residual solvents (*GC*),>< water content (*KF*)>, <heavy metals (*ICP-MS*)>, and <residue on ignition (*Ph. Eur.*)>.

***Bio: The following text may be used***

<The active substance release <and shelf life> specification shown in Table 1 includes tests for <*mention the latest specification and the analytical methods in brackets, for example*: <appearance (*clarity, colour*), >, <pH>, <microbial assurance (*bacterial endotoxins and bioburden*)>, <identity (*peptide mapping and IEC-HPLC*)>, <purity and impurities (*CE-SDS reduced/non-reduced, IEC-HPLC, SEC-HPLC, HIC-HPLC, residual HCP*)>, <concentration> and <potency>.

Table 1: active substance specification

Insert the specifications table

<Text>

***Bio and Chem: The following text may be used:***

<The proposed analytical procedures and corresponding limits are adequate for routine control of the active substance <at release> <and shelf life.>> <They are <generally> in line with ICH guidelines > <and Ph. Eur.> <and batch release data><and stability data>.

**Bio and Chem:**

Confirm that stated impurities have been studied in nonclinical and clinical studies as relevant.

<Text>

***Chem: The following text may be used:***

<Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.>

**Chem:**

Discussion regarding specific impurities or other materials (e.g. catalysts, residual solvents etc) may be expanded to consider specific issues such as those potentially impacting safety or efficacy are relevant.

Mention if the use of more than one sources of the active substance affects the specifications and the acceptability of this.

**Bio:**

If shelf-life specifications are different from the release specifications, briefly discuss whether these are sufficiently justified.

If testing for certain impurities (e.g. DNA, Protein A etc.) has been omitted from the specifications, briefly discuss the data provided to support this.

<Text>

**Bio and Chem:**

State clearly whether the AS is going to be released by real time release testing (RTRT). If RTRT is proposed, comment on the appropriateness of controls of the critical process parameters and critical materials attributes that would justify RTRT.

<Text>

**Chem (in case of CEP):**

Refer to the CEP, if there is one. Additional tests considered to be necessary, apart from the Ph. Eur. monograph, should be mentioned.

<Text>

***Chem (in case of CEP): The following text may be used :***

<The control tests were carried out to comply with the specifications and analytical procedures of the Ph. Eur. Monograph.>

*In case of additional parameters:* <Additional specifications have been set for <additional parameters>. All additional analytical procedures have been adequately validated and described according to ICH guidelines.>

***Analytical procedures and reference standards***

**Bio and Chem:**

Discuss whether the proposed procedures have been satisfactorily described and validated and if they are adequate to control the AS on a routine basis, i.e. as a release, or for stability testing purposes. Consider elaborating on specialised / pivotal analytical methods e.g. potency assays. Comment on the adequacy of information regarding the reference standards or materials, (or cross refer to the finished product section, as appropriate).

In case of analytical procedure flexibility, mention the method for which it is requested and if it is acceptable.

<Text>

***Bio and Chem: The following text may be used :***

<The analytical procedures used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines>. <Satisfactory information regarding the reference standards used for <assay> <and> <impurities> testing has been presented.>

***Batch analysis***

**Bio and Chem:**

Include a comment on the adequacy of batch analysis results, the batch size of the tested batches and batch-to-batch consistency.

<Text>

***Bio and Chem: The following text may be used :***

<Batch analysis data (*number of batches and scale*) of the active substance are provided.> <The results are within the specifications and confirm consistency of the manufacturing process.>

* + 1. Stability

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Chem:**

Clearly state the re-test period and storage conditions. Describe the proposed container closure system. Indicate whether stability studies / conditions were according to ICH guidelines and, if not, discuss if they are acceptable. Comment on the scale of batches and their representativeness of the commercial product.

If more than one synthetic route is proposed, discuss whether stability data are representative of all suppliers and whether there are any differences in stability.

Discuss if photostability study complies with ICH Q1B and mention the conclusions.

Summarise the stability results (including photostability and stress stability studies in a brief yet informative manner. Discuss any relevant findings identified during the stability studies. Discuss any out of specifications results and mention the conclusions in this respect.

Any supportive data should be discussed briefly (e.g. from previous versions of the synthesis or laboratory scale batches).

Mention the outcome of forced degradation/stress studies and discuss if analytical methods are stability indicating and if they are the same or different as those used for routine analysis; if different comment if the analytical procedures were sufficiently validated.

If a CEP is provided and contains a re-test period, make only reference to the CEP.

<Text>

***Chem: The following text may be used regarding stability***

The retest period of <*number*> <months> <years> <*storage conditions*> in the proposed container is justified by the available stability data.

<The commercial active substance is packaged in *<material>>* <which complies with Commission Regulation (EU) 10/2011, as amended.>

Stability data from <*number, scale*> batches of active substance from the <proposed> manufacturer(s) stored <in the intended commercial package><in a container closure system representative of that intended for the market> <*if not describe the package*> for up to <*number*> months under long term conditions (25 ºC / 60% RH) and for up to <*number*> months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. <Photostability testing following the ICH guideline Q1B was performed on <*number*> batches. <Results under stress conditions <*describe the stress conditions*> were also provided. Degradation was observed in <…> conditions. The stability indicating nature of the methods was confirmed.

The following parameters were tested*: <list the latest shelf life specifications> or* The parameters tested are the same as for release.> <The analytical procedures used were the same as for release (*if not mention, which additional analytical methods were used)* and were stability indicating as demonstrated through studies under <forced> <stressed> conditions.>

<All tested parameters were within the specifications.> <Degradation products increased under accelerated conditions but remained within the specification.>

<The observed physical and chemical changes were small, and are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.>

<The observed out of specification results do not pose any concern because <*explain the reasons*>.>

<The active substance is <not> sensitive to light.> <The active substance is <not> sensitive to <acidic>, <alkaline>, <heat>, <humidity>, <oxidative>, <hydrolysis> conditions.>

**Bio:**

Clearly state the maximum storage / shelf life period and storage conditions. Describe the container closure system intended for the market. Discuss whether stability studies / conditions were according to ICH guidelines and, if not, if they are acceptable. Comment on the scale of batches and their representativeness of the commercial product, including the container closure system.

Discuss if photostability study complies with ICH Q1B and mention the conclusions.

If relevant, mention supportive stability data generated with batches from earlier versions of the manufacturing process.

Discuss any relevant findings identified during the stability studies. Discuss any out of specifications results and mention the conclusions in this respect.

Mention the outcome of forced degradation/stress studies and discuss if analytical methods are stability indicating and if they are the same or different as those used for routine analysis; if different comment if the methods were sufficiently validated.

<Text>

***Bio: The following text may be used regarding stability***

The shelf life period of <*x*> months <*storage conditions*> in the proposed container is justified by the available stability data.

The commercial active substance is packaged in *<material(s)>.*

Real time, real condition stability data on <number, scale> batches of active substance from the <commercial manufacturing process> stored <in the intended container> for <*number*> months and for up to <*number*> months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

<Photostability testing following the ICH guideline Q1B was performed on <*number*> batches.><The active substance is <not> sensitive to light.>

*<*The parameters tested are the same as for release. *(if not mention, which additional analytical procedures were used)* > <All tested parameters were within the specifications.>

<The observed physical and chemical changes were small, and are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.>

<The observed out of specification results do not pose any concern because <*explain the reasons*>.>

<Results on stress conditions <describe the stress conditions> were also provide on <*number*> batches.>

* 1. Finished medicinal product
     1. Description of the product and pharmaceutical development

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

***Description of the product***

**Bio and Chem:**

Describe all components of the finished product as intended for marketing (physical description, pharmaceutical form, available strengths and differentiation thereof, devices). Such information typically includes the dosage form, the container closure system, reconstitution solvent (if included in the product package), information about overages/overfill, medical devices, etc. if applicable. Include the table from dossier section 3.2.P.1 detailing the qualitative and quantitative composition of the finished product and the function of each ingredient, if indicated.

<Text>

Table 2: composition of finished product

Insert composition table

***Pharmaceutical development***

**Bio and Chem:**

The objective of the pharmaceutical development should be described (e.g. to create a sterile parenteral product, or an immediate release solid oral formulation). Discuss whether the choice of pharmaceutical form/strength adequately addresses the clinical needs (i.e. QTPP; bioavailability, patient’s compliance, ease of administration, dosing regimen, target population (e.g. paediatrics), medical devices, etc.).

<Text>

***Bio and Chem: The following text may be used:***

<The aim of the pharmaceutical development was to develop a <*specify*>.>

<The quality target product profile (QTPP) was suitably defined and the critical quality attributes were identified.>

**Bio and Chem:**

Discuss whether the chosen formulation adequately accommodates the active substance’s physicochemical properties (stability, incompatibilities, solubility, route of administration etc.).

Indicate whether the commercial formulation development is supported by clinical studies. Elaborate, on the differences (if any) and their relevance between the intended commercial formulation and those used during pivotal clinical studies.

**Chem:**

Where relevant, state if equivalence between commercial product and clinical trial product, is established and how (bioequivalence study, in vitro biowaiver, in vitro-in-vivo correlation (IVIVC), other modelling studies) if relevant.

**Bio and Chem:**

Discuss whether the rationale for the choice, including the safety of the excipients is acceptable. Where applicable (e.g. paediatrics), reference to the non-clinical and/or clinical section can be given.

Discuss whether there are any novel excipients and cross refer to 3.2.A.3, Novel Excipients as appropriate.

The impact of specific excipients or excipient preparations on the performance of the product should be discussed in more detail (e.g. permeation enhancers or excipients which control release in vivo).

<Text>

***Bio and Chem: The following text may be used:***

<All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards>. <The choice of excipients has been justified.> <There are no novel excipients used in the finished product formulation.>

***Manufacturing process development***

**Bio and Chem:**

Indicate whether the choice of process has been justified taking into account the active substance physicochemical properties and /or product particularities (e.g. conversion of polymorphic form, dry/wet granulation, biological products that cannot be terminally sterilised by heat treatment).

Comment on the selection of the sterilisation process, e.g. whether terminal sterilisation is performed, if possible and applicable. Summarize the key aspects/stages of the manufacturing process development that are essential in providing reassurance with regard to the FP quality e.g. briefly describe important process changes through clinical/pharmaceutical development. Confirm whether any differences in the manufacturing processes of the commercial product and clinical trial material are adequately explained and, as appropriate, differences in product quality are adequately discussed and justified.

Confirm that any site transfers during pharmaceutical development were successfully completed.

Highlight the main conclusions of manufacturing process development and the relevant studies performed in order to define the control strategy (e.g. how critical process parameters and in-process controls have been identified). Confirm whether process parameter ranges are satisfactorily investigated/supported by pharmaceutical development.

Briefly discuss proposals for real time release testing (RTRT) and their acceptability when these are requested by the applicant.

<Text>

***Bio and Chem: The following text may be used:***

<The manufacturing development has been evaluated through the use of <risk assessment> <design of experiments> <other modeling techniques> to identify the critical product quality attributes and critical process parameters. <Critical quality attributes and critical process parameters have been adequately identified>. <The control strategy is considered acceptable> .

**Bio:**

Studies aimed at demonstrating comparability between the commercial manufacturing process and earlier versions of the manufacturing process, between different manufacturing sites, or between different formulations (e.g. lyophilised versus liquid) should be summarised.

Highlight any issues with the way the comparability exercise was conducted taking into account in particular differences between pivotal clinical batches and what is intended for commercial production. With respect to changes, present and discuss the outcome of critical assessment of the significance of changes and impact on comparability between batches used for clinical trials vs commercial batches. Discuss any uncertainties and provide a clear conclusion.

<Text>

**Bio and Chem:**

Summarise relevant process characterisation studies related to the control strategy (e.g. how critical process parameters have been identified). Mention if QbD elements have been used in the pharmaceutical development/ manufacturing development / process design (risk assessment, prior knowledge, DoE to support Design Space, etc.); and confirm if the approach is acceptable. Briefly discuss how acceptable ranges for process parameters and in-process controls were established and if the data provided in support of the ranges is acceptable.

<Text>

**Bio and Chem: If QbD, the following text may be used, consider including the most appropriate statement:**

<The manufacturing process has been evaluated using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DOE) studies, models, <…> .>

<The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space>.

**Bio and Chem:**

Conclude whether the suitability of the packaging material is justified and whether it complies with the relevant requirements as outlined in the AR. Indicate if the container closure system is/ is not suitable for use based on development studies, (compatibility and stability studies, ISO criteria, etc..

<Text>

* + 1. Manufacture of the product and process controls

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

Mention the names of the manufacturing site(s) (not testing or secondary packaging sites) and whether satisfactory GMP documentation has been provided. Summarise the manufacturing process and focus on the critical steps and their process control . Unusual or non-standard processing steps should be outlined in more detail. Include the flowchart if complementary to the narrative description.

Discuss the adequacy of the overall control strategy, including whether process parameters and in-process controls are adequately set to control the process leading to consistent quality.

State if holding times are proposed and discuss whether bulk packaging and holding times are acceptable.

Provide a brief summary of process validation / verification protocols and studies as applicable and discuss if they are adequate e.g. type of studies, scale, models used and cover the proposed commercial process. Conclude whether the presented validation data is sufficient or outline whether further process validation data are needed. The acceptability of protocols should be indicated.

<Text>

**Bio:**

For **ATMPs** mention here if the applicant has requested an exemption from re-testing batches upon import into the EU as per paragraph 11.17 of the EU GMP guideline for ATMPs.

<Text>

***Bio and Chem: The following text may be used :***

<The finished product is manufactured at … mention the manufacturing site(s) (not testing or secondary packaging sites)>. <Satisfactory evidence of GMP compliance has <not> been provided.>

<The manufacturing process consists of <*number*> main steps: <*list the steps*>. <The process is considered to be a <non> standard manufacturing process.>

Insert FP flow diagram

Figure 3: finished product manufacturing process

<The manufacturing process and its control, as well as critical equipment have been described in sufficient detail in sections P.3.3 and P.3.4.>

<The validation protocol submitted by the applicant is considered acceptable. The process will be validated prior to commercialization by (explain briefly validation strategy, e.g. XX consecutive batches at YY scale).>

<The manufacturing process has been validated on XX consecutive batches at YY scale.>

<It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this <type of manufacturing process> <and> <pharmaceutical form>. >

**Bio and Chem:**

**If a Design Space is claimed**, describe which steps of the process it covers and at which scale the Design Space was developed. State if it is acceptable and explain whether verification of the Design Space is needed at commercial scale.

Include a table outlining the agreed Design Space(s) (parameters and ranges).

Confirm the acceptability of the Design Space.

<Text>

**Bio and Chem:**

**The following specific text may be used in case of Design Space:**

<Design spaces have been proposed for the following steps of the manufacturing process of the medicinal product: <e.g. milling, dry granulation, film-coating>.

<The design space has been developed at commercial scale <lab/pilot scale>. For lab/pilot scale:<Since the parameters of the design space are scale independent the design space developed at lab/pilot scale is also valid at commercial scale>.<The design space is only partly verified at commercial scale, but an appropriate verification scheme has been provided to support moves to other areas of the approved design space.>

<The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space>.

***Bio and Chem:***

***If PAR, the following specific text may be used:***

<Proven acceptable ranges have been suitably defined for the manufacturing process of the finished product.> <The available development data, the proposed control strategy and batch analysis data support the proposed PARs.>

* + 1. Control of Finished Product

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

***Specifications***

**Bio and Chem:**

A table of the proposed commercial specifications should be included. Outline whether the proposed release and shelf life specifications, and related analytical tests are acceptable.

Discuss the acceptability of the proposed acceptance criteria, mention briefly how they have been established/ justified and if this is in accordance with ICH Q6A or Q6B as appropriate. Discuss if the acceptance criteria of stated impurities have been justified based on general ICH thresholds where applicable or qualified in non-clinical and clinical studies or clinically justified by other means as appropriate. Conclude if the control strategy on the elemental impurities as per ICH Q3D and on the potential presence of nitrosamines is adequate.

State clearly whether the Finished Product is going to be released by real time release testing (RTRT). If RTRT is proposed, comment on the appropriateness of controls of the critical process parameters and critical materials attributes that would justify RTRT.

<Text>

***Chem: The following text may be used***

The finished product release <and shelf life> specifications shown in Table 3 include appropriate tests for this kind of dosage form including: *<include the latest specification parameters at release with the tests in brackets>*<appearance>,< identity (IR, HPLC)>, <assay (HPLC)>, <impurities (HPLC)>, <residual solvents (GC),>< water content (KF)>, <heavy metals (ICP-MS)>, and <residue on ignition (Ph. Eur.)>, <device functionality tests>.

***Bio: The following text may be used***

<The finished product release <and shelf life> specification shown in Table 3 includes tests for <*mention the latest specification and the analytical methods in brackets, for example*: <appearance (clarity, colour), >, <pH>, <microbial assurance (bacterial endotoxins and bioburden)>, <identity (peptide mapping and IEC-HPLC)>, <purity and impurities (CE-SDS reduced/non-reduced, IEC-HPLC, SEC-HPLC, HIC-HPLC, residual HCP)>, <concentration> and <potency>, <device functionality tests>.

<The majority of analytical procedures are used to control both the active substance and finished product, except for …>

**Table 3: finished product release specifications**

*Insert specifications table*

<Text>

***Bio and Chem: The following text may be used :***

<The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product <at release> <and shelf life.>> <They are <generally> in line with ICH guidelines > <and Ph. Eur.> <and batch release data><and stability data>.

<Impurities present at higher than the qualification threshold according to ICH Q3B were qualified by toxicological and clinical studies and appropriate specifications have been set.>

<The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.>

*Plus, as applicable:* <Batch analysis data from <n> batches using a validated <ICP-MS> method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.> Based on the risk assessment <and the presented batch data> it can be concluded that <it is not necessary to include any elemental impurity controls> *or* <the following elemental impurities <list> are included> in the finished product specification. The information on the control of elemental impurities is satisfactory.>

<A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed according to the applicable guidance. <Based on the information provided, there is no risk of nitrosamine impurities in the finished product. Therefore, no specific control measures are deemed necessary.> <A risk was identified <*explain what>*. Confirmatory testing was carried out with a validated and sufficiently sensitive analytical method <*explain the test results*>. <Based on the information provided, the following control measures are deemed necessary. Specifically <*mention the control measures*>.>

***Analytical procedures and reference standards***

**Bio and Chem:**

Discuss whether the proposed procedures have been satisfactorily described and validated and if they are adequate to control the finished product on a routine basis, i.e. as a release, or for stability testing purposes. Consider elaborating on specialised / pivotal methods e.g. potency assays. Comment on the adequacy of information regarding the reference standards or materials, (or cross refer to the active substance section, as appropriate).

In case of analytical procedure flexibility, mention the method for which it is requested and if it is acceptable.

<Text>

***Bio and Chem: The following text may be used :***

<The analytical procedures used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines>. <Satisfactory information regarding the reference standards used for <assay> <and> <impurities> testing has been presented.>

***Batch analysis***

**Bio and Chem:**

Include a comment on the adequacy of batch analysis results, the batch size of the tested batches and batch-to-batch consistency.

<Text>

***Bio and Chem: The following text may be used :***

<Batch analysis data (*number of batches and scale*) of the finished product are provided.> <The results are within the specifications and confirm consistency of the manufacturing process.>

* + 1. Stability of the product

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

Mention the proposed shelf life and storage conditions

<Text>

***Bio and Chem: The following text may be used :***

The shelf life of <*number*> months <*storage conditions*> in the proposed container, as stated in the SmPC, is justified by the available stability data.

***Container closure system***

Describe the Container closure system and confirm that the description and specification of the containers proposed for routine storage are acceptable.

<Text>

***Bio and Chem: The following text may be used :***

<The container closure system is <*include description*> and it is considered appropriate for intended storage. Its specifications are acceptable and are in compliance with appropriate standards such as the Ph. Eur.> <Compliance with ISO standards for child-resistant closures has also been confirmed>.

**Bio and Chem:**

If the medicinal product includes components which are classified as medical devices (e.g. needles, catheters, etc.), confirm whether they comply with the relevant medical devices legislation. In accordance with Article 117 of the Medical Device Regulation (EU) 2017/745, where a medicinal product is used in combination with a single-use integral medical device, applicants should provide the relevant documentation from a Notified Body (Opinion or EU certificate) confirming compliance of the device with the relevant General Safety and Performance Requirements in Annex I.

<Text>

***Stability data***

**Bio and Chem:**

State clearly the claimed shelf-life/ in-use period and storage conditions as per the SmPC.

Include background information to understand the basis for the approved storage conditions, including in-use storage conditions, where relevant.

Confirm whether stability studies / conditions were performed according to ICH guidelines and if not why they have been accepted. Comment on the scale of batches and their representativeness of the commercial product.

In case bracketing/matrixing is used, discuss the acceptability.

Conclude on the stability results and if they showed significant changes or trends, and conclude on whether the observed physical and chemical changes are (not) likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. If any out of specifications results were observed, mention the conclusions in this respect.

Stability in refrigerated/freezer conditions and any information on temperature cycling testing should be reflected, especially for critical formulations.

Conclude on results from in-use stability studies if relevant.

Conclude on results from photostability and stress studies.

Conclude on the stability recommendations as indicated in the SmPC after opening (in-use), reconstitution, dilution, mixing with food etc., or compatibility with administration devices and the performance of the Ph. Eur. preservative efficacy test as appropriate; – link in with the SmPC.

State if further stability data are required as part of a post-approval measure(Recommendation), e.g. additional in-use stability studies, full scale data following introduction of a lately introduced additional manufacturing facility while comparability and primary stability data already available.

**Chem:**

Mention stability studies outside the primary container, only if such data/information has been submitted (should not be requested otherwise) (relevant e.g. for tablets).

<Text>

***Bio and Chem: The following text may be used :***

<Real time stability data from <number, scale> batches of finished product from the <proposed> manufacturer(s) stored <in the intended commercial package><in a container closure system representative of that intended for the market> <*if not describe the package*> for up to <number> months under long term conditions (25 ºC / 60% RH) and for up to <number> months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.>

<The following parameters were tested*:> <list the latest shelf life specifications> or <*The parameters tested are the same as for release.> < The analytical procedures used were the same as for release and were stability indicating as demonstrated through studies under <forced> <stressed> conditions. (*if not mention, which additional methods were used)*.>

**Bio and Chem:**

Summarise the stability results in a brief yet informative manner.

<Text>

***Bio and Chem: The following text may be used :***

<All tested parameters were within the specifications.>, <Degradation products increased under accelerated conditions but remained within the specification.>

<Photostability testing following the ICH guideline Q1B was performed on <*number*> batches. <Results indicate that the product needs protection from light>, <the packaging provides adequate protection from light,> <is not sensitive to light conditions tested>.

<Results under stress conditions <*describe the stress conditions*> were also provided. Degradation was observed in <…> conditions. The stability indicating nature of the methods was confirmed.>

<The stability results justify the proposed shelf life of <*x*> <months> <years> <*storage conditions*> in the proposed container.>

**For biosimilar products the below section 4.3.5 applies**

* + 1. < Biosimilarity exercise >

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Present an outline of the analytical comparability exercise performed at the quality level.

Detailed information (such as batch number and country of origin) of the batches used in the analytical comparability exercise (quality, non-clinical and clinical) should be provided in tabular format if possible.

Highlight any issues with the design of the comparability exercise (e.g. number of batches, scale, choice of reference, parameters compared, analytical procedures used, QTPP etc). Discuss how the reference ranges were established (number of batches, age of batches, statistical tools etc.). Discuss if batches used in the biosimilarity exercise are representative of the commercial process.

If a global development approach has been followed confirm whether acceptable bridging between non-EU comparator and EU reference medicinal product has been presented.

Present the results of the analytical comparability exercise in a tabular format, including quality attributes compared, analytical procedure used and key findings (see example below).

| <Insert/Delete the table as appropriate> | | | |
| --- | --- | --- | --- |
| Molecular parameter | Attribute | Methods for control and characterization | Key findings |
| Primary structure | Amino acid sequence | Reducing peptide mapping (MS) | Identical primary sequence |
| Higher order structure | Secondary and tertiary structure | CD spectroscopy | Comparable higher order structure |
| …*add lines as needed* |  |  |  |

Discuss the results of the analytical comparability exercise and any uncertainties, how they are linked with S/E aspects and provide a clear conclusion on whether analytical comparability at the Quality level has been sufficiently demonstrated.

<Text>

* + 1. Post approval change management protocol(s)

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

If a post approval change management protocol (PACMP) has been proposed explain briefly what aspect it relates to and if it can be accepted..

<Text>

* + 1. Adventitious agents

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

Provide the conclusions from the presented information on non-viral adventitious agents and adventitious viruses. Highlight any TSE aspects of starting materials, reagents, excipients, adjuvants, active substance and confirm the adequacy of information.

<Text>

***Bio and Chem: The following text may be used :***

<Valid TSE CEP(s) from the supplier(s) of <….> used in the manufacture is/are provided.>

< No excipients derived from animal or human origin have been used.>

**Bio and Chem:**

Indicate whether the information concerning viral safety in relation to starting materials, adequacy of virus removal steps, routine testing, and virus validation studies is considered acceptable.

<Text>

* + 1. <GMO>

This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

**Bio and Chem:**

Provide the conclusions on environmental risk assessment relating to GMO products.

<Text>

* 1. Discussion and conclusions on quality aspects

This section should be completed **independently** by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into one consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement, or a major omission that needs to be addressed.

**Please also refer to “Assessor’s overall conclusions on quality” of the D80 Quality AR guidance document.**

Mention only the significant points of discussion as described in sections 4.2 and 4.3 to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment. Mention those aspects from the active substance and finished product that are related, e.g. specifications of active substance are too wide which result in too wide limits for finished product.

Contextualise important outstanding issues during the procedure which could impact the CHMP Opinion and explain how these adversely affect the benefit risk assessment (see sections 10.3.1, 10.4.1 and 10.6.2 below).

Any unresolved issues during the assessment procedure, along with their associated questions, should only be included in the discussion section if they directly pertain to a potential modification of the SmPC text, influence the Benefit-Risk discussion in the overview, if the Rapporteurs assert that it should be explicitly mentioned in the EPAR or e.g., GMP issues that trigger an inspection.

In relation to the Quality aspects impacting the benefit-risk balance, indicate if there is any quality aspect either in the active substance or in the finished product which could lead to impact on the benefit-risk balance. Consider particularly the following aspects:

- Is the control strategy sufficient to guarantee consistent/ satisfactory quality/performance of the product?

- Is there sufficient stability data to ensure safe use?

- Are the batches used in clinical trials representative with regard to the commercial product to guarantee that the latter will be the same as the clinical batches?

Indicate if a paediatric formulation has been developed or is to be developed. Indicate in which paediatric age groups the formulation would be used. Indicate if there is a need to request an Opinion from the PDCO.

**Bio:**

For biosimilars, conclude if the available quality data support biosimilarity versus the EU reference medicinal product. In addition, if applicable, conclude if any non-EU comparator used in pivotal clinical trials is representative of the EU reference medicinal product.

At the time of a positive Opinion:

- For standard non-contentious products a standard wording may be used along the following lines:

<Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.>

In case quality issues have been identified for inclusion in Annex II as conditions or specific obligations (conditional MA), use the following statement. Any measure identified as a condition or specific obligation needs to be well motivated in the CHMP AR, notably the need for a condition or specific obligations should be explained in the context of a positive benefit-risk balance:

<The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:>

Plus, if relevant:

<At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit-risk balance of the product.>

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

Alternatively, in the case of a **negative quality report**, contributing to a **negative CHMP Opinion**, the **main** quality problems need to be highlighted here and repeated in the final benefit-risk statement, later in the report (section 5).

<Text>

* + 1. Recommendation(s) for future quality development

<In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:>

***This section is to be filled, if applicable at the end of the procedure, i.e. usually from D180 LOI and afterwards. There should be a link between the recommendations listed in this section and the scientific discussion. It should be clear to the reader why CHMP gives these recommendations.***

1. Non-clinical aspects

The Rapporteur is responsible for incorporating the factual data, comprehensive discussion, and conclusions from the D80 non-clinical report. This entails summarising the essential findings and determinations articulated within the report's non-clinical data. The Co-Rapporteur should add their assessment sections (directly in the boxes) and only add to any factual section already included by the Rapporteur if there is a major omission or mistake.

Any unresolved issues during the assessment procedure, along with their associated questions, should only be included in the discussion section if they directly pertain to a potential modification of the SmPC text, influence the Benefit-Risk discussion in the overview, if the Rapporteurs assert that it should be explicitly mentioned in the European Product Assessment Report or e.g., Good Laboratory Practice issues that trigger an inspection.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues that have led to an additional question (LoOI), with an indicator, using (MO) for major objections or (OC) for other concerns.

Note: this overview document is intended to be a summarisation of the data included in the D80 reports, not a direct copy/paste. As the report evolves from D80 to EPAR, arguments should be re-formulated; this document is not a chronological reflection of what happened during assessment, but as the EPAR, needs to summarize the aspects that underpin the benefit/risk of the product and the claims in the product information as well as the content of the RMP.

* 1. Introduction

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Short summary (1 paragraph) of the development program. Highlight which studies were conducted under GLP.

<Text>

* 1. Analytical methods

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Short summary (1 paragraph) of the analytical methods used.

<Text>

* 1. Pharmacology
     1. Pharmacodynamics
        1. Primary pharmacodynamics

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should address PD studies in relation to the disease to be treated and the proposed indications including factual data on relevant points e.g. proof of concept (in-vitro and in-vivo – avoiding any redundancy with the clinical section), mode of action, relevant animal models, interspecies comparison, activity (e.g. ED50) including the species used in toxicology studies, preliminary PK (plasma concentration) in animal models (PK/PD relationship), duration/reversibility of effects, pharmacologically active metabolites and chiral implications(relative contribution to pharmacodynamics). Consider specificity of pharmacodynamics for anti-infectives as well (e.g. spectrum of activities, mechanism of resistance, etc.) and prophylactic vaccines (immunogenicity, i.e. the ability to induce a humoral and/or cell-mediated immune response). Be brief and summarise the content of the D80 report.

<Text>

* + - 1. Secondary pharmacodynamics

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should provide factual data on pharmacological effects (off-target, on-target/off-tissue) other than the primary therapeutic activity (previously general pharmacology). Studies/data on secondary pharmacodynamics should be summarised by organ system, where appropriate, and evaluated in this section. Be brief and summarise the content of the D80 report.

<Text>

* + - 1. Safety pharmacology

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should provide factual data on safety pharmacology studies performed. Be brief and summarise the content of the D80 report. Describe any unexpected or off-target effects (cardiovascular, central nervous, respiratory, renal, gastrointestinal, autonomic nervous, haematological, etc…) observed in safety pharmacology studies.

<Text>

* + - 1. Pharmacodynamic drug interactions

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe any important findings related to possible drug-drug interactions. A table summarizing the in-vitro studies performed and their results and the predicted concentration of drugs and metabolites at the site of interaction (plasma, intestine, liver and kidneys) could be considered in case of possible drug-drug interactions. If in vitro studies did not indicate any possible issues, do not include every single one.

<Text>

* + 1. Pharmacokinetics

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Include short summary of PK profile observed in animal studies. The sub-sections below do not all need to be used; please try to summarise as much as possible and focus only on relevant aspects, rather than filling each section, especially if no concerning results.

* + - 1. <Absorption>

Use this section to highlight any issues e.g. with bioavailability, dose proportionality or gender differences.

<Text>

* + - 1. <Distribution>

Use this section to highlight any issues with e.g. degree of distribution in relation to target organs, plasma protein binding, distribution across blood-brain barrier, placenta or excretion in milk. Also discuss phototoxicity issues if relevant.

<Text>

* + - 1. <Metabolism>

Use this section to highlight any metabolic pattern differences between animals and humans. Relevant CYP inductions/inhibitions or effects on transporters should be discussed in the clinical section.

<Text>

* + - 1. <Excretion>

Use this section to highlight any routes of excretion that could be relevant for organ-specific toxicity.

<Text>

* + - 1. <Pharmacokinetic drug interactions>

Only use this section to highlight any relevant information based on non-clinical studies. In vitro inhibition or induction of CYP enzymes should be included in the clinical section.

<Text>

* + - 1. <Other pharmacokinetic studies>

If relevant, use this section to highlight issues in juvenile animals, pregnant animals or in animal models of disease.

<Text>

* 1. Toxicology
     1. <Single-dose toxicity>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the acute toxic effects of the drug, and the dose at which they occur.

<Text>

* + 1. Repeat-dose toxicity

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the sub-chronic and chronic toxic effects of the drug.

Specific organs or tissues that are particularly sensitive to toxicity should be mentioned, as should any histopathological findings in major organs after exposure to the drug. Also mention reversibility of findings and if a no observed adverse effect level (NOAEL) can be defined.

<Text>

* + 1. Genotoxicity

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the findings from genotoxicity studies, including evidence of DNA damage, mutations, or chromosomal aberrations. If genotoxicity studies have not been performed, include the justification provided by the applicant.

<Text>

* + 1. Carcinogenicity

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Give a short description of the studies that have been performed. If carcinogenicity studies have not been performed, include the justification provided by the applicant. This also includes any weight of evidence considerations. Give a short summary of results including neoplastic changes as well as relevant non-neoplastic changes, as appropriate. Non-neoplastic changes should be discussed with reference to the observations in repeat-dose toxicity studies.

<Text>

* + 1. Developmental and reproductive toxicity

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe any studies which examined the effects on fertility, embryofoetal or pre-/postnatal development. Describe whether DART studies have been conducted or if the conclusions are based solely on data from specific endpoints of repeat-dose toxicity studies. This also include any weight of evidence considerations.

<Text>

* + 1. Toxicokinetics and exposure margins

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please summarise with factual TK data from all toxicity studies (repeat-dose toxicity, developmental and reproductive toxicology, in-vivo genotoxicity, carcinogenicity studies etc.). Describe the exposure margins and how they were determined.

<Text>

* + 1. Local tolerance

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If applicable, describe any local tolerance studies performed or any local tolerance endpoints included in general toxicity studies.

<Not applicable><Text>

* + 1. Other toxicity studies

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If applicable, describe any other toxicity studies performed.

<Not applicable><Text>

* + 1. Ecotoxicity/environmental risk assessment

Copy/paste the table from the D80 non‑clinical report below. In case of more active substances in the same medicinal products separate tables per active substance should be included. However, where the ERA stops after Phase I the Phase II section (Table 7) can be deleted.

Table 6: Summary of main study results: Phase I

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Substance (INN/Invented Name): | | substance name | | |
| CAS-number (if available): | | XX-XX-X | | |
| PBT/vPvB screening | | | | |
| Study type | Test protocol | | Result | Conclusion |
| Bioaccumulation potential- log Kow | OECD <107>/<123> | | X *at pH* Y  X *at pH* Y  Xat pHY | Potential PBT: <Y>/<N> |
| PBT/vPvB assessment | | | | |
| Property | Parameter | | Result | Conclusion |
| Bioaccumulation | log <kow>/<dow> | | Xat pH Y | <potentially B>/<not B> |
| BCFKgl | | X L/kgww | <Not B>/<B>/<vB> |
| Persistence | Ready biodegradability | | <Y>/<N> | <potentially P>/<not P> |
| DT50,X at 12°C | | X d | <not P>/<P>/<vP> |
| Toxicity | NOECaquatic  C, M, R  STOT RE 1 or 2\* | | X mg/L | <T>/<not T> |
| **PBT/vPvB statement:** | substance name is considered to be not PBT, nor vPvB  substance name is considered to be PBT  substance name is considered to be vPvB  substance name is considered to be PBT and vPvB | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| Phase I | | | |
| Parameter | Value | Unit | Conclusion |
| PECsw,*<*default>/<refined> (<prevalence> / <treatment regime>) | X | µg/L | ≥ 0.01 threshold: <Y>/<N> |
| Other concerns (e.g. chemical class) |  |  | <Y>/<N> |

Table 7: Summary of main study results: Phase II

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phase II Physical-chemical properties and fate** | | | | | | | | | |
| **Study type** | **Test protocol** | | **Result** | | | **Remarks** | | | |
| Water solubility | OECD 105 | | *X* mg/L at *X °C* | | | <shake flask>/<generator column> | | | |
| Dissociation in Water | OECD 112 | | p*K*a, 1 = *X*  p*K*a, 2 = *X* | | |  | | | |
| Adsorption-Desorption  Soil 1 = *Type (e.g. sandy loam / clay / loamy sand)* | OECD 106 | | *K*FOC, soil 1 = *X* L/kgoc | | |  | | | |
| Soil 2 = *Type* |  | | *K*FOC, soil 2 = *X* L/kgoc | | |  | | | |
| Soil 3 = *Type* |  | | *K*FOC, soil 3 = *X* L/kgoc | | |  | | | |
| Sludge 1 = *Type (e.g. municipal)* |  | | *K*FOC, sludge 1 = *X* L/kgoc | | |  | | | |
| Sludge 2 = *Type* |  | | *K*FOC, sludge 2 = *X* L/kgoc | | |  | | | |
| Ready Biodegradability Test | OECD 301*<*A>/<B>/<C>/<D>/<E>/<F> | | *X* % (*Y* d)  <(not)>readily biodegradable | | |  | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems  Sediment 1 = *Type (e.g. sandy loam / clay / loamy sand)* | OECD 308 | | DT50, water 1 = *X* d  DT50, sediment 1 = *X* d  DT50, whole system 1 = *X* d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | *X* °C  CO2 and NER values at test end | | | |
| Sediment 2 *= Type* |  | | DT50, water 2 = *X* d  DT50, sediment 2 = *X* d  DT50, whole system 2 = *X* d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | *X* °C  CO2 and NER values at test end | | | |
| Transformation products |  | | >10% = *<*Y>/<N>  TP1 (max) = *X* %  DT50 TP1: *X* d  *List each relevant TP#* | | | at day *X*, sed *#*  *identity* | | | |
| Aerobic and anaerobic transformation in soil  Soil 1 = *Type (e. g. sandy loam / clay / loamy sand)* | OECD 307 | | DT50, soil1 = d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | at *X* °C  CO2 and NER values at test end | | | |
| Soil 2 = *Type* |  | | DT50,soil2 = d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | at *X* °C  CO2 and NER values at test end | | | |
| Soil 3 = *Type* |  | | DT50,soil3 = d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | at *X* °C  CO2 and NER values at test end | | | |
| Soil 4 = *Type* |  | | DT50,soil4 = d  CO2 = *X* %  NERtotal = *X* %  NERtype I = *X* % | | | at *X* °C  CO2 and NER values at test end | | | |
| Transformation products |  | | >10% = *<*Y>/<N>  TP1 = %  DT50 TP1: d  *List each relevant TP#* | | | at day *X*; *soil #*  *identity* | | | |
| ***Phase II Aquatic effect studies*** | | | | | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | | **Value** | **Unit** | | | **Remarks** | |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | <NOEC> / <EC10> | |  | *µg*/L | | | growth rate | |
| *Daphnia* sp*.* Reproduction Test/ *Daphnia magna* | OECD 211 | <NOEC> / <EC10> | |  | *µg*/L | | | *applicable endpoint(s)* | |
| Fish, <ELS>/<FSDT>/<FFLC>*/Species* | OECD <210>/<234>/ <240> | <NOEC> / <EC10> | |  | *µg*/L | | | *applicable endpoint(s)* | |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | <NOEC> / <EC10> | |  | *µg/*L | | | total respiration | |
| ***Phase II Sediment effect studies*** | | | | | | | | | |
| Sediment Dwelling Organism Test/*<*Chironomus riparius> / <Lumbriculus variegatus> | OECD *<*218>/<219>/ <225> | <NOEC> / <EC10> | |  | *mg*/kgdw | | | *applicable endpoint(s), normalised to 10% o.c.* | |
| ***Phase II Soil effect studies*** | | | | | | | | | |
| Soil Microorganisms: Nitrogen Transformation Test | OECD 216 | *X* / <NOEC> / <EC10x> | |  | <%> */*  <mg>/  <kgdw> | | | at day <28>/<100> | |
| Terrestrial Plants, Growth Test/*Species* | OECD 208 | <NOEC> / <EC10> | |  | *mg*/kgdw | | | *applicable endpoint(s)* | |
| <Enchytraeid>/<Earthworm>*,* Chronic Toxicity Test/*Species* | OECD *<*220>/<222> | <NOEC> / <EC10> | |  | *mg*/kgdw | | | *applicable endpoint(s)* | |
| Collembolan Reproduction Test/*Folsomia* | OECD 232 | <NOEC> / <EC10> | |  | *mg*/kgdw | | | *applicable endpoint(s)* | |
| ***Phase II Secondary poisoning*** | | | | | | | | | |
| Bioaccumulation Test/*Species*  Test 1 = *X* µg/L  Test 2 = *X* µg/L | OECD 305 | <BCFKgL, 1><BCFKgL, 2> | |  | L/kg  L/kg | | |  | |
| Mammal or Bird Test*/*  *Species* | OECD *XXX* | NOAEL | |  | *mg*/kgbw/d | | | *applicable endpoint(s)* | |
| ***Risk characterisation*** | | | | | | | | | |
| **Compartment** | **PEC** | **PNEC** | | **RQ** | | | **Conclusion** | |
| STP | *X µg/L* | *X µg/L* | | *X* | | | <No risk> / <Risk> | | |
| Surface water | *X µg/L* | *X µg/L* | | *X* | | | <No risk> / <Risk> | | |
| Groundwater | *X µg/L* | *X µg/L* | | *X* | | | <No risk> / <Risk> | | |
| Sediment | *X mg/kgdw* | *X mg/kgdw* | | *X* | | | <No risk> / <Risk> | | |
| Soil | *X mg/kgdw* | *X mg/kgdw* | | *X* | | | <No risk> / <Risk> | | |
| Secondary Poisoning | *X µg/L* | *X µg/L* | | *X* | | | <No risk> / <Risk> | | |

#Long chemical names and/or structural formulas are to be inserted below the table for reasons of space.

*Choice of minimal standard sentences suggested for the CONCLUSION of the Risk (Options 1, 2 or 3) and the PBT/ vPvB (Options 4 or 5) assessments in the CHMP AR/EPAR, or (option 6) where further data are required.*

*1- For active substances for which the ERA consists of a justification for not submitting ERA studies (e.g. vitamins, electrolytes etc.):*

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, <active substance> is not expected to pose a risk to the environment.

*Or*

*2- For active substances that remain in Phase I:*

PECsurfacewater for <active substance> is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required.

*Or*

*3- For active substances that reach Phase II (see table):*  
- Considering the above data from Phase I and Phase II, <active substance> is not expected to pose a risk to the environment.

or

- Considering the above data from Phase I and Phase II, <active substance> may pose a risk to the <aquatic><terrestrial>environment and to <predators consuming contaminated prey (secondary poisoning)>. Risk mitigation including statements in relevant sections of the Product information (SmPC and Patient Leaflet) should be included as appropriate.

*And*

*4- For active substances that remain in PBT/vPvB Screening Decision tree:*

A bioaccumulation potential is not indicated based on the log KOW < 4.5. A definitive PBT/vPvB assessment is not required.

*Or*

*5- For active substances that reach definitive PBT assessment:*

- Considering the above dataof the definitive hazard assessment, <active substance> is not a PBT or vPvB substance.

or

- Considering the above data of the definitive hazard assessment, <active substance> is a PBT or vPvB substance. Risk mitigation including statements in relevant sections of the Product information (SmPC and Patient Leaflet) should be included as appropriate.  *6- For dossiers requiring additional ERA data:*As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of <active substance> to the environment or the PBT/vPvB assessment.

*[At the time of opinion:]*

The Applicant commits to perform the following studies as follow-up measures:

[list of tests to be performed and timeframe for completion]

<Text>

* 1. Overall discussion and conclusions on non-clinical aspects

ASSESSMENT. This section (and subsections) should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

It is anticipated that the phrasing of issues in the discussion section, as addressed in the day 80 report, may require some adjustment, or even potentially be disregarded. Typically, a broad and comprehensive high-level discussion of the main findings and integration with clinical safety findings, occurs in the discussion section, along with further exploration of any areas where deviations have occurred from e.g., Scientific Advices, or Regulatory Guidelines. Comment on confirmation of non-clinical findings as appropriate

Any unresolved issues during the assessment procedure, along with their associated questions, should only be included in the discussion section if they directly pertain to a potential modification of the SmPC text, influence the Benefit-Risk discussion in the overview, if the Rapporteurs assert that it should be explicitly mentioned in the European Product Assessment Report or e.g., Good Practice issues that triggers an inspection.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues that have led to an additional question (LoOI) with an indicator, using (MO) for major objections or (OC) for other concerns.

The Co-Rapporteur's input is imperative, specifically when a dissenting viewpoint or notable omissions require addressing. In such cases, the Co-Rapporteur should actively contribute by providing supplementary insights or concerns that may have arisen during the assessment process. This collaborative effort ensures a thorough and well-rounded evaluation of the non-clinical data, enhancing the overall assessment process.

* + 1. Discussion

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

By D80, the Rapporteur should copy/paste their discussion section from the stand-alone D80 non-clinical report. The Co‑Rapporteur should copy/paste their discussion section by D82.

By D120 the Discussion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + 1. Conclusions

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

The conclusions should not repeat the discussion and should be brief.

By D80, the Rapporteur should copy/paste their conclusion section from the stand-alone D80 non-clinical report. The Co‑Rapporteur should copy/paste their conclusion section by D82.

By D120 the Conclusion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

1. Clinical aspects

The Rapporteur is responsible for incorporating the factual data, comprehensive discussion, and conclusions from the D80 clinical report. This entails summarising the essential findings and determinations articulated within the report's clinical data. The Co-Rapporteur should add their assessment sections (directly in the boxes) and only add to any factual sections already included by the Rapporteur if there is a major omission or mistake.

Any unresolved issues during the assessment procedure, along with their associated questions, should only be included in the discussion section if they directly pertain to a potential modification of the SmPC text, influence the Benefit-Risk discussion in the overview, if the Rapporteurs assert that it should be explicitly mentioned in the European Product Assessment Report or e.g., Good Clinical Practice issues that trigger an inspection.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues that have led to an additional question (LoOI), with an indicator, using (MO) for major objections or (OC) for other concerns.

Note: this overview document is intended to be a summarisation of the data included in the D80 reports, not a direct copy/paste. As the report evolves from D80 to EPAR, arguments should be re-formulated; this document is not a chronological reflection of what happened during assessment, but as the EPAR, needs to summarize the aspects that underpin the benefit/risk of the product and the claims in the product information as well as the content of the RMP.

* 1. Introduction
     1. GCP aspects

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

<The Clinical trials were performed in accordance with GCP as claimed by the applicant>

<The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.>

Discuss the need for a triggered GCP inspection as part of the evaluation e.g.:

* concerns raised during the assessment regarding compliance with GCP
* issues related to data accuracy,
* implausible results or biologically unlikely findings between studies or sites,
* poor protocol compliance, and related regulatory and ethical requirements

Describe the trigger for a GCP inspection, especially novel therapies, vulnerable populations (e.g., paediatrics, mentally impaired, subjects without alternative therapy, institutionalized subjects, populations in developing countries).

<Text>

After the CHMP discussion, the following sentence should be added and adapted to the outcome.

Based on the review of clinical data <and the above-mentioned reports>, CHMP <did not><did> identify the need for a <further> GCP inspection of the clinical trials included in this dossier (see section 3.4.3).

In case CHMP does trigger an inspection, add details of the studies/sites to be inspected.

<Text>

* + 1. Tabular overview of clinical trials

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Complete the tables below with information on all relevant clinical trials submitted, including study number, design and number and characteristics of patients in treatment arms (this table should be in accordance with CTD tables 2.7.2.1 and 2.7.3.1).

This table can be copied from the D80 clinical AR (section 2 and section 3.1).

Table 11: Tabular overview of main clinical studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Design, control type, duration | Treatment | Subject population | Study objectives and primary endpoint | Number of subjects total and per group randomised (treated)/completed study |
| <Phase 2> <Therapeutic exploratory> | | | | | |
| EXAMPLE 1 (Ex-0001) | RD/DB/PC 28-week treatment period with a 12-week follow-up | Product 200 mg Q4W SC or placebo | Adults aged 18-75 yrs with moderate to severe asthma | Efficacy, safety, PK, immunogenicity, PD. Primary endpoint: change (expressed as ratio) in number of airway submucosal inflammatory cells/mm2 of bronchoscopic biopsies from baseline up to week 28 | 116 randomised and treated 200 mg SC Q4W: 59/58  Placebo SC Q4W: 57/56 |
| <Text> | <Text> | <Text> | <Text> | <Text> | <Text> |
| <Phase 2b> | | | | | |
| EXAMPLE 2  (Ex-0002) | RD/DB/PC  52-week treatment period with 12-week safety follow-up | Dose-ranging Product SC 50 mg Q4W, 200 mg Q4W, 250 mg Q2W SC or placebo | Adults aged 18-75 yrs with severe uncontrolled asthma | Efficacy, safety, PK, immunogenicity, PD.  Primary endpoint: annualised AER vs placebo at week 52. | 550 randomised and treated.  250 mg SC Q2W: 137 (137)/115  200 mg SC Q4W: 137 (137)/122  50 mg SC Q4W: 138 (138)/127  Placebo Q2W: 138 (138)/130 |
| <Text> | <Text> | <Text> | <Text> | <Text> | <Text> |
| <Phase 3> <Therapeutic confirmatory> | | | | | |
| EXAMPLE 3  (Ex-0003) | RD/DB/PC  52-week treatment period with 12-week safety follow-up for subjects not rolling over to long-term extension | Product 200 mg Q4W SC or placebo | Adults and adolescent subjects aged 12-80 yrs with severe uncontrolled asthma. | Efficacy, safety, PK, immunogenicity, PD.  Primary endpoint: cumulative odds ratio product vs placebo for categorised percent reduction from baseline in daiy OCS dose at week 48 whilst not losing asthma control. | 1062 randomised / 1059 treated  200 mg SC Q4W: 529 (528)/509  Placebo SC Q4W: 532 (531)/505 |
| <Text> | <Text> | <Text> | <Text> | <Text> | <Text> |

Delete any abbreviations that do not appear in the table; add any others that do.

<RD = randomised; DB = double blind; PC = placebo controlled; SA = single arm; OL =open label; yrs = years; SC = sub-cutaneous; Q4W = every 4 weeks; Q2W = every 2 weeks>

* 1. Clinical pharmacology
     1. Methods

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should cover all the bioanalytical methods used to support clinical pharmacology (PK, PD and immunogenicity) in the MAIN studies. Do not describe all methods used for all studies, it is not necessary; consider which ones are key. In a sentence mention what are the type of analytical methods that have been used and if these have been validated. Add further detail only if needed to explain issues raised.

<Text>

* + 1. Pharmacokinetics

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Briefly summarise only relevant PK data from the D80 AR. Tabulated format could be used where possible. All information listed in the SmPC should be described and justified. Depending on the application at hand headings can be deleted if not relevant.

* + - 1. Introduction

Describe the role of the pharmacokinetics for the specific product, e.g. mainly descriptive, used for dose adjustments etc. Considering the type of application conclude on the quality of the pharmacokinetic documentation with special emphasis on identified deficiencies.

<Text>

* + - 1. Evaluation and qualification of models
         1. Population Pharmacokinetics

Briefly describe the PK modelling leading to regulatory decisions or claims in the SmPC.

<Text>

* + - * 1. Physiology based pharmacokinetic model

Briefly describe PBPK modelling if this has been deemed adequate and the analyses support regulatory decisions or SmPC claims regarding DDIs. Delete the section if no relevant data is available.

<Text>

* + - 1. Absorption

This section should include rate and extent of drug absorption e.g. Cmax, Tmax and AUC (Ctrough if relevant) single dose/steady-state for the clinical dose. Describe involvement of active transport proteins in absorption.

Information on absolute bioavailability and whether there is first pass metabolism should be provided (and lack of absolute bioavailability discussed).

If factors could influence bioavailability (e.g. gastric pH and food), they should be mentioned.

If data allows present BCS-class

<Text>

* + - 1. <Bioequivalence>

Please include data from pivotal bioequivalence studies between formulations, e.g. between commercial formulation and formulation used in pivotal phase 3 studies. Other bioequivalence studies may be briefly presented, but the focus should be on the final formulation to be marketed.

For biological or biotechnology products this part should also cross-refer to non-clinical and functional assays.

If relevant for the Application at hand the reference product (used in clinical trials) should be indicated, and it should be clear if the reference product is authorised in the EU. .

<Text>

* + - 1. Distribution

Please describe data related to volume of distribution, if available, data regarding concentration in tissues and other body fluids, e.g. cerebrospinal fluid, protein binding, blood to plasma ratio, for parent drug and pharmacologically active metabolites where relevant.

<Text>

* + - 1. Metabolism

Please summarise data on metabolites (major and minor) including their contribution to efficacy and safety, metabolic routes, enzymes involved in metabolism, extent of metabolism. Include a figure of the proposed metabolic pathway

If an active moiety is used, this should be described (e.g. protein binding, potency, molecular weight, etc).

If present for chiral products describe in vivo inter-conversion including possible clinical consequences of inter-conversion.

<Text>

* + - 1. Elimination

Please describe the main pathways of elimination (metabolism, excretion unchanged renally and biliary), a figure could be helpful. Present data on clearance, half-life, as well as information on any potential accumulation. Describe involvement of transporter proteins in the elimination process.

<Text>

* + - 1. Dose proportionality and time dependency

Describe whether the PK of the product is dose-proportional or not, if not describe the reason. If time-dependent PK is concluded describe the reason for this.

When relevant, add information regarding the impact of anti-drug antibodies (ADAs) on PK.

<Text>

* + - 1. Pharmacokinetics in the target population

Please describe if PK data of parent compound and pharmacologically active metabolites in the target population have been collected and differ from healthy volunteers including intra- and inter-individual variability in patients. Summarise the exposure expected in the target population at steady state.

Mention the no‑effect boundaries with a cross-reference to section 6.2.5 where the main results are to be presented.

<Text>

* + - 1. Special populations

In this section, provide the available PK of parent drug and active metabolites in special populations such as organ impairment, age, gender, rapid or slow metabolizers etc. State whether studies in paediatric subjects have been conducted or not. In case extrapolation is used to support a paediatric indication, available data on exposure supporting the indication should be reported here.

<Text>

* + - 1. Pharmacokinetic interaction studies

If the headings below do not apply, delete them. Also add new headings as appropriate.

State for which transporters and enzymes there is a positive in vitro signal (inhibition or induction) for parent compound and, when relevant, major metabolites. State if all mandatory enzymes and transporters have been evaluated in vitro and if all positive signals have been further evaluated.

Please summarise drug-drug interaction studies; single or multiple dose, duration and main PK-results.

* + - * 1. <Special populations>

<Text>

* + - * 1. <PK drug-drug interactions>

<Text>

* + - * 1. <Dose proportionality/time independence/accumulation>

<Text>

* + 1. Pharmacodynamics
       1. Mechanism of action

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please describe the mechanism of action including the specific biochemical or physiological processes (including binding affinity, target engagement and downstream effects. Please mention whether the drug exhibit selectivity for its intended target(s) over other related targets or pathways. Please state whether there is evidence of receptor occupancy, and whether it correlates with pharmacodynamic effects. IMPORTANT: avoid any redundancy/repetition with the non‑clinical section above.

<Text>

* + - 1. Primary and secondary pharmacology

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should include a summary of studies on the mode of action and/or effects of the drug in relation to its desired therapeutic target. The focus is to describe the mechanism of action of the drug, proof of concept (PoC) and characterise the range of exposures or doses that are likely or not to have a therapeutic effect in patients and to be further investigated in dose ranging efficacy and safety trials.

Please also add early dose finding studies (the main dose-finding study will be described in later clinical section).

In addition, please describe covariate effects on primary pharmacology i.e. effects of age or genetic polymorphism on PD (or PK/PD) relationships, including special studies (e.g. immunogenicity and microbiology).

Please also describe secondary pharmacology and its underlying mechanism, including specific targets, pathways and duration of effects.

Please describe whether a clear dose-response relationship is established between drug, dose exposure and secondary pharmacological effects.

<Text>

* + - 1. Pharmacodynamic interactions with other medicinal products or substances

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please describe interactions of interest with other medicines and any kind of substances with an impact on the dosing recommendations. The proposed text for the SmPC with precautions or warnings should be also mentioned here.

<Text>

* + - 1. Genetic differences in PD response

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please summarise any genetic difference in PD response as well as potential differences in the paediatric population (e.g. due to maturation).

<Text>

* + - 1. <Immunological events>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please summarise data on antibody formation regarding safety (e.g. neutralising antibodies, auto-antibodies, species-specific antibodies, such as HAMA (human anti-mouse antibodies) or HAHA (human anti-human antibodies) in the case of monoclonal antibody products). Discuss the validity/usefulness of the assay.

<Text>

* + 1. Pharmacokinetics/pharmacodynamics (PK/PD)

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Briefly summarise relationship between plasma concentration and efficacy and safety

If available, drug-exposure-response and PK/PD approaches based on data across studies should be described here.

Please summarise the PK/PD model approach and its rationale, exposure-response model and simulation methods together with all covariate analyses (hepatic, renal impairment the degree of the severity, gender, ethnic factors, prior use of medications) taken into account, including the rationale PK/PD analyses in healthy subjects as well patients should be outlined. Any effects on potential biomarkers and/or disease progression should be mentioned.

Please indicate if the selection of dose(s) and study duration for phase III was supported by these analyses.

In addition, the covariate effects on PK/PD and drug-exposure-response relationships should be presented to identify clinical scenarios when the benefit-risk profile of the medicine may be altered resulting in the need for specific risk minimisation measures.

<Text>

* + 1. Dose selection and therapeutic window

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please provide a summary of how PK/PD influenced the doses selected throughout the development programme, including, but not limited to, covariate analyses, exposure-response analyses, and simulations to justify the proposed posology.

Reference to model-independent (allometric scaling) or model-based (PK and physiologically based PK) approaches based on non-clinical data to determine the appropriate dose in humans, could be made, if relevant.

Please do not duplicate information included later in clinical section 6.3.1. this section should focus on the PK/PD drivers for dose selection.

<Text>

* + 1. Overall discussion and conclusions on clinical pharmacology
       1. Discussion

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

By D80, the Rapporteur should copy/paste their discussion section from the stand-alone D80 clinical report. The Co‑Rapporteur should copy/paste their discussion by D82.

By D120 the Discussion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues that have led to an additional question (LoOI) with an indicator, using (MO) for major objections or (OC) for other concerns.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + - 1. Conclusions

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

By D80, the Rapporteur should copy/paste their conclusions section from the stand-alone D80 clinical report. The Co‑Rapporteur should copy/paste their conclusions by D82.

By D120 the Conclusions section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. Clinical efficacy
     1. Dose response study(ies)

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Dose-response studies: not applicable for biosimilars.

Please briefly describe study designs and methods of studies contributing to selection of one or more doses used in the main (pivotal) studies. Please consider size, number and range of studied doses and justification of endpoints.

Describe the objectives of dose and dosing schedule selection, characterisation of exposure/response relationship and Proof of Concept. However, please avoid repetition of section PK/PD dose selection. and use cross-references where possible.

In case dose response studies are lacking, please provide the justification for the choice of dose provided by the applicant in this section.

If the pivotal trial has a dose-escalation phase, please mentioned it briefly here and include it in section later with the overall study design.

<Text>

* + 1. Main <study><studies>
       1. <Study #1 identifier> [ie the name or code – do not use the full title here]
          1. Study title

Insert study title in full.

<Text>

* + - * 1. Study design

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the main design elements of the study: phase, randomisation, open‑label or blinded, active treatment, comparator, posology, number of study arms, duration of treatment, etc. Keep it brief.

Insert a schematic representation of the study design.

If applicable, elaborate on any adaptive elements mentioned in the study design, including any planned adaptations based on interim data. The section should be purely descriptive. Discussion and assessment should only be in the dedicated discussion section below.

You can use the headings below as a guide on how to structure this section.

<Treatment>

<Text>

<Randomisation>

<Text>

<Blinding>

<Text>

Patient population

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the main inclusion/exclusion criteria, the inclusion (or not) of special populations, and any relevant patient recruitment and retention strategies. Do not simply copy/paste all inclusion/exclusion criteria. Be selective.

Describe any patient population enrichment/selection and the rationale for it.

The actual patient numbers, discontinuations etc. should be part of the results section below. Here only the study plan, i.e. inclusion/exclusion criteria and what was planned should be described. The section should be purely descriptive. Discussion should only be in the dedicated discussion section below.

<Text>

* + - * 1. Objectives and estimands

Primary objective

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please add the primary objective of the study. In case of multiple studies with similar objectives please provide a summary of the common methodology.

<Text>

Estimand<s> for the primary objective

**Table 12: Estimand<s> for primary objective**

|  |  |
| --- | --- |
| Population | Choose those that apply and delete the rest  <Patients with {condition and applicable specifiers} <who would encounter the Intercurrent Event of {intercurrent event} if assigned to {treatmentName}.>>  <Patients with {condition and applicable specifiers} <who would not encounter the Intercurrent Event of {intercurrent event} <if assigned to {treatmentName}.>>  <Patients with {condition and applicable specifiers} <who would encounter the Intercurrent Event of {intercurrent event} under any treatment assignment.>>  <Patients with {condition and applicable specifiers} <who would not encounter the Intercurrent Event of {intercurrent event} under any treatment assignment.>> |
| Treatment condition<s> | Choose the statement that applies (modifications allowed) and delete the rest  <Assignment to {treatmentName}, regardless of discontinuation, compared to assignment to {comparatorName}, regardless of discontinuation.>  <Assignment to {treatmentName} and {additional medication} as needed, regardless of discontinuation and use of additional medications, compared to assignment to {comparatorName} and {additional medication} as needed, regardless of discontinuation and use of additional medications.>  <Assignment to {treatmentName}, regardless of discontinuation and added to {background medication} compared to assignment to {comparatorName}, regardless of discontinuation, added to {background medication}.>  <Assignment to {treatmentName} in the hypothetical scenario of no discontinuation compared to assignment to {comparatorName} in the hypothetical scenario of no discontinuation.>  <Assignment to {treatmentName} and {additional medication} as needed, in the hypothetical scenario of no discontinuation compared to assignment to {comparatorName} in the hypothetical scenario of no discontinuation and use of additional medications.>  <Assignment to {treatmentName} and {additional medication} as needed, in the hypothetical scenario of no discontinuation, added to {background medication}, compared to assignment to {comparatorName}, regardless of discontinuation, added to {background medication}.> |
| Endpoint (variable) | {name of the variable or outcome to be observed from every participant} at {timepoint} <or before the occurrent of the {intercurrent event}> |
| Population-level summary | {Population-level summary, e.g. difference in means} |
| Intercurrent events and strategy to handle them | |
| <Intercurrent event 1> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> |
| <Intercurrent event n> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> |

Describe the clinical question of interest (i.e. a **short** description of the estimand(s) in plain language), followed by intercurrent events and the strategies applied. The description should be based on the table above and not be too lengthy.

<Text>

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Briefly summarise the content of section 3.3.1.3 in the D80 clinical report. Include a very concise description of the analysis sets and the main analysis methods for the primary endpoint.

Describe methods for multiplicity control, for handling of missing data and for any sensitivity or supplementary analysis. Be factual throughout.

<Text>

<Secondary> objective<s>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Only include any additional objectives/goals that are directly relevant to the discussion and contribute to gaining further insights into the drug's performance.

Please describe also any objectives that include patient experience data (PED) that may be relevant.

<Text>

Estimand<s> for the <secondary> objective<s>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the clinical question of interest (i.e. a short description of the estimand(s) in plain language), the intercurrent events and strategies applied, followed by the specific attributes in the table above. It is advised to include a table for at least the key secondary estimand(s); in such case copy and paste in this section Table 12 above used for primary objective estimands, including the text and the commenting boxes. The table could also refer to another estimand table to avoid duplications of text. If applicable, please substantiate the use of surrogate endpoints.

<Text>

<Statistical methods for estimation and sensitivity analysis on the secondary estimand<s>>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section is optional. Only use of there is any sensitivity analysis on the key secondary estimands that have an impact on B/R. Briefly summarise the content of section 3.3.1.3 in the D80 clinical report. Include a very concise description of the analysis sets and the main analysis methods for the primary endpoint.

Describe methods for multiplicity control, for handling of missing data and for any sensitivity or supplementary analysis. Be factual throughout.

<Text>

<Tertiary> objective<s>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Only include any additional objectives/goals that are directly relevant to the discussion and contribute to gaining further insights into the drug's performance.

Please describe also any objectives that include patient experience data (PED) that may be relevant.

<Text>

Estimand<s> for the <tertiary> objective<s>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the clinical question of interest (i.e. a short description of the estimand(s) in plain language), the intercurrent events and strategies applied, followed by the specific attributes in the table above. It is advised to include a table for at least the key secondary estimand(s); in such case copy and paste in this section Table 12 above used for primary objective estimands, including the text and the commenting boxes. The table could also refer to another estimand table to avoid duplications of text. If applicable, please substantiate the use of surrogate endpoints.

<Text>

<Statistical methods for estimation and sensitivity analysis on the tertiary estimand<s>>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section is optional. Only use of there is any sensitivity analysis on the key secondary estimands that have an impact on B/R. Briefly summarise the content of section 3.3.1.3 in the D80 clinical report. Include a very concise description of the analysis sets and the main analysis methods for the primary endpoint.

Describe methods for multiplicity control, for handling of missing data and for any sensitivity or supplementary analysis. Be factual throughout.

<Text>

* + - * 1. Results

Participant flow and numbers analysed

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Present the progress of study participants in a table or picture format, including total subjects assessed for eligibility. You can copy/paste from the same section in the D80 clinical report.

Include the initiation date (first patient enrolled) and completion date (last patient last visit).

For each treatment group, provide the numbers and reasons for participants excluded, randomized, allocated to intervention, and those who did or did not receive intended treatment, with explanations.

Report the number of participants in each treatment group who completed follow-up, withdrew, or discontinued prematurely (from treatment or study) and distinguish between treatment and study discontinuations.

Differentiate between treatment discontinuation and study discontinuation numbers.

For each treatment group, state the number of participants analysed for primary estimation and those not analysed, along with explanations.

Provide the numbers of patients experiencing intercurrent events for the primary objective, specifying which instances led to missing data.

Explain how patients and data points were included or excluded in the analysis, and provide a justification based on the selected strategy and estimator.

Present the median follow-up at the data cut-off date.

Include a reference to the relevant eCTD section(s).

<Text>

Deviations from study plan

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please describe any deviations from the original study plan, e.g. protocol amendments, SAP amendments and/or important protocol violations that might impact the results.

<Text>

Baseline data

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

A table format for data presentation is preferred.

Describe the demographic and clinical characteristics of each group, describe particularly any asymmetry in characteristics across treatment arms.

Include a reference to the relevant eCTD section(s) under each data table.

<Text>

Outcomes and estimation

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe outcomes and estimations starting with the primary objective, the estimates and the endpoints.

Minimize the use of text; use preferably data tables combined with if applicable, e.g. Kaplan-Meier curves and Forest Plots (where applicable).

Include a reference to the relevant eCTD section under each data table and plot.

If critical to the interpretation of the study, include brief data tables (or plots) for important secondary endpoints that provide additional information. Secondary endpoints that are highly correlated to the primary endpoint, tertiary and exploratory endpoints need not be discussed.

Provide a summary of results with estimated precision (e.g. 95% CI).

<Text>

<Pre-defined and post-hoc subgroup analyses>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If relevant and important to the assessment, describe outcomes and estimations of all pre-defined and/or post hoc important subgroup analyses.

Minimize the use of text and rather use preferably data tables combined with if applicable, e.g. Kaplan-Meier curves and Forest Plots.

Include a reference to the relevant eCTD section under each data table.

<Text>

<Pre-defined and post-hoc sensitivity analyses>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If relevant and important to the assessment, describe outcomes and estimations of all pre-defined and/or post hoc important sensitivity analyses.

Minimize the use of text and rather use preferably data tables combined with if applicable, e.g. Kaplan-Meier curves and Forest Plots.

Include a reference to the relevant eCTD section under each data table.

<Text>

<Ancillary analyses>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should only be used in cases where additional analyses not described above were performed. For analyses performed across studies, don’t use this section, but add in section 6.3.6.

Examples that could be included here are post-hoc analyses, adjusted analyses, including pre-specified ones and other post hoc techniques.

This section can also be used in the case that raw data was submitted by the applicant and analyses performed on that data set not by the applicant, but by the Rapporteurs (or EMA/contractor at the request of the Rapporteurs).

<Text>

* + - 1. <Study #2 identifier> <Study title>

Delete this section if there is only 1 pivotal study.

If there is a second or third pivotal trial, copy/paste all the subsections above from the first study.

<Text>

* + 1. Clinical studies in special populations

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Not applicable for biosimilars.

Please paste here the table from section 3.4 of the D80 clinical report.

**Table 13: Clinical studies in special populations**

|  | Controlled Trials | Non-controlled trials |
| --- | --- | --- |
| Renal impairment\* patients (Subjects number /total number) |  |  |
| Hepatic impairment\*\* patients (Subjects number /total number) |  |  |
| Paediatric patients <18 years (Subjects number /total number) |  |  |
| Older patients; Age 65-74 (Subjects number /total number) |  |  |
| Age 75-84 (Subjects number /total number) |  |  |
| Age 85+ (Subjects number /total number) |  |  |
| Other (Subjects number /total number) |  |  |

\* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

\*\* Hepatic impairment is defined as having Child-Pugh score B or C

Describe briefly any results in special populations that are of relevance for the SmPC and/or RMP.

<Text>

* + 1. <In vitro biomarker test for patient selection for efficacy>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If no biomarker test is used, please state “not applicable”.

In vitro biomarker assays that are used for patient selection (for efficacy and/or safety) define the patient population that was investigated in clinical trials and considered for benefit-risk assessment of a medicinal product, with direct impact on its use in clinical practice.

Evaluating the assay performance in terms of robustness and reliability to measure biomarker(s) is therefore key to understand the benefit-risk of the product in the intended population.

The Applicant should provide sufficient data on the assay used in the clinical study(ies)to get an insight in its properties and robustness when approving the medicinal product. Any uncertainties should be flagged in the AR. Therefore, the following aspects should be addressed:

Scientific rationale:

Scientific rationale for the choice of the predictive biomarker (e.g. prevalence, relation to disease mechanism) and the analytical method by which it is measured. Please consider whether the biomarker that is measured has other roles beyond being (assumed as) predictive for treatment effect/safety (e.g. diagnostic, prognostic).

Analytical validation aspects of the biomarker assay

* Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out.
* To verify the suitability of an assay used in the pivotal study(ies), the selected analytical validation parameters, such as, specificity, sensitivity, precision, limit of detection (LoD), limit of quantitation (LoQ), measuring range, linearity depending on the analytical platform (qualitative vs.(semi-) quantitative) should be described. The corresponding analytical validation results should be discussed, and a conclusion should be drawn regarding the robustness of the testing data ensuring its appropriateness for benefit /risk assessment.

Clinical validation aspects

Clinical validity of the pivotal assay should be described by correlation with a clinical endpoint.

Justification for the definition of the selected population:

a. Cut-point selection:

* Clarification whether the cut-off is determined by the analytical sensitivity of the assay platform or determined otherwise.
* For binary biomarkers: indicate the threshold (i.e. cut-point) defining a patient as biomarker positive; provide evidence why this cut-point was selected; discuss other possible cut-point definitions that (could) have an impact on the efficacy of the medicinal product.
* For continuous biomarkers: describe how cut-points for the trial were selected and if this selection has been shown to be robust and reliable. In case no data are available for biomarker negative populations a solid justification must be provided based on preclinical and literature data.

b. In case of multimarker panels (e.g. panels of genetic/genomic aberrations): definition and justification for the panel chosen, e.g. which genetic aberration(s) define(s) patients selected.

<Text>

* + 1. <Supportive study(ies)>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please provide concise descriptions of any additional experimental studies (not RWE studies, for those, please use section 6.3.7 below) that are supportive of the indication and not captured in previous sections.

<Text>

* + 1. Analysis performed across trials (pooled analyses and meta-analysis)

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please provide a concise description of any analysis performed across studies. If none, please state “not applicable”.

<Not applicable><Text>

* + 1. <Observational data><Data from registries>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If any Real-World Data (RWD), such as data from registries or observational data has been utilized by the applicant to support their claims, describe the specific data sources used and their intended purpose.

If RWD was employed to establish an external control arm this should be integrated into the corresponding pivotal study and detailed in the methods section of the assessment rather than in this section.

If patient experience data were collected as part of RWD, please describe it in this section.

<Text>

* + 1. <Patient experience data (PED)>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Patient experience data (PED) are data collected through a variety of methodologies, including patient engagement activities, that directly reflect the experience of a patient or caregiver without interpretation by a healthcare professional, other third party, or (AI-based) device.

If patient experience data were submitted, provide a summary of such data. This may include PED from quantitative sources (e.g., patient-reported outcome or experience measures, patient preference surveys), as well as PED from qualitative sources (any information obtained as part of patient engagement activities that reflect the wider perspective of patients’ experience, e.g., outcomes of focus groups or interviews).

Describe whether the data come directly from the patients or caregivers, or if it was collected and submitted by other parties (advocacy group, researcher, developer, etc.).

If PED were submitted by the applicant, please describe their intended purpose (e.g., specify whether the data were collected to gather insights on an exploratory trial outcome, to inform the benefit-risk assessment, to enhance understanding of patient quality of life, or for other specific uses). In cases where there was CHMP early dialogue with patient organisations, please summarise the information received.

<Text>

In cases where there was CHMP early dialogue with patient organisations, please summarise the information received.

<Text>

* + 1. <Healthcare professional engagement>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If applicable, provide a brief summary of HCP engagement, including examples of specific guidance on using endpoints, assessments, disease impact, etc.In cases where there was CHMP early dialogue with healthcare professional organisations, please summarise the information received.

<Text>

In cases where there was CHMP early dialogue with healthcare professionals organisations, please summarise the information received.

<Text>

* + 1. Overall discussion and conclusions on clinical efficacy

ASSESSMENT. This section (and subsections) should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

It is anticipated that the phrasing of issues in the discussion section can be copied from the day 80 report, but the text may require some adjustment. Typically, a broad and comprehensive high-level discussion of the main findings occurs in the discussion section, along with further exploration of any areas where deviations have occurred from e.g. Scientific Advices, or Regulatory Guidelines.

Any unresolved issues during the assessment procedure, along with their associated questions, should be included in the discussion section, especially if they directly pertain to a potential modification of the SmPC text or influence the Benefit-Risk discussion. This section should be modified as issues and questions are resolved.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues, that have led to an additional question (LoOI), with an indicator, using (MO) for major objections or (OC) for other concerns.

The Co-Rapporteur's input is imperative, specifically when a dissenting viewpoint or notable omissions require addressing. In such cases, the Co-Rapporteur should actively contribute by providing supplementary insights or concerns that may have arisen during the assessment process. This collaborative effort ensures a thorough and well-rounded evaluation of the clinical data, enhancing the overall assessment process.

* + - 1. Discussion

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

By D80, the Rapporteur should copy/paste their discussion section from the stand-alone D80 clinical report. The Co‑Rapporteur should copy/paste their discussion by D82.

By D120 the Discussion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

If efficacy studies are considered for imposition, ensure this is consistent with Part IV of the RMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + - 1. Conclusions on the clinical efficacy

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to update this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

By D80, the Rapporteur should copy/paste their conclusion section from the stand-alone D80 clinical report. The Co‑rapporteur should copy/paste their conclusion by D82.

By D120 the conclusion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. Clinical safety

Do not delete the text below. It is an important explanation that should be left at the beginning of the section.

Please refer to the table of studies in section 6.3.2

For the purpose of this document, the following definitions apply:

‘Adverse event – AE’ means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

‘Serious adverse event – SAE’ means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

‘Adverse Drug Reaction – ADR’ means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

* + 1. Safety data collection

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe how safety data was collected – through diaries, phone calls etc; what was the schedule of safety visits, and what was the follow up; if safety data are pooled the pooling needs to be described.

<Text>

* + 1. Patient exposure

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please list clinical studies contributing to safety (Cut-off date should be stated).

Please provide numbers and characteristics of included patients (age, stage/severity of disease) and healthy subjects, (could be included in the summary table). The size of the database at X months (X = relevant time period) if appropriate for long-term treatment should be included.

Particularly indicate the safety database for paediatric patients by age groups where appropriate.

<Text>

**Table 14: Patient exposure (cut off)**

|  | Patients enrolled | Patients exposed\* | Patients exposed to the proposed dose range | Patients with long term\*\* safety data |
| --- | --- | --- | --- | --- |
| Blinded studies (placebo-controlled) |  |  |  |  |
| Blinded studies (active -controlled) |  |  |  |  |
| Open studies |  |  |  |  |
| Post marketing |  |  |  |  |
| Compassionate use |  |  |  |  |

\* Received at least 1 dose of active treatment

\*\* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

<Text>

* + 1. Adverse events

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should include adverse events reported during clinical studies with the medicinal product. There are sections dedicated to special populations and drug-drug interactions later in the document, so this section should be based on the integrated summary of safety.

The information should be presented in table format, according to the MedDRA system organ classification. The system organ class (SOC) should be presented and adverse event descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse events should be assigned to the most relevant SOC related to the target organ. For example, PT ‘Liver function test abnormal’ should be assigned to the SOC ‘Hepatobiliary disorders’ rather than to the SOC ‘Investigations’.

The summary table can be the same as in eCTD Table 2.7.4.3. Data should be pooled across studies where possible and appropriate comparisons with placebo or standard of care arms (if available) provided.

Table 15: Summary of adverse events (full analysis set)

<Table>

<Text>

* + - 1. Adverse drug reactions

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Based on the AE section above, this section should describe, purely factually, the ADRs that have been included by the applicant in the SmPC. A table presentation is preferred. The discussion of whether or not the Rapporteurs agree with the proposal by the applicant, should be reserved for the discussion section.

**Table 16: Summary of ADRs proposed for inclusion by the applicant in the SmPC**

Add/delete rows as required. Use the actual frequency of events rather than the Common/Uncommon/Rare classifications.

|  |  |
| --- | --- |
| <System Organ Class> | |
| {Event} | {Frequency} |
| {Event} | {Frequency} |
| {Event} | {Frequency} |
| <System Organ Class> | |
| {Event} | {Frequency} |
| {Event} | {Frequency} |
| {Event} | {Frequency} |

Provide details on the methodology employed by the applicant for defining ADRs proposed for inclusion. If applicable, explain why not all AEs were considered as ADRs. Remain factual, simply explain the applicant’s position.

<Text>

* + 1. Adverse event of special interest, serious adverse events and deaths, other significant events

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Following the overall safety profile, a separate analysis of the AEs of special interest, the serious adverse events and deaths should be provided.

Results should be presented by the SOC (preferred term) including data on severity of serious adverse events. Summary tables as in eCTD (2.7.4.3 and 2.7.4.6) is necessary.

This section should focus only on describing SAEs and deaths reported in the clinical programme. There should be no discussion on whether or not these should be included in the SmPC in this section. Please use the discussion section below for that.

Possible relationship with manufacturing/quality issues should be mentioned if relevant (e.g. antigenic compounds).

A table format is encouraged.

**Table 17: AEs of special interest, SAEs and deaths (full analysis set)**

<Table>

<Text>

* + 1. Discontinuation due to adverse events

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Please summarise information on temporary or permanent discontinuations which are related to adverse events. It should also be clear whether subjects discontinued treatment or discontinued from the study. It should also be clear which events were AEs and which, if any, were SAEs.

Also, it is important to include information on the need for dose reductions or dose interruptions during the trial - did patients continue therapy but at lower dose due to tolerability issues? This section should remain completely factual.

<Text>

* + 1. Safety in special populations

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Provide a brief summary of available data from non-clinical and clinical studies of the safety in special populations (e.g. elderly, children, pregnancy, hepatic or renal impairment, etc).

Consider utilizing exposure/response (safety) analyses and graphs, as they can offer valuable insights.

For the majority of medicinal products, the tables below are pertinent and can be copied from the D80 clinical report. Ensure that safety information is specifically addressed for the older population, or acknowledge if such information is unavailable.

Complete the tables below, adjusting columns and rows as needed. Avoid copying images from eCTD; editable text is preferred, so please copy/paste the tables from the D80 clinical report. If certain sections are not applicable, feel free to remove columns related to comparator treatments or placebo.

**Table 18: AEs by age range**

Copy table from D80 clinical report

<Table>

<Text>

**Table 19: AE by special population**

Copy table from D80 clinical report

<Table>

< Text>

* + 1. Immunological events

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission

Include a short description of the bioanalytical methods, ADAs in clinical samples of healthy volunteers and patients, impact of ADAs on efficacy and safety including hypersensitivity reactions (injection site reactions also by ADA status), etc. The impact of ADAs on PK should be described in the pharmacology section 6.2.3.5.

Alternatively, this information could be presented in the related sections (PK, efficacy and safety) with cross references. For biosimilars, it is preferable to present all data related to immunogenicity in the same section and cross refer as needed.

< Text>

* + 1. Safety related to drug-drug interactions and other interactions

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section focuses on providing pharmacokinetic and pharmacodynamic interaction information directly related to safety. Only data submitted should be reported, without any assessment. Reserve the assessment for the discussion section.

< Text>

* + 1. Vital signs and laboratory findings

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Provide a succinct summary focusing on critical information rather than an exhaustive account of all findings.

Note that safety laboratory markers can be highly sensitive in detecting clinical safety issues, though not always specific. They may also serve as predictive indicators of Adverse Events (AEs).

If applicable, incorporate any findings associated with physical examinations, such as instances of weight loss.

<Text>

* + 1. Post marketing experience

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Is additional relevant information identified from post-marketing experience? If none is available, state “not applicable”.

<Not applicable><Text>

* + 1. <In vitro biomarker test for patient selection for safety>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

If no biomarker test is used, please state “not applicable”.

If applicable, please provide the scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).  
Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

Analytical and clinical validation strategy:

* Analytical validity: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform
* Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay
* Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

<Not applicable><Text>

* + 1. Overall discussion and conclusions on clinical safety

ASSESSMENT. This section (and subsections) should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

It is anticipated that the phrasing of issues in the discussion section to a large extent can be copied from the day 80 report. However, the text may require some adjustments. Typically, a broad and comprehensive high-level discussion of the main findings occurs in the discussion section, along with further exploration of any areas where deviations have occurred from e.g. Scientific Advices, or Regulatory Guidelines. Any warnings included in section 4.4 of the SmPC should also be discussed: describe the proposal from the applicant and then critically discuss whether this is appropriate or not, and if not, why not.

Any unresolved issues during the assessment procedure, along with their associated questions, should only be included in the discussion section if they directly pertain to a potential modification of the SmPC text, influence the Benefit-Risk discussion, if the rapporteurs assert that it should be explicitly mentioned in the European Product Assessment Report or e.g., Good Practice issues that trigger an inspection.

To maintain clarity, it is strongly recommended to label unresolved outstanding issues, that have led to an additional question (LoOI), with an indicator, using (MO) for major objections or (OC) for other concerns.

The Co-Rapporteur's input is imperative, specifically when a dissenting viewpoint or notable omissions require addressing. In such cases, the Co-Rapporteur should actively contribute by providing supplementary insights or concerns that may have arisen during the assessment process. This collaborative effort ensures a thorough and well-rounded evaluation of the clinical data, enhancing the overall assessment process.

If the submission includes data from a paediatric study conducted as part of an approved PIP, please check for non-conformity.

* + - 1. Discussion

By D80, the Rapporteur should copy/paste their discussion section from the stand-alone D80 clinical report. The Co‑Rapporteur should copy/paste their discussion by D82.

By D120 the discussion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

* + - * 1. Overall assessment of available safety data

ASSESSMENT. This section (and subsections) should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Based on the data provided by the applicant, and described in the sections above, each Rapporteur should include their assessment below.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + - * 1. Adverse drug reactions (ADRs) in the SmPC

ASSESSMENT. This section (and subsections) should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Section not applicable to biosimilars.

Based on the AEs described in the sections above, this section should focus on the events where, in accordance with the definition provided at the beginning of the safety section, after thorough assessment by the Rapporteurs, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

A table format is encouraged and should include a short explanation for the event being classed as Adverse Drug Reaction (ADR) and if this is in line with the applicant’s proposal or not. Where there is disagreement with the applicant’s proposal, it should be clear why the (Co)-Rapporteur/CHMP disagrees.

ADRs in the SmPC should be categorized by System Organ Class (SOC) with clear justification for their inclusion.

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 6.4.3.1 above.

By D90/120 the two boxes below should be merged into 1 consolidated CHMP position.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Rapporteur’s position:** [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Table 20: ADRs proposed for inclusion in the SmPC by the Rapporteur  Add/delete rows as required. Use the actual frequency of events rather than the Common/Uncommon/Rare classifications.   |  |  | | --- | --- | | <System Organ Class> | | | {Event} | {Frequency} | | {Event} | {Frequency} | | {Event} | {Frequency} | | <System Organ Class> | | | {Event} | {Frequency} | | {Event} | {Frequency} | | {Event} | {Frequency} |   Where there is disagreement with the applicant’s proposal, it should be clear why the Rapporteur disagrees.  <Text> |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Co-Rapporteur’s position:** [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  Table 21: ADRs proposed for inclusion in the SmPC by the Co-Rapporteur  Add/delete rows as required. Use the actual frequency of events rather than the Common/Uncommon/Rare classifications.   |  |  | | --- | --- | | <System Organ Class> | | | {Event} | {Frequency} | | {Event} | {Frequency} | | {Event} | {Frequency} | | <System Organ Class> | | | {Event} | {Frequency} | | {Event} | {Frequency} | | {Event} | {Frequency} |   Where there is disagreement with the applicant’s proposal, it should be clear why the Co-Rapporteur disagrees.  <Text> |

* + - 1. Conclusions on clinical safety

By D80, the Rapporteur should copy/paste their conclusion section from the stand-alone D80 clinical report. The Co‑Rapporteur should copy/paste their conclusion by D82.

By D120 the conclusion section should be integrated by the Rapporteur into a single consolidated section for adoption by CHMP.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

1. Risk management plan

At D80 the CAT/CHMP Rapporteur should assess the safety specification within the RMP and fill in Sections 7.1 and 7.3 below only. Sections 7.2 and 7.4 are to be filled by the PRAC Rapporteur.

The PRAC Rapporteur should complete their box in Section 7.1 as well as Sections 7.2 and 7.4 by D94.

Comments from MS should be incorporated by the Rapporteurs into the relevant sections, ultimately reflecting the Committee position.

For biosimilars and fixed combination products without new active substance, the RMP(s) of the reference/combined product(s) should be followed and cases of divergence (if any) need to be discussed and highlighted.

Generic products have a different template, in use for some time and unchanged, and will not be using this one. The process for generics will remain unchanged.

* 1. Safety specification
     1. Proposed safety specification

FACTUAL. CAT/CHMP Rapporteur to also copy/paste the “Summary of safety concerns” table from the RMP (Table SVIII.1) proposed by the applicant. Please be mindful not to include any Personal Data (e.g. patient identifiers).

If the RMP covers more than one product and there are safety concerned related to only some products (e.g. due to specific excipients or administration modes) / indications (e.g. risk related to administration in a certain population)/ active substances (e.g. in fixed dose combinations), include all tables applicable and highlight the safety concerns applicable to only some products/indications/active substances.

If there are no safety concerns in the proposed RMP, please state that there are no safety concerns related to the product.

<Text>

The applicant proposed the following summary of safety concerns in the RMP:

**Table 22: Summary of safety concerns in the proposed RMP**

| Summary of safety concerns | |
| --- | --- |
| Important identified risks | <List> |
| Important potential risks | <List> |
| Missing information | <List> |

* + 1. Discussion on proposed safety specification

ASSESSMENT. This section should be completed by the CAT/CHMP Rapporteur. In the subsequent rounds of assessment, it is the responsibility of the CAT/CHMP Rapporteur to update this section.

Does the information in the RMP align with the (non-)clinical assessment?

Are there any major errors or inconsistencies in the safety specifications in the RMP provided by the Applicant?

Could potential comments lead to requests for an updated version of the RMP? Flag any inconsistency in RMP Part II, i.e. SI to SVIII, that will lead to an Other Concern.

If no major errors or inconsistencies are found, is the presentation in the RMP considered acceptable?

To establish the list of important identified and potential risks for inclusion, please consider the following questions:

* What is the strength of evidence supporting the causal association with the medicinal product?
* Do the important identified or important potential risks lead to undesirable clinical outcomes?
* If further characterised and confirmed, would the proposed important identified or important potential risks have an impact on the risk-benefit balance of the medicinal product?
* What is the relation between the clinical impact of the risk and the severity of the indication?
* What is the target population? There is no need to consider risks that will not affect the indicated population.
* What are the clinical practices? There is no need to include risks that are fully characterised and appropriately managed in routine clinical practice.

Please also consider that important identified and potential risks usually warrant further evaluation as part of the pharmacovigilance plan or additional risk minimisation activities.

To establish the list of Missing information, please consider the following:

* Are there gaps in knowledge about the safety of the medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication?
* Is there reasonable evidence of a potential different safety profile in the said populations?
* It always must be relevant to the approved indications. e.g. missing information in children should not be part of the List of Safety Concerns if the product would only be authorised in adults

The commenting boxes should be merged by D195 by the CHMP/CAT Rapporteur into one consolidated CHMP/CAT and PRAC position on the safety specification.

|  |
| --- |
| CAT/CHMP Rapporteur’s position:  <Text> |

CAT/CHMP Co-Rapporteur only flags comments arising from their safety assessment (e.g. clinical safety summary) that might have an impact on the safety specification; the co-Rapporteur does not have any primary RMP assessment task.

|  |
| --- |
| CAT/CHMP Co-Rapporteur’s safety comments:  <Text> |

|  |
| --- |
| PRAC Rapporteur’s comments on the list of safety concerns: [The PRAC Rapporteur is kindly encouraged to add their comments on the safety concerns in this section of the AR by D94; in addition, they can also send the comments as a concerned MS, through the CAT or CHMP delegations]  <Text><None, the PRAC Rapporteur agrees with the assessment by the CAT/CHMP Rapporteur> |

* 1. Pharmacovigilance plan

This section should be completed by the PRAC Rapporteur by D94. It should be updated after D120 and D180, to reflect updates made to the RMP by the Applicant and the re-assessment of the PRAC Rapporteur. After the discussion at PRAC (e.g. D166), this section should be updated to reflect the PRAC position.

Comments from MS should be incorporated by the Rapporteurs into the relevant sections, ultimately reflecting the Committee position.

* + 1. Proposed pharmacovigilance plan.

FACTUAL. PRAC Rapporteur to summarise the pharmacovigilance plan proposed by the applicant. If not too extensive, a copy/past of the RMP table is acceptable.

Briefly summarise the applicant’s proposed routine pharmacovigilance activities.

<Text>

If the applicant proposed some additional PV activities:

In addition, the applicant has proposed the following additional pharmacovigilance activities:

Copy and paste the table from the RMP Part III.3.

**Table 23: Planned additional pharmacovigilance activities**

<Table>

If none are proposed:

<The applicant did not propose any additional pharmacovigilance activities.>

* + 1. Discussion on the Pharmacovigilance Plan

ASSESSMENT. This section should be completed by the PRAC Rapporteur by D94. It should be updated after D120 and D180 responses to reflect updates made to the RMP by the Applicant. After the discussion at PRAC (e.g. D166), this section should be updated to reflect the PRAC position.

* + - 1. Routine pharmacovigilance activities

Discuss whether routine pharmacovigilance is sufficient or whether additional activities are warranted. Discuss whether proposed routine PhV activities are appropriate.

<Text>

* + - 1. Additional pharmacovigilance activities

If there are no additional pharmacovigilance activities proposed, discuss whether this is acceptable or not. If the applicant has proposed a study/activity, discuss the need and usefulness of the study/activity to address the safety concern(s), their feasibility, and the timeliness of milestones of such activities. Propose amendments or any additional ones if needed. If a study aims to evaluate the effectiveness of risk minimisation measures, this needs to be made explicit in the study summary of objectives.

<Text>

* 1. Plans for post-authorisation efficacy studies

This section should be completed by the CAT/CHMP Rapporteur at D80 and updated at subsequent steps.

The purpose of RMP Part IV is to provide a comprehensive view of studies imposed or requested as part of the marketing authorisation; the assessment of imposed efficacy studies should be reflected in the efficacy section of the assessment report.

Copy and paste the table from the RMP Part IV.1.

**Table 24: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.**

<Insert Table>

|  |
| --- |
| CAT/CHMP Rapporteur position:  Comment on whether the summary table in RMP Part IV is consistent with the impositions in Annexes IID and/or IIE of the proposed marketing authorisation, and with the efficacy section of the assessment report.  <Text> |

|  |
| --- |
| PRAC Rapporteur’s comments on the plans for post-authorisation efficacy studies: [The PRAC Rapporteur is encouraged to add comments on any proposed plans for PAES in this section of the AR; in addition, they can also send the comments as a concerned MS, through the CAT or CHMP delegations]  <Text><None, the PRAC Rapporteur agrees with the assessment by the CAT/CHMP Rapporteur> |

* 1. Risk minimisation measures

This section should be completed by the PRAC Rapporteur by D94. It should be updated after D120 and D180, to reflect updates made to the RMP by the Applicant and the re-assessment of the PRAC Rapporteur. After the discussion at PRAC (e.g. D166), this section should be updated to reflect the PRAC position.

* + 1. Proposed risk minimisation measures

FACTUAL. PRAC Rapporteur to summarise the risk minimisation measures proposed by the applicant. If not too extensive, a copy/past of the RMP table is acceptable. Please make sure all safety concerns from Part II: Module SVIII are listed.

Copy and paste the table from the RMP Part V.1.

**Table 25: Planned routine risk minimisation measures**

<Table>

<Text>

If the applicant proposed some additional risk minimisation measures:

In addition, the applicant has proposed the following additional risk minimisation measures:

<Text>

If none are proposed:

<The applicant did not propose any additional risk minimisation measures.>

* + 1. Discussion on the risk minimisation measures

ASSESSMENT. PRAC Rapporteur to discuss acceptability of the risk minimisation measures.

* + - 1. Routine risk minimisation measures

Discuss whether the routine risk minimisation activities as proposed by the applicant are sufficient or whether additional risk minimisation measures are needed.

<Text>

* + - 1. Additional risk minimisation measures

Discuss whether the additional risk minimisation activities as proposed by the applicant are acceptable or not acceptable. Further, discuss if the proposed aRMM(s) are sufficient or whether they need to be updated or whether other risk minimisation measures are needed. If there are no additional risk minimisation measures proposed, state “The applicant did not propose any additional risk minimisation measures.”. If aRMM(s) are necessary for additional safety concerns, describe risks that need to be considered for additional risk minimisation measures and, if appropriate, describe what measures should be proposed.

<Text>

* + - 1. <Patients engagement on the risk minimisation activities>

If patient experience data on risk minimisation preferences were submitted through third parties’ consultation, include them here and explain if they were considered, and if not, why not.

<Text>

* 1. RMP Summary and RMP Annexes overall conclusion

ASSESSMENT. PRAC Rapporteur to include any comments on the RMP summary and/or annexes.

Include points for the Applicant to address in the RMP Summary and the RMP Annexes.

<Text>

<The RMP Part VI and the RMP Annexes are acceptable>

* 1. PRAC Outcome at <D166><D105>

ASSESSMENT. The EMA PL in collaboration with the PRAC Rapporteur will draft and add this part in the AR.

<PRAC endorsed the PRAC Rapporteur’s assessment of the RMP and its conclusions, without further additions.>

<PRAC discussed and agreed the following comments and recommendations:>

List the topics that PRAC discussed and proposed to be added in the AR and LOQ/LOI, to be addressed in an updated RMP; focus on differences from the Rapporteurs’ recommendations (use the headers “safety specification”, “pharmacovigilance plan” and “risk minimisation measures” as necessary); do not include discussed points that do not result in additional changes proposed. Be concise and only capture the final position of the Committee, not all the discussions. Phrase recommendations as text that could be reused for RMP MO/OCs. PRAC Rapporteur should ensure that the RMP sections above and the outstanding issues are updated accordingly, to account for the PRAC recommendations.

* <topics to be addressed>
  1. Overall conclusion on the Risk Management Plan

ASSESSMENT. At each milestone the CHMP/CAT and PRAC Rapporteur should choose one of the options below. By D195 all options, except the final relevant one, should be deleted.

[A) If the RMP is acceptable

The <CAT><CHMP> and PRAC consider that the risk management plan version [insert RMP version] is acceptable.

<In addition, the following minor revisions are recommended to be taken into account with the next RMP update:>

<Text [insert revisions to the RMP recommended with the next RMP update]>

[B) If the RMP could be acceptable with revisions required

The <CAT><CHMP> and PRAC consider that the risk management plan version [insert RMP version] could be acceptable if the applicant implements the changes to the RMP requested in the <list of questions><list of outstanding issues>:

<Text>

[C) If the RMP is not acceptable, in case of negative opinion. A major objection on the RMP should be raised.

The <CAT><CHMP> and PRAC, having considered the data submitted in the application, were of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

1. Pharmacovigilance
   1. Pharmacovigilance system

At each milestone, CHMP Rapporteur is to choose one of the following by ticking the appropriate box.

<The CHMP Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<The CHMP Rapporteur, having considered the data submitted in the application, was of the opinion that it was not appropriate to conclude on the pharmacovigilance system at this time.><See list of questions.>

<The CHMP Rapporteur, having considered the data submitted in the application, was of the opinion that a pre-authorisation pharmacovigilance inspection is required.>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.>

At final opinion, the above should be deleted and only the following retained:

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

* 1. Periodic Safety Update Reports submission requirements

ASSESSMENT. At each milestone the PRAC Rapporteur should choose one of the options below. By D195 all options, except the final relevant one, should be deleted.

For EU-M4all choose the following and delete the rest.

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on [insert date of initial scientific opinion].

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every [insert frequency] until otherwise agreed.

*For new EU-M4all for which there’s already an existing entry in the EURD list (EU-M4All/CAP), it is recommended to align the PSUR frequency with that reflected in the EURD list for the existing CAP product*

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines’ web-portal.

For all medicinal products, except EU-M4all products, delete the above and choose one of the following options by checking he relevant box.

For the LOQ:

<The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

Option 1: If the substance is not already included in the EURD list, the new EURD list entry will be based on the IBD or EBD; request the applicant to indicate whether they wish to align the EBD to IBD with an additional question in the list of question and use the following statement:

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points.> The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. <The applicant did <not> request an alignment of the PSUR cycle with the IBD>. <The IBD is {DD.MM.YYYY.}>.

Option 2: If the substance is already included in the EURD list, evaluate whether the relevant entry is valid for the MAA. If the relevant entry could not be valid for the MAA (e.g. a specific entry for a particular indication/pharmaceutical form/legal basis is needed), the PRAC Rapporteur should verify if a separate entry is needed

In case the already existing entry is valid for the MAA, use the following statement:

<The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

In case a separate entry is needed, in addition to the already existing one, complete the following statement, providing the rationale for such addition of entry and request the applicant to clarify whether they wish to align the EBD to IBD in the list of question

<Based on [provide scientific reason], the PRAC Rapporteur is of the opinion that a separate entry in the list of Union reference dates (EURD list) for [invented name] is needed, as it cannot follow the already existing entry for [active substance]. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is [DD.MM.YYYY]. The new EURD list entry will therefore use the <European birth date (EBD)><IBD> to determine the forthcoming Data Lock Points.>

In case the already existing entry needs to be amended on the basis of the data submitted with the MAA, complete the following statement, providing the rationale for such amendment

<Based on [provide scientific reason], the CHMP is of the opinion that the already existing entry in the list of Union reference dates (EURD list) for [name of active substance] needs to be amended as follows: the PSUR cycle for the medicinal product should follow a <half-yearly> <yearly> cycle. The next data lock point will be [insert date]. >

1. Product information
   1. Summary of Product Characteristics (SmPC)

Section 9.1 and respective subsections of the Assessment Report should be completed by the Rapporteur.

For EMA only: Once the document is prepared for final EPAR text under section 9.1 (only – no subsection) should be deleted.

If specific comments are warranted, these should be incorporated in the complete version of the original SmPC highlighting the proposed changes. Any comments should be put in a boxed area within the text.

See attached edited product information including <both> Rapporteur <and Co-Rapporteur> assessment<s>.

The intent instead of the below specific sections is to capture in a very concise manner the rationale for the text that is approved in the SmPC. Please be very brief and state the main justification for the approved text for the sections outlined below. Focus on the most important aspects (sub sections – except 4.1 – can be deleted or new ones added). It is not necessary to copy/paste the final approved SmPC text below. The next sections are structured to focus on the “critical” sections of the SmPC, not every single section. If other sections are considered to merit justification, these can be included.

* + 1. SmPC section 4.1 justification

This section of the Assessment Report should be completed by the Rapporteur before the final CHMP opinion. Co-Rapporteur only to add if in disagreement or major omission.

How is the indication supported by the data provided in the dossier?

How is the target population determined? Do specific factors like age groups, weight ranges, particular genotypes, or other criteria justify this selection? If the indication statement is 100% aligned with the population studied, there is no need to state much more than “The approved indication is aligned with the population studied in the pivotal clinical trial(s)”.

Please align with the CHMP “wording of indication” document.

<Text>

* + 1. <SmPC section 5.1 justification>

This section of the Assessment Report should be completed by the Rapporteur before the final CHMP opinion, if relevant. Co-Rapporteur only to add if in disagreement or major omission.

There are often discussions at CHMP regarding what should and should not be included in section 5.1 of the SmPC. Without going into too much granularity (e.g. why this P value, why that data point…), please explain the considerations that went into the content of section 5.1. For example, if the pivotal study included a wider population than the final indication, explain what data were included and which were not. Explain the rationale for including any secondary endpoints in section 5.1 of the SmPC. If a specific sub-group analysis was included but not others, explain why.

Only cover the MAIN considerations, not everything that is mentioned in 5.1. Focus on any aspects where the content of 5.1 deviates from the applicable guidelines.

Please also refer to the latest version of the Guide for assessors on section 5.1 of the SmPC.

<Text>

* + 1. <SmPC section X justification>

This section of the Assessment Report should be completed by the Rapporteur before the final CHMP opinion, if relevant. Co-Rapporteur only to add if in disagreement or major omission.

If there is any other section in the SmPC which merits inclusion in the assessment report (e.g. Pregnancy and Lactation) please use this section to explain the content of that SmPC section in detail. For example, if there is a recommendation to exclude pregnant women, please explain what data this is based on. Similarly, if there is a contraindication for a specific population, please explain the basis and the rationale.

<Text>

* 1. Labelling

Section 9.2 and respective subsections of the Assessment Report should be completed by the Rapporteur.

* + 1. Package leaflet (PL)

For EMA only: Once the document is prepared for final EPAR, the section 9.2.1 (only – no following sections) should be deleted.

If specific comments are warranted, these should be incorporated in the complete version of the original PL highlighting the proposed changes. Any comments should be put in a boxed area within the text.

See attached edited product information including <both> Rapporteur <and Co-Rapporteur> assessment<s>.

* + 1. User consultation

For EMA only: Once the document is prepared for final EPAR, only conclusion text on user testing is to be kept under this section (9.2.2). The rest of the text is to be deleted.

[For guidance please see section 16 for the “QRD checklist for the review of user testing results”

[For EU-M4all: In case a user testing was not submitted, please include the following sentence:

< A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.>]

* + - 1. Conclusion from the checklist for the review of user consultation

The conclusion template text reported here below is to be completed based on the assessment provided by the Rapporteur as per the appended “QRD checklist for review of user testing consultation”

This section should only be completed once the applicant has submitted the report on user consultation with target patient groups.

Please choose one of the statements below, as appropriate, and if needed include the necessary justifications.

<The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.>

<The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not yet meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The applicant will <submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability prior to placing the product on the market> <address the following minor issues concerning the user consultation with target patient group population on the package leaflet.>

<A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found <acceptable> <unacceptable> for the following reasons:>

<No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to <name(s) of product(s)>. The bridging report submitted by the applicant has been found <acceptable> <unacceptable>.>

If “unacceptable in any of the 2 options above”:

<The applicant will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use prior to placing the product on the market.>

For Art.58 submissions choose:

<A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a Scientific Opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.>

* + 1. <Quick Response (QR) code>

<The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here: [Quick Response (QR) code)](https://www.ema.europa.eu/en/documents/template-form/quick-response-qr-code_en.doc).>

The outcome of the review of the QR code request should be reflected here. If acceptable, all elements agreed to be provided through the QR code should be listed. If not acceptable, the rational should be explained.

A request to include a QR code in the <labelling><package leaflet> for the purpose of <……> has been submitted by the applicant and has been found <acceptable><unacceptable>.

<The following elements have been agreed to be provided through a QR code: <…>.>

* + 1. <Labelling exemptions>

*EMA should complete* *based on the feedback from the QRD group plenary assessment of the labelling exemption request or delete this section if not relevant.*

For requests of omission of certain particulars falling under Art.63.1 and Art.63.3:

<A request to omit certain particulars from the labelling as per <Art.63.1> <Art.63.3> of Directive 2001/83/EC has been submitted by the applicant and has been found <acceptable> <unacceptable> by the QRD Group for the following reasons:>

The extract from the QRD plenary minutes reflecting the outcome of the QRD Group decision should be included here.

<The particulars to be omitted as per the QRD Group decision described above will, however, be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.>

For requests of translation exemption falling under Art.63.1:

<A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found <acceptable> <unacceptable> by the QRD Group for the following reasons:>

The extract from the QRD plenary minutes reflecting the outcome of the QRD Group decision should be included here.

<The labelling subject to translation exemption as per the QRD Group decision above will, however, be translated in all languages in the Annexes published with the EPAR on the EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.>

* 1. <Additional monitoring>

EMA should complete or delete this section if not relevant

A medicinal product shall be under additional monitoring (mandatory scope) when at least one of the following criteria is met:

* It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
* It is a biological product that is not covered by the previous category and authorised after 1 January 2011;
* It has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];
* It has obligations for stricter recording/monitoring of suspected adverse drug reactions [REG Art 9(4)(cb), DIR Art 21a(c)];
* It is approved under a conditional marketing authorisation [REG Art 14-a]
* It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

A medicinal product may be under additional monitoring (optional scope) when at least one of the following criteria is met:

* It has measures for ensuring the safe use of the medicinal product included in the risk management system [REG Art 9(4)(ca), DIR Art 21a(a)];
* It has conditions or restrictions with regard to the safe and effective use of the medicinal product [REG Art 9(4)(c), DIR Art 21a(d)];
* It has conditions with regard to the existence of an adequate pharmacovigilance system [DIR Art 21a(e)];
* It has an obligation to conduct post-authorisation efficacy studies [REG Art 9(4)(cc), Art 10a(1)(b), DIR Art 21a(f), Art 22a(1)(b)];
* It has an obligation to operate a risk management system due to concerns about the risks affecting the risk-benefit balance of the medicinal product [REG Art 21(2), DIR Art 104a(2)].

If any reason from the optional scope for additional monitoring is included, a short justification reflecting the PRAC consultation should be added.

<Pursuant to Article 23(1) of Regulation No (EU) 726/2004, [Invented name] ([INN]) is included in the additional monitoring list since <include reason(s)>.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

1. Benefit-risk assessment

This section is not applicable for biosimilars, unless a different indication is proposed (similar to a hybrid application). For biosimilars, please delete this section and instead use the section called ‘biosimilarity assessment’ (see section 11 further below).

The Co-Rapporteur's input is imperative, specifically when a dissenting viewpoint or notable omissions require addressing. In such cases, the Co-Rapporteur should actively contribute by providing supplementary insights or concerns that may have arisen during the assessment process. This collaborative effort ensures a thorough and well-rounded evaluation of the data, enhancing the overall assessment process.

* 1. Therapeutic context

This section should include an overview of the mechanism of action, the proposed indication and the dosage regimen (posology). It is essential that this section remains concise and primarily aligns with the content outlined in the proposed Summary of Product Characteristics (SmPC) sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration). Finally, provide a succinct yet comprehensive description in the 2 sections below.

* + 1. Disease or condition, <proposed> therapeutic indication

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Provide a concise description of disease, disease epidemiology and available treatments essential for the BR evaluation. It should also cover any uncertainties and limitations in the current understanding of the condition.

* If patient experience data has been submitted that relates to the disease or condition and its impact on daily life, functioning, etc. and is considered relevant, it should be mentioned (briefly!) in this section.
* Section 3.1 should not be repeated here (include a reference to section 3.1).
* At D80, D120, etc, present the proposed indication. By the end of the procedure, briefly summarise the agreed indication (or the CHMP’s position on it, if an agreement cannot be reached – e.g. negative opinion). Please do not provide a comprehensive explanation of how the final indication was derived in this section but will be discussed in the balance section. This section is meant to be brief and simply an introduction to the BR.

eCTD 2.5.6.1, 2.5.6.1.1, 2.5.6.1.2.

<Text>

* + 1. Available therapies and unmet medical need

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

A concise description of available therapies (if any) in the EU and the overall unmet medical need in the proposed indication and patient population is expected.

* Describe briefly the (relevance of) pharmacological rationale of the product e.g. 2nd in class, new MOA.
* Provide a comprehensive (yet very brief!) summary of Section 3.1. At the final stage of the procedure, this summary should be tailored to reflect the final therapeutic indication.

For a detailed description, please see section 3.1 of this document.

<Text>

* 1. Main clinical studies

Do not delete this text with the cross-reference.

For a detailed description of the main clinical studies supporting this application, please refer to section 6.3.2 of this document.

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Include a concise description of the design of the pivotal clinical trial(s), covering the key basic design aspects; study population characteristics, investigational medicinal products, comparator treatments, dosage regimens, administration routes, treatment duration, randomization methodology, blinding procedures, control groups, the number of participants in the different arms and the total number of participants, essential for evaluating key favourable and unfavourable effects within the context of benefit-risk assessment.

Please focus only on the most important features and do not repeat the clinical study descriptions from the Clinical section above.

Indicate which studies are considered pivotal for the B/R evaluation. Overall, no more than half a page.

<Text>

* 1. Favourable effects

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

* This section should be objective, avoid interpretation and value judgements such as, “it was convincingly shown that overall survival was greatly improved for treatment X”.).
* State only the key favourable effects (i.e., primary endpoint and key secondary endpoints of clinical relevance) relevant to the BR balance and the regulatory decision and describe them shortly (arm, effect estimate, precision).
* Ensure the identification of a manageable number of key favourable effects to support informed decision-making, typically fewer than 10 effects in total (favourable and unfavourable) and ideally fewer than 7. Clearly document these effects in this section, with particular attention to complex cases involving composite endpoints.
* When selecting the key favourable effects, ensure that there is no redundancy or double counting of outcomes. This pertains e.g. to acknowledging marginal differences in effect estimates, the representation of both an overarching group and its subgroups, and the characterization of the same favourable effect employing varying thresholds or time frames.
* Strive for clarity and unambiguity (metrics) in presenting effect estimates and the level of uncertainty (e.g. point estimates, confidence intervals) and the “Strength of Evidence” in terms of inferential statistics (difference, confidence intervals, p values if appropriate). Consider, in case clinically relevant, and important for the final SmPC text, describing key effects in important subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, or genetic polymorphism).
* Describe the “Strength of Evidence” of the favourable effects, which indicates the confidence in the robustness and reliability of findings supporting an effect (both short and long term). This goes beyond describing effect’s magnitude and precision. Besides statistical rigor it encompasses various factors like study type, internal and/or external validity, consistency of findings, and supporting evidence from secondary endpoints that may reinforce or demonstrate additional benefits.
* This section should be consistent with the key favourable effects described in the Effects Table and with the SmPC section 5.1, if applicable.
* This section does not need to be updated during the procedure unless new key results are submitted.
* No new results should be introduced here that have not been described in detail in the previous sections of the AR.

eCTD 2.5.6.2

<Text>

* + 1. Uncertainties and limitations about favourable effects

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Uncertainty and limitations are inherently intertwined with the strength of evidence. While a high strength of evidence suggests greater confidence in the findings, uncertainty reflects the lack of complete confidence due to limitations in the available information.

* Describe only key uncertainties and limitations of the selected favourable effects that impact the benefit-risk balance for the proposed/final indication.
* Describe the factors that characterize the specific information gaps and if applicable specific post-authorization measures imposed to address residual efficacy uncertainties and outstanding concerns. Sources and factors that may contribute to uncertainty and limitations concerns e.g. imprecision of effect estimates (both short and long term), statistical uncertainty, study design and conduct limitations, questionable internal and/or external validity, inconsistency of findings, and lack of supporting evidence from secondary endpoints.
* Remove uncertainty issues that have been resolved by means of questions, or not been fully resolved but no longer being pursued.
* This section should be updated throughout the various assessment phases to encompass only the ongoing or unresolved quality, non-clinical, and clinical issues related to adverse effects that are relevant to the current stage of the review process.
* The results presented in this section must have been detailed in other sections of the AR.
* Not all uncertainties included in the LoQ need to be reflected in this section.

eCTD section 2.5.6.2.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. Unfavourable effects

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

This section should be objective, avoid interpretation and value judgements (e.g., low-grade toxicity for treatment X was significant).

* Describe the extent of exposure and size of the safety population.
* State only the key unfavourable effects relevant to the BR balance and the regulatory decision and shortly describe them (arm, effect estimate and if considered appropriate, precision).
* Ensure the identification of a manageable number of key unfavourable effects to support informed decision-making, typically fewer than 10 effects in total (favourable and unfavourable) and ideally fewer than 7.
* The identification of key unfavourable effects should be focused on adverse drug reactions (ADRs) that have a plausible link to the medicine. However, in terms of reporting frequencies, the incidences of the key unfavourable effects should be based on treatment-emergent adverse events (TEAEs).
* When selecting key effects, ensure that there is no redundancy or double counting of unfavourable outcomes. This pertains e.g. to acknowledging marginal differences in effect estimates, the representation of both an overarching group and its subgroups, and the characterization of the same unfavourable effect employing varying thresholds or time frames.
* Describe the “Strength of evidence” of the key unfavourable effects, which indicates the confidence in the robustness and reliability of findings supporting an unfavourable effect (severity, frequency, onset time, duration, and reversibility). This goes beyond describing effect’s magnitude, and if presented precision of effect, but encompasses various factors like study type, internal and/or external validity, consistency of findings, and supporting evidence from other unfavourable effects.
* This section should be consistent with the important identified risks described in the section Risk management plan, and the SmPC Section 4.3/4.4/4.8. Check relevant risks/warnings included.
* This section does not need to be updated during the procedure unless new key results are submitted.
* No new results should be introduced here that have not been described in detail in the previous sections of the clinical AR.

eCTD 2.5.6.3

<Text>

* + 1. Uncertainties and limitations about unfavourable effects

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Describe only important uncertainties and limitations about the knowledge of the described unfavourable effects that are important for the benefit-risk balance. During the procedure, remove uncertainty issues that have not been fully resolved but are no longer being pursued. Ensure that quality, non-clinical, and clinical uncertainty issues, while not critical for assessing the benefit-risk balance but are nonetheless considered important to be specifically addressed and have been resolved through methods such as SmPC changes, post-authorization measures, conditions, and recommendations, are briefly summarized in this section. A more detailed explanation of these issues should be provided in the respective discussion sections.

* This section should be revised to include solely the ongoing or unresolved significant quality, non-clinical, and clinical issues associated with adverse effects that are relevant to the current review stage.
* Describe the factors that characterize the specific information gaps. Sources and factors that may contribute to uncertainty and limitations concerns specific information about the severity, frequency, onset time, duration, reversibility and mitigating effect of dose reduction, tapering, or discontinuation of the study drug, potential reaction mechanisms, adverse reactions in the context of drug-drug interactions, statistical uncertainty, study design limitations, questionable internal and/or external validity, and inconsistency of findings.
* When combining individual trial data sets (pooled safety data), has a careful evaluation been done to ensure that the data is comparable and that the statistical accuracy of the combined results is not compromised, particularly in terms of matching the incidence rates of adverse effects seen in key pivotal trials?
* Concerns regarding the external validity or representativeness of the patient population expected to use the product are addressed from an unfavourable effect perspective.
* No new information should be introduced here that have not been described in detail in the previous sections of the clinical AR.
* Not all uncertainties included in the LoQ need to be reflected in this section or in the section on importance of favourable and unfavourable effects.

eCTD 2.5.6.3.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. Effects Table

The Effects table (ET) should be completed by the Rapporteur in its entirety at D80. The Co‑Rapporteur should by D82 provide a description of the effects that in their opinion contribute to the B/R (see separate dedicated table below the effects table). A full BR table can be provided by the Co-Rapp if wished, but it is not required. By D120, the effects table should capture 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to adapt the ET if considered necessary. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

The Effects Table is entirely based on the assessment of the key favourable and unfavourable effects, the strength of evidence, limitations and uncertainties described in the previous sections. As such, there is no new element in the table that has not been described elsewhere.

The Effects Table serves to complement the narrative in the benefit-risk balance section of the assessment report; therefore, it should contain and should be limited to the key favourable and unfavourable effects (less than 10, preferably less than 7) concluding on the benefit-risk balance, including the uncertainties.

To effectively document the data in the Effects table, it is advisable to organize the content by prioritizing (see ‘importance’ section) the key favourable effects and unfavourable effects for decision making in an order of importance. This method emphasizes the importance of the benefits and risks, allowing for a clear understanding of the medication's overall impact.

The Effects Table should not replace the textual description of effects in the respective sections; however, consistency is expected.

* **Effect (short description):** Describes here the main effect and the way it is quantified. Provide a very short definition of the effect (e.g., if the variable (endpoint) is overall survival, OS, this could be "duration of survival from randomisation to death regardless of cause”). Make sure complex acronyms or specific tools are explained in footnotes (the purpose is that a reader not thoroughly familiar with the therapeutic area can quickly understand what the effect is being described). The unit and descriptive statistical measures of the parameter are displayed after the brief description of the effect, separated by a dash.
* **Treatment group columns:** Summarise the key effects driving the benefit-risk discussion for each treatment group. The purpose is to provide a clear and concise comparative display. Separate column(s) is (are) included for each treatment group for which sufficient clinical data are available (e.g., placebo, different dosages of the new substance, active controls). If needed, reference(s) to the specific studies describing the effect can be included in the footnotes. The column headers ("Treatment", "Control") should be modified with the name or acronym of the different drugs (and columns can be added as appropriate). If external (historical controls) are used these should be entered in the appropriate column. The results of classes or categorical variables are expressed as number/total number and percentage in parentheses "- number/total number (%)". The results of continuous variables are expressed in summary statistics such as the mean, median, and the degree of uncertainty preferably through confidence intervals.
* **Strength of evidence/Uncertainties column:** Briefly describes the strength of evidence and any major uncertainty or limitation for each effect (e.g., differences between groups, measures of uncertainty such as confidence intervals). A short textual representation of similarities and differences with other relevant secondary outcome measures must be mentioned to further inform the strength of evidence (SoE) or uncertainty (Unc).
* **References column (optional):** This column has multiple purposes. For effects where particularly complex issues have arisen, this column provides a reference to the relevant part of the text, e.g., major objection or other concern, risk-minimisation measure, SmPC section. This column can also be used to refer to specific sources of data (e.g., the acronym of a study in case of evidence from multiple studies or publications).
* **How To Describe Multiple Studies:** In the case of multiple studies, the focus should be on the main studies that drive the evidence of the benefit-risk discussion. If needed, reference(s) to the specific studies describing the effects can be included in the reference column or footnotes. Effects from supportive studies can similarly be described under strength of evidence and don’t need to be mentioned as separate point estimates. If applicable, the use of scientifically justified meta-analytic effect measures could be used.

For illustrative purposes, the table below includes an arbitrary example. Please delete the example rows when finalising the table.`

**Table 26: Effects Table for {insert product name and indication} <(data cut-off: {insert date})>.**

By D80 the Rapporteur fills this effects table. The Co-Rapporteur fills the simplified table below this one.

| Effect (short description) | Treatment | | Control | Uncertainties/  Strength of evidence | Ref |
| --- | --- | --- | --- | --- | --- |
| **Favourable Effects** | | | | | |
| Example | Treatment X 40 µg/day/Kg | Treatment X 120 µg/day/Kg | Placebo |  |  |
| SBA response (≥ 70% reduction in sBA or ≤70 μmol/L after 24 weeks) - no./total no. (%) | 10/23  (43.5) | 4/19  (21.1) | 0/20  (0) | **SoE:** PE; Proportion Difference (Treatment X - Placebo) (95% CI): 40 µg: 0.441 (0.2361, 0.6464); 120 µg: 0.216 (-0.0050, 0.4380).  **Unc:** Clinical relevance unclear, no US patients were responders. | Study 005 |
| Pruritus response (Positive Assessment for >50% of time after 24 weeks) - no./total no. (%) | 17/23  (73.9) | 9/19  (47.4) | 4/20  (20.0) | **SoE:** SE; OR (Treatment X – Placebo) (95% CI) 40 µg: 16.2 (2.540, 106.320) 120 µg: 3.1 (0.718, 18.700). |
| Mean change in liver score (PELD/MELD) after 24 weeks - (95% CI) | -2.43  (-4.35, -0,51) | -1.10  (-3.51, 1.31) | -0.66  (-2.89, 1.57 | **Unc:** No evidence shows Treatment X delays SBD or OLT, but short-term data suggest an effect on liver-related outcomes. |
| Mean change in height (z-scores) after 24 weeks - (95% CI) | 0.05  (-0.16, 0.26) | 0.00  (-0.32, 0.32) | -0.16  (-0.36, 0.04) | **SoE:** SE: Growth catch-up pooled data (48 weeks, studies 005 and 008): 40 µg, 0.52 (0.134); 120 µg, 0.66 (0.177). |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |
| **Unfavourable Effects** | | | | | |
| Diarrhoea (including haemorrhagic, frequent, soft) - no./total no. (%) | 9/23  (39.1) | 4/19  (21.1) | 1/20  (5.0) | **Unc**: Due to overlapping symptoms and safety profiles, the actual safety profile during active disease is unclear. | Study 005 |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |
| <Text> | <Text> | <Text> | <Text> | **SoE:** <Text> **Unc:** <Text> |  |

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.

**Table 27: Co-Rapporteur’s description of the effects that contribute to the B/R**

By D82 the Co-Rapporteur only needs to complete this table. If preferred, a full effects table can replace this one. Please do not amend the Rapporteur’s table; keep the 2 separate at D82. This table can be deleted post D100, once the Rapporteurs agree on the content of the effect table above.

|  |
| --- |
| Effect (short description) |
| **Favourable effects** |
| <Text> |
| <Text> |
| <Text> |
| **Unfavourable effects** |
| <Text> |
| <Text> |
| <Text> |

**Summary:**

* **Effects Table Content:** The Effects Table shall only include key favourable and unfavourable effects that contribute to the conclusion on the benefit-risk balance, including uncertainties. The number of effects shall be limited to fewer than 10, and ideally fewer than 7.
* **Effects Table Organization:** The content of the Effects Table shall be organized by prioritizing key favourable and unfavourable effects for decision-making, as outlined in the ‘importance’ section.
* **Effect Description:** In the "Effect" column, a clear description of the main effect shall be provided, including a brief definition. Complex acronyms or specific tools shall be explained in footnotes for clarity. The unit and descriptive statistical measures of the parameter shall be displayed after the brief description of the effect, separated by a dash.
* **Treatment Group:** In the "Treatment group" columns, the key effects driving the benefit-risk discussion shall be summarized for each treatment group. Separate columns shall be included for each treatment group.
* **Results Presentation:** Results for categorical variables shall be expressed as number/total number and percentage in parentheses. Continuous variable results shall be presented in summary statistics such as mean, median, and confidence intervals.
* **Strength of Evidence/Uncertainties:** In the "Strength of evidence/Uncertainties" column, a brief description of the strength of evidence and any major uncertainties or limitations for each effect regarding clinical relevance shall be provided.
* **Supportive Studies:** Favourable effects from supportive studies shall be described under the strength of evidence without unnecessary repetition as separate point estimates.
* **Integrated Data Presentation:** When presenting integrated (pooling) individual trial data sets, a thorough assessment and discussion has to be conducted to ensure comparability and to prevent compromising the statistical integrity of the aggregated estimates, especially regarding the consistency of unfavourable effect incidences with those observed in pivotal trials.
  1. Benefit-risk assessment and discussion
     1. Importance of favourable and unfavourable effects

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

* In this section, the Assessor should now provide clinical value judgements to further justify the importance of the effects and the impact of any associated uncertainties and limitations of the data described in earlier sections. Quantitative data and study descriptions should not be repeated in detail.
* The importance section should clearly prepare the BR balance discussion and decision, summarise the important effects and uncertainties and apply clinical judgment in the interpretation of the evidence.
* It is important to include only decision-relevant information.
* To describe the value judgments, the general approach is to discuss the importance of the favourable and unfavourable effects hierarchically in order of importance.

First phase; efficacy evaluation:

* The measures ensuring that the evaluation of the medicine's efficacy is based on robust and methodologically sound evidence should be articulated.
* In determining efficacy, the starting point is that the key favourable effects of the medicine should be statistically significant, as evidenced by the data analysis, demonstrating a robust level of confidence with a predefined acceptable probability of Type I error. Additional sources, such as previous regulatory decisions or existing scientific knowledge, should inform this assessment. However, in the absence of a statistically significant difference it is imperative that be thoroughly discussed and justified (second phase).

Second phase: assessing importance:

* The descriptions of the importance of the key favourable and unfavourable effects should be sufficiently detailed in terms of the nature of the effect, factual effect, uncertainty, and clinical relevance to demonstrate their respective impacts on clinical decision-making in the claimed and in line with their clinical relevance.
* The importance should be clearly articulated, and there should be justification for the level of clinical relevance of both the favourable and unfavourable effects, also in terms of relative importance. The section should prioritize the effects based on their level of importance.

General:

* If relevant, discuss important outstanding uncertainties that may influence the assessment of the B/R balance, e.g. issues related to the proposed indication, GCP, dosing, non-clinical findings and quality of the product.

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| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + 1. Balance of benefits and risks

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Having highlighted the relevant aspects of the individual favourable and unfavourable effects and their importance, this section should outline the trade-off between benefits and risks, considering the magnitude, robustness, and clinical relevance of favourable effects against the safety profile. The assessment should take into account the underlying condition, clinical prognosis, and uncertainties.

Key Considerations:

* Provide a clear judgement on whether the benefits outweigh the risks
* Clearly articulate challenges in balancing favourable and unfavourable effects, such as determining clinical relevance
* Consider incorporating explicit trade-off statements or approaches to address a favourable or unfavourable balance of benefits and risks
* If possible, quantify trade-offs by evaluating the magnitude, likelihood, and relative importance of each effect
* Contextualise outstanding risks related to the quality of the commercial product, for example how this may differ from the quality of the product used in pivotal clinical studies, and how this might affect the clinical performance (safety and / or efficacy). (Possible text: The <explain quality deficiency> means that <explain clinical impact><and> <that> <the quality of the commercial product may differ from that used in pivotal clinical studies>.)
* If applicable, discuss any actions needed to address important limitations or uncertainties, such as warnings in the product information, restriction of indication, contraindication, need for future studies (unless already described above).

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + 1. <Additional considerations on the benefit-risk balance>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

* + - 1. <Questions <to be> posed to additional experts>

If no consultation is required, delete the section.

Include any need for or outcome of additional expert involvement including (a proposal for) questions to the experts;

1. SAG/ad hoc experts group (AHEG)
2. Pharmacovigilance expertise (for example review specific safety concerns or to assess the appropriateness and feasibility of draft protocols in the Pharmacovigilance)
3. The PDCO (related to aspects of the paediatric development).
4. Special expertise in relation with novel emerging therapies (e.g. cellular, tissue products, gene therapy).

Once CHMP agrees, or not, on the consultation, please combine the Rapp and Co-Rapp boxes into 1 consolidated CHMP position.

Even after the SAG/AHEG meeting, this section should focus on the questions posed. A brief summary of the output from the meeting goes in the next section.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + - 1. <Input from additional experts>

If no consultation is required, delete the section.

If a SAG/AHEG was conducted, include the following sentence:

<The minutes from the <SAG><AHEG> convened on {insert date} are appended to this report.>

In addition, after the SAG/AHEG, the Rapporteur should include here a brief description of the outcome (don’t copy/paste the full minutes). Remain factual.

<Text>

Following the description of the SAG outcome, each Rapporteur should include their considerations. These should then be replaced by the CHMP position.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

* + - 1. <Conditional marketing authorisation>

Delete this section if the applicant did not request CMA and the Rapporteurs/CHMP did not propose it either. It is worth keeping the section available until D180, by which time it should be clear whether CMA is an option or not.

* + - * 1. <Applicant’s request for Conditional Marketing Authorisation>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Rapporteur to describe the reasons put forward by the applicant for these claims by including the applicant’s claims for each of the following indents. This section should only provide the applicant’s position. CHMP position is in the conclusion section.

In cases where more than one therapeutic indication is applied for, but the CMA is requested requested/granted only for one specific indication (as such specific obligations refer only to one indication) this should be made clear.

<The applicant requested <in the initial submission><during the assessment> consideration of its application for a Conditional Marketing Authorisation <,upon proposal from CHMP,> in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

The benefit-risk balance is positive in the following indication: Add indication <Text>

It is likely that the applicant will be able to provide comprehensive data. {Summarise in general terms the applicant’s claim that they provide comprehensive data} <Text>

Unmet medical needs will be addressed, as {include the applicant’s claim on why the product will provide major therapeutic advantage over the authorised methods. When assessment of major therapeutic advantage over existing methods is needed, avoid the expression ‘significant benefit’, in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.} <Text>

The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. {Summarise the applicant’s claims} <Text>

* + - * 1. <Discussion on the comprehensiveness of data in the context of a Conditional Marketing Authorisation>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

In regards to the request for conditional Marketing authorisation the Rapporteur/CHMP consider that the following is to be accounted in terms of comprehensiveness of the dossier:

Regardless of whether the B/R is positive or negative, discuss the "comprehensiveness” of the data in the context of regulatory options for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances).

If applicable, elaborate on the detailed reasons (scope, requirements) for conditional approval; in the frame of this discussion, each of the following criteria/questions should be considered and discussed when assessing whether the clinical data submitted in the marketing authorisation application can be considered comprehensive. In particular *please discuss the missing data that are not available in the submitted dossier justifying the conditional marketing authorisation.*

If applicable, elaborate on the detailed reasons (scope, requirements) for conditional approval or an approval under exceptional circumstances; in the frame of this discussion each of the following criteria should be considered and discussed when assessing whether the clinical data submitted in the marketing authorisation application can be considered comprehensive:

* Quality of evidence (including feasibility considerations)

Methodological strengths and weaknesses of the clinical program, with focus on pivotal trial(s). Credibility /attributability of treatment effect and safety findings (both efficacy and safety). Trial conduct and GCP (prohibitive GCP findings?). The judgment of “Quality of evidence” should include feasibility considerations.

Which data/trial designs (e.g. RCT or SAT) can be reasonably expected based on epidemiological considerations? Are there limitations due to the rarity of disease? Is randomization feasible?

* Efficacy: precision of effect size

Precision to measure/determine effect size/quantify efficacy, biostatistical considerations.

* Efficacy: clinical meaningfulness of the endpoint

Clinical endpoint versus biomarker or endpoint with clear mechanistic link to clinical outcome measure. Biomarker could also reflect pharmacological activity but not necessarily reflect clinically relevant outcome.

* Efficacy: duration of efficacy

Maturity of efficacy follow-up in the context of disease setting and aim of treatment

* Safety: exposure

e.g. patient numbers to understand the safety profile, in the context of what can be expected based e.g. on the mechanism of action of the product and specific characteristics of the disease. Have AEs of special interest been captured?

* Safety: length of follow-up

Detection of acute, medium, long-term toxicities. Maturity of follow-up and granularity of AE/ADR detection.

* Target population vs study population

Has the target population (e.g. age, line of treatment) been covered in the trial population or is part of the indicated patient population missing? If extrapolation is used, is an explicit confirmation by data (post approval) required? Is efficacy driven by a subpopulation which is not representative of the target population?

* Pharmacological rationale

Strong pharmacological rationale e.g. monogenetic disease treated by replacement of the defected gene or gene product by gene therapy or enzyme replacement therapy

* Natural history/ course of the disease

Is additional information added/included that helps in the interpretation of the data and adds context?}

If relevant, discuss results in subgroups and, in particular, if data in some important subgroups are missing

If applicable, discuss any actions needed to address important limitations or uncertainties, such as warnings in the product information, restriction of indication, contraindication, need for future studies or consultation with experts. For conditional approval state expectations on data to be submitted in order to confirm the positive B/R balance and provide comprehensive data on safety and efficacy of the medicinal product.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

* + - * 1. <Conclusions and recommendation on Conditional Marketing Authorisation>

ASSESSMENT. This section should be completed by the Rapporteur once CHMP has agreed a position on the CMA.

As opposed to section 10.6.3.3.1, where the applicant’s claims are described, this section should reflect the CHMP conclusions.

As comprehensive data on the product are not available <as discussed above>, a conditional marketing authorisation <was requested by the applicant in the initial submission> <was requested by the applicant during the assessment> <was proposed by the CHMP during the assessment, after having consulted the applicant.>.

In case a conditional marketing authorisation is supported [select text as applicable, at least one of the options must apply]:

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the <treatment> <prevention> <medical diagnosis> of a <seriously debilitating> <life-threatening> disease. <In addition the product <is to be used in emergency situations in response to public health threats duly recognised by the <World Health Organisation> <EU>> <and> <is designated as an orphan medicinal product>>.

Include corresponding discussion to support life-threatening or seriously debilitating nature of the disease.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

During the procedure, the (Co)Rapporteur should assess the validity of the reason(s)/data put forward by the applicant according to the [Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (EMA/CHMP/509951/2006, Rev.1](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-and-practical-arrangements-necessary-implement-commission-regulation-ec-no-5072006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf)) and document in this section that CHMP considers that all criteria are met. This can be succinct. Additional arguments may be included where appropriate.

* The benefit-risk balance is positive in Add indication <Text>, as discussed.
* It is likely that the applicant will be able to provide comprehensive data. {Summarise the studies (and, only for emergency situations, preclinical / quality specific obligations) to be conducted and why they are considered feasible}
* Unmet medical needs will be addressed, as {include detailed discussion why there are no satisfactory methods authorised at all, or why the product will provide major therapeutic advantage over the authorised methods. When assessment of major therapeutic advantage over existing methods is needed, avoid the expression ‘significant benefit’, in particular for orphan medicines as it has a distinct regulatory meaning in the context of the parallel COMP assessment of maintenance of the orphan drug designation.}.
* The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. {Summarise the reasons for this conclusion}

In case the CMA is agreed:

<The CHMP considers the following measures necessary to address the missing data in the context of conditional marketing authorisation:>

Add SOBs

**Table 27: Specific obligations in relation to the CMA**

| Description | Due date |
| --- | --- |
| <Post-authorisation efficacy study (PAES): {insert study title or description}> | <DD Month YYYY> |
| <Post-authorisation safety study (PASS): {insert study title or description}> | <DD Month YYYY> |
| <Other> | <DD Month YYYY> |

<Text>

In case a conditional marketing authorisation is not recommended [select text as applicable, at least one of the options must apply]:

<The CHMP considers that the product does not fall under the scope of a Conditional Marketing Authorisation as it is not intended for the treatment, prevention or medical diagnosis of a seriously debilitating or life-threatening disease.>

<The product is not recommended for a Conditional Marketing Authorisation as , <the benefit-risk balance is negative (as discussed)>, <the applicant is unlikely to be able to provide comprehensive data after authorisation>, <it has not been demonstrated that the product will address an unmet medical need>, <and> <the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required>.

All scientific arguments of the applicant should be discussed. For reasons of (a) disease not being considered life-threatening or seriously debilitating, (b) comprehensive data unlikely to be generated post-authorisation, (c) not addressing unmet medical need and (d) benefits of immediate availability not outweigh the risks, include here corresponding discussion.

* + - 1. <Marketing authorisation under exceptional circumstances>

Delete this section if the applicant did not request MA under exceptional circumstances and the Rapporteurs/CHMP did not propose it either. It is worth keeping the section available until D150, by which time it should be clear whether MA under exceptional circumstances is an option or not.

* + - * 1. <Applicant’s request for a Marketing Authorisation under exceptional circumstances:>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Rapporteur to describe the reasons put forward by the applicant for these claims by including the applicant’s claims for each of the following indents. This section should only provide the applicant’s position. CHMP position is in the conclusion section.

<The applicant requested <in the initial submission><during assessment> consideration of its application for a Marketing Authorisation under exceptional circumstances <,upon proposal from CHMP,> in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following:>

The benefit-risk balance is positive in the following indication: Add indication <Text>

It is not likely that the applicant will be able to provide comprehensive data. {Summarise in general terms the applicant’s claim that they are not able to provide comprehensive data} <Text>

* + - * 1. <Discussion on comprehensiveness of data in the context of a Marketing Authorisation under exceptional circumstances:>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

In regard to the request for Marketing authorisation under exceptional circumstances the Rapporteur/CHMP consider that the following is to be accounted in terms of comprehensiveness of the dossier:

*Regardless of whether the B/R is positive or negative, in the case of limited data (e.g. for orphan conditions) discuss the "comprehensiveness” of the data in the context of regulatory options for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances).*

*If applicable, elaborate on the detailed reasons (scope, requirements) for an approval under exceptional circumstances; discuss the comprehensiveness of the data that are available in the submitted dossier and whether it is not possible to provide comprehensive data due to one of the following reasons:*

* the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
* in the present state of scientific knowledge, comprehensive information cannot be provided, or
* it would be contrary to generally accepted principles of medical ethics to collect such information.

If applicable, discuss any actions needed to address important limitations or uncertainties, such as warnings in the product information, restriction of indication, contraindication, need for future studies or consultation with experts.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D210 report which captures the CHMP position]  <Text> |

* + - * 1. <Conclusions and recommendation on Marketing Authorisation under exceptional circumstances>

ASSESSMENT. This section should be completed by the Rapporteur once CHMP has agreed a position on the MA under exceptional circumstances.

For exceptional circumstances, the (Co)-Rapporteurs should assess the validity of the reason(s) following those listed in Section 6 of Part II of Annex I to the Commission Directive 2001/83/EC, as amended and the [guideline for granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) No 726/2004(EMEA/357981/2005](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-procedures-granting-marketing-authorisation-under-exceptional-circumstances-pursuant-article-14-8-regulation-ec-no-7262004_en.pdf)). In brief: address particularly the relevant indent (rarity, ethics or stage of scientific knowledge) and the type of specific obligations that may be necessary. For an approval under exceptional circumstances, it is in principle not foreseen that the applicant can provide comprehensive data on efficacy and safety.

<As comprehensive data on the product are not available <as discussed above>, a marketing authorisation under exceptional circumstances <was requested by the applicant in the initial submission> <was proposed by the CHMP during the assessment, after having consulted the applicant.>

In case a marketing authorisation under exceptional circumstances is recommended [select text as applicable, at least one of the options must apply]:

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because <the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence> <in the present state of scientific knowledge, comprehensive information cannot be provided> <it would be contrary to generally accepted principles of medical ethics to collect such information>.

Include corresponding discussion on this conclusion. Without necessarily repeating all the discussion from the previous section, please ensure that the decision to grant the MA under exceptional circumstances is substantiated and justified here.

<Text>

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

In case a marketing authorisation under exceptional circumstances is not recommended.

It is considered that the absence of comprehensive data cannot be addressed by considering the benefit-risk balance in the context of a marketing authorisation under exceptional circumstances, as the applicant has not sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use. {Include discussion why arguments of the applicant are not supported.>

* + - 1. <Areas for further treatment optimisation>

This section will be deleted by EMA ahead of the publication of the EPAR.

This section comes as a proposal from the Cancer Medicines Forum, endorsed by CHMP at their PROM meeting in February 2024. It is intended for oncology products but can also be used for others if considered useful.

The aim of this section is to highlight gaps in the knowledge of the product that do not necessarily preclude the granting of the MA, such as dose optimisation e.g. to reduce toxicity, improvements in posology, biomarkers, etc. These are merely “suggestions” and not in any way binding to the applicant.

**Do not include imposed studies or recommendations in this section.**

These points cover gaps identified during the evaluation of the MAA and are usually highlighted in the discussion of the clinical efficacy section as well as in the "Uncertainty and limitations of favourable effect" sections.

These identified gaps cover areas which would require further research but would not preclude a Marketing Authorisation. They would aim at improving treatment for patients and would not necessarily be conducted by the Applicant.

**Table 28: Areas for further development**

|  |  |
| --- | --- |
| Problem statement | Objectives of study or further research |
| <Text> | <Text> |
|  |  |
|  |  |

* + - 1. <Third party intervention(s)>

NOTE: any interventions on an ongoing assessment that are not from the applicant, the EU Regulatory Network, or a third-party regulator, are considered as Third-Party Interventions. These may be received at any time during the assessment and should be immediately forwarded to the EMA Product Lead who will process them as required.

If more appropriate, this section can be also located in another part of the CHMP AR (e.g. discussion on chemical, pharmaceutical or biological aspects, discussion on non-clinical aspects, discussion on clinical efficacy aspects or clinical safety aspects).

First, the EMA PL should summarise any received interventions here. Then both Rapporteur and Co-Rapporteur can add their positions on the intervention(s) in the boxes below.

< Text>

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. Benefit-risk conclusions

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Subsections for each milestone have been added to help drafting. At each milestone previous sections should be deleted.

This section should be a conclusion on the information included in the previous section. State clearly whether the B/R is positive or negative and why. Do not repeat the information from the discussion section above. One or two sentences at most are sufficient.

* + 1. At <Day 60><Day 80> - individual Rapporteur conclusions

Rapporteur and Co-Rapporteur to add their independent conclusions.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* + 1. At <Day 90><Day 120> - <CAT><CHMP> conclusions

Rapporteur to delete the previous milestone and capture below the current conclusions on B/R.

<Text>

* + 1. At Day 180 - <CAT><CHMP> conclusions

Rapporteur to delete the previous milestone and capture below the current conclusions on B/R.

<Text>

* + 1. At Day 210 – Final CHMP conclusions

Rapporteur to delete the previous milestone and capture below the current conclusions on B/R.

<Text>

1. <Biosimilarity assessment>

Delete this section for products that are not biosimilars. For biosimilars, this section replaces the Benefit-risk balance section above.

* 1. <Comparability exercise and indications claimed>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

State the claimed indications and if the applicant is claiming all or only part of the approved indications of the reference product.

Briefly summarise (in a few sentences) the main aspects of the comparability exercise conducted (including analytical, functional (e.g. biological activity), non-clinical, and clinical data) and whether the development plan followed respective EMA guidelines and/or CHMP advice.

<Text>

* 1. <Results supporting biosimilarity>

FACTUAL. This section is to be completed by the Rapporteur. Co-Rapporteur only to add if in disagreement or major omission.

Describe the results of the comparability exercise in terms of quality, non-clinical and clinical PK/PD, efficacy, safety and immunogenicity data that support a claim of biosimilarity.

<Text>

* 1. <Uncertainties and limitations about biosimilarity>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Describe concerns/uncertainties with regard to biosimilarity due to observed differences in analytical, functional, non-clinical and/or clinical aspects (e.g. comparability margins not met; differences in immunogenicity or infusion-related reactions; new drug reactions or signals compared to reference product) or due to missing relevant data.

This section should be updated during the procedure. If there are no remaining uncertainties and limitations that have an impact on the biosimilarity conclusion, this section can be completed with “There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. <Discussion on biosimilarity>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Describe the importance of the data supporting or questioning similarity in terms of efficacy and safety.

Discuss the impact of any uncertainties or issues with the comparability exercise in terms of efficacy and safety, e.g. are the differences observed relevant and expected to have an impact on the efficacy and/or safety/immunogenicity of the biosimilar candidate in comparison to the reference product.

Describe if the comparability exercise has been successful and state explicitly if similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy has been established. Discuss the strength of evidence.

Successful comparability exercises do not require trade-offs (see general guidance) but a justification about whether the comparability exercise has been successful according to conventional scientific standards to conclude similarity in efficacy and safety.

If applicable, discuss any actions needed to address important limitations or uncertainties (e.g. post-marketing study to provide a more precise estimate of an identified risk).

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. <Extrapolation of safety and efficacy>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

When clinical comparability has been shown in one indication, and the applicant is applying for several indications of the reference product, the possibility of extrapolation of a conclusion of similar safety and efficacy to the other indications should be discussed in this section, taking into account the totality of data from the comparability exercise. Discuss as appropriate quality, non-clinical, clinical data, mechanism of action, receptor(s) mediating the effects, supporting extrapolation and if comparability between the biosimilar candidate and the reference can be concluded for all claimed indications of the reference product.

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

* 1. <Additional considerations>

ASSESSMENT. This section should be completed independently by Rapp and Co-Rapp (see individual boxes below). By D120, the two boxes should be amalgamated into 1 consolidated position for CHMP adoption. In the subsequent rounds of assessment, it is the responsibility of the Rapporteur to fill out this section. The Co-Rapporteur should only contribute if there is a significant disagreement or a major omission that needs to be addressed.

Discuss what is recommended to advance knowledge (e.g., recommended further studies, if not already described in earlier sections).

If no additional considerations apply, this section can be completed with “Not applicable.”

Discuss the potential for misuse and off-label use (e.g. in case not all indications or routes of administration of the reference product are approved for the biosimilar).

If appropriate, add a section on ‘Third party intervention’. The addition of this section should be considered on a case-by-case basis. If more appropriate, this section can also be located in another part of the AR (e.g. discussion on chemical, pharmaceutical or biological aspects, discussion on non-clinical aspects, discussion on clinical efficacy aspects or clinical safety aspects).

|  |
| --- |
| Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

|  |
| --- |
| Co-Rapporteur’s position: [Title to be deleted and sections merged when preparing the D90/D120 LOQ]  <Text> |

1. <D90\*><D120> List of Questions

[\*in case of accelerated assessment]

Rapporteur and Co-Rapporteur should add questions directly in the relevant sections. At D60/D80, please make clear whether it is a Rapp or Co-Rapp question by adding (Rapp) or (Co-Rapp) in brackets after the question.

The questions from the Rapporteur and Co-Rapporteur should be presented directly in this template document, with a new section added at each milestone and all questions deleted for the final EPAR.

The applicant will respond to the questions directly in a corresponding responses template, including comment boxes for Assessor’s review. The response document will be submitted in both PDF and MS Word versions at the time of response.

ASMF-related questions are answered separately. The applicant may choose whether one joint or several separate response documents are prepared. Regarding multiple response documents, an informative title should be added on the front page.

**Numbering:** Automatic numbering of questions has been added but can be quickly disrupted if people copy/paste incorrectly. Please copy/paste only the question text. Questions are numbered from 1 (the first MO in the Quality section) and continue from there. Each question should have its own unique number (i.e. no Q1 for quality and Q1 for efficacy, for example). Numbering will be fixed by EMA after the Peer Review TC when the list of questions is finalised.

To add a new question number, use the **insert caption** function as explained at the beginning of this document:

A screenshot of a question

Description automatically generated

Definitions of questions:

**“Major objections”** preclude a recommendation for marketing authorisation or granting an ancillary claim (new active substance status, and/or additional year of marketing protection/data exclusivity). In principle, one major objection may entail more than one question and using bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary, along with a reference to guidance documents. The objection should clarify to what kind of response/action is expected from the applicant.

**“Other concerns”** address issues that are relevant but not critical enough to be decisive for benefit-risk (B/R). Overall, the other concerns should have at least a potential impact on the Product information/Summary of the Product Characteristics (PI/SmPC), Risk Management Plan (RMP) and/or the European Public Assessment Report (EPAR) content. Questions that, irrespective of the applicant’s response, are not expected to have any impact on the PI, RMP and/or EPAR content, should not be included in the list of questions. This does not mean that an identified concern and/or deficiency must not be mentioned in the assessment. Instead, in such a case, a justification in the assessment report why this is not considered relevant for B/R and/or PI and therefore not raised as a question, can be added.

The applicant should respond to the following questions using the response document template available on the EMA website here: [Marketing authorisation templates | European Medicines Agency (europa.eu)](https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/marketing-authorisation-guidance-documents/marketing-authorisation-templates). The response document should be submitted both as PDF and as a WORD document (in the Working Documents folder in eCTD).

* 1. Quality Aspects

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

NB: This document should only address questions not related to the ASMF.

Questions on the Applicant’s Part and Restricted Part of the ASMF can be found in a separate document.

### Major Objections

[delete any sections that don’t apply]

* + - 1. Drug substance

Question 1

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 2

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

* + - 1. Drug product

Question 3

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 4

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Drug substance

Question 5

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 6

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

* + - 1. Drug product

Question 7

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 8

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

* 1. Non-clinical Aspects

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

### Major Objections

[delete any sections that don’t apply]

* + - 1. Pharmacology

Question 9

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 10

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Pharmacokinetics

Question 11

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 12

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Toxicology

Question 13

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 14

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Pharmacology

Question 15

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 16

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Pharmacokinetics

Question 17

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 18

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Toxicology

Question 19

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 20

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Clinical Aspects

### Major Objections

[delete any sections that don’t apply]

* + - 1. Clinical Pharmacology

Question 21

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 22

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Efficacy

Question 23

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 24

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Safety

Question 25

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 26

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Clinical Pharmacology

Question 27

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 28

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Efficacy

Question 29

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 30

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Safety

Question 31

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 32

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Risk Management Plan

[delete any sections that don’t apply]

### Major Objections

Question 33

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 34

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

Question 35

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 36

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Pharmacovigilance

[delete any sections that don’t apply]

### Major Objections

Question 37

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 38

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

Question 39

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 40

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Delete any sections below that don’t apply, amend as needed

* 1. <Orphan similarity and derogations>

### Major Objections

Question 41

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 42

<Text>

### Other Concerns

Question 43

<Text> 

Question 44

<Text> 

* 1. <New active substance status claim>

### Major Objections

Question 45

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 46

<Text>

### Other Concerns

Question 47

<Text>

Question 48

<Text>

* 1. <Additional data exclusivity/Marketing protection>

### Major Objections

Question 49

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 50

<Text>

### Other Concerns

Question 51

<Text>

Question 52

<Text>

1. <D120\*><D180> List of Outstanding Issues < to be addressed in writing <and/or in an Oral Explanation\*>

[\*in case of accelerated assessment]

Delete the previous section (D90/D120 LoQ) so that the numbering below will automatically restart at 1.

Rapporteur and Co-Rapporteur should add questions directly in the relevant sections.

The questions from the Rapporteur and Co-Rapporteur should be presented directly in this template document, with a new section added at each milestone, previous questions sections deleted (for clarity/brevity) and all questions deleted for the final EPAR.

Numbering should re-start from 1 when the previous section is deleted.

The applicant should respond to the following questions using the response document template available on the EMA website here: [Marketing authorisation templates | European Medicines Agency (europa.eu)](https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/marketing-authorisation-guidance-documents/marketing-authorisation-templates). The response document should be submitted both as PDF and as a WORD document (in the Working Documents folder in eCTD).

* 1. Quality Aspects

NB: This document should only address questions not related to the ASMF.

Questions on the Applicant’s Part and Restricted Part of the ASMF can be found in a separate document.

### Major Objections

[delete any sections that don’t apply]

* + - 1. Drug substance

Question 53

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 54

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

* + - 1. Drug product

Question 55

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 56

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Drug substance

Question 57

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 58

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

* + - 1. Drug product

Question 59

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  M3 completeness.

Question 60

<Text>

* 1. Non-clinical Aspects

### Major Objections

[delete any sections that don’t apply]

* + - 1. Pharmacology

Question 61

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 62

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Pharmacokinetics

Question 63

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 64

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Toxicology

Question 65

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 66

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Pharmacology

Question 67

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 68

<Text>

* + - 1. Pharmacokinetics

Question 69

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 70

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Toxicology

Question 71

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 72

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Clinical Aspects

### Major Objections

[delete any sections that don’t apply]

* + - 1. Clinical Pharmacology

Question 73

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 74

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Efficacy

Question 75

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 76

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Safety

Question 77

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 78

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

[delete any sections that don’t apply]

* + - 1. Clinical Pharmacology

Question 79

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 80

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Efficacy

Question 81

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 82

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* + - 1. Clinical Safety

Question 83

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 84

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Risk Management Plan

[delete any sections that don’t apply]

### Major Objections

Question 85

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 86

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

Question 87

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 88

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

* 1. Pharmacovigilance

[delete any sections that don’t apply]

### Major Objections

Question 89

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

For each pasted question, please also indicate whether the outcome of the question affects the B/R, SmPC etc by ticking the appropriate boxes.

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 90

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

### Other concerns

Question 91

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Question 92

<Text>

The outcome of this question has an impact on  B/R;  SmPC;  Final EPAR;  RMP.

Delete any sections below that don’t apply, amend as needed

* 1. <Orphan similarity and derogations>

### Major Objections

Question 93

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 94

<Text>

### Other Concerns

Question 95

<Text>

Question 96

<Text>

* 1. <New active substance status>

### Major Objections

Question 97

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 98

<Text>

### Other Concerns

Question 99

<Text>

Question 100

<Text>

Question 101

<Text>

Question 102

<Text>

* 1. <Additional data exclusivity/Marketing protection>

### Major Objections

Question 101

Each Rapporteur adds their questions. To add a new question header, go to “References”, “Insert caption” and under “Label”, choose “Question”. The numbering should be automatic.

<Text>

Question 102

<Text>

### Other Concerns

Question 103

<Text>

Question 104

<Text>

1. Re-examination

In case of positive opinion, EMA to delete this section at the time of D210 opinion.

In case of negative opinion, retain the text below at D210. Following re-examination (if applicable) the text below should be replaced with the re-examination report, copy/pasted from the stand-alone report before the adoption of the final opinion on the re-examination.

In the case of a re-examination following negative opinion, the re-examination report will be pasted here ahead of the final EPAR publication.

1. Appendi<x>/<ces>

EMA to delete/adapt the below according to the milestone.

<Divergent position(s) to the majority recommendation >

<CHMP/CAT AR on similarity dated >

<CHMP/CAT AR on derogations dated >

<CHMP/CAT AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies – Article 14(11)

<CHMP/CAT AR on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication – Article 10(5)

<CHMP/CAT AR on the significant non-clinical or clinical data in relation to the claimed new indication – Article 74a

<CHMP/CAT AR on new active substance claim dated >

Divergent positions on the B/R, NAS, similarity, derogations or + 1year requests should be appended to the CHMP AR.

<SAG/AHEG/WP consultation> minutes

1. QRD checklist for the review of user testing results

For factual data, Co-Rapporteur only to add if additional data are of relevance. In this case, please insert relevant boxes for Co-Rapporteur assessment as applicable.

Disclaimer: This guidance has been developed to provide practical information on how to evaluate user testing reports which are based on the readability testing method as described in the Annex to the EC Readability Guideline. This does not exclude the submission and evaluation of user testing reports based on other methods than the one outlined above, for which specific assessment guidance may be issued once experience has been gained.]

Useful links: More detailed practical guidance can be found in the following documents:

* EC Readability Guideline <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf>
* “Operational procedure on Handling of “Consultation with target patient groups” on Package Leaflets (PL) for Centrally Authorised Products for Human Use <https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/operational-procedure-handling-consultation-target-patient-groups-package-leaflets-centrally_en.pdf>
* “Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test-Recommendations for Bridging” <https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_100_2007_clean.pdf>
* “Position paper on user testing of package leaflets” <https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011_Rev01_2016_12_clean.pdf>

***PRODUCT INFORMATION***

| Name of the medicinal product: |  |
| --- | --- |
| Name and address of the applicant: |  |
| Name of company which has performed the user testing: |  |
| Type of Marketing Authorisation Application: |  |
| Active substance: |  |
| Pharmaco-therapeutic group  (ATC Code): |  |
| Therapeutic indication(s): |  |
| Orphan designation | yes  no |
| Rapporteur/CoRapporteur |  |

- Full user testing report provided  yes no

- Focus test report provided  yes no

- Bridging form provided[[1]](#footnote-2)  yes no

*[In case full user testing or focus test reports have been provided, please use the checklist for review of user testing results included in this document.]*

- In case bridging form1 has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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- Is the justification for bridging acceptable?  yes  no

- Is the justification for not submitting a report acceptable?  yes  no

Reasons *\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

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*[The following are examples of what are not considered valid justifications for not performing user testing:*

*Administration in a hospital setting only,*

*Orphan indication, therefore difficult to recruit participants from this population,*

*Administration by a healthcare professional only,*

*Compliance with the QRD templates,*

*Long established use of the product.*

Reasons *[assessor’s views on acceptability or not of the justification*

*for not submitting user testing report or bridging form]*

*\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

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* 1. Technical assessment
     1. **Recruitment**
* Is the interviewed population acceptable?  yes  no  no information

Comments/further details:

**Guidance regarding Recruitment**

The following points should be taken into consideration when assessing recruitment methods:

* Is the recruitment method well defined? Is it clear that serious thought was given to the composition of the test group? (e.g. in terms of variables such as sex, age, education, previous job titles (in case of retirement, change of employment), job description and professional experience (e.g. vocational training, complete qualifications, use of information technology) in order to assess their level of education, experience with the medicinal product, existing knowledge of the complaint, access to information technologies, etc.). Is a detailed description of the subjects’ profiles available?- How has the test group been recruited? Are they new users or patients, parents or carers?
* Is a listing of any respondents who volunteered previously in user testing and how often they have done so available?
* Is it clear how many people were involved in the test/test rounds?
* Is that number sufficient? (The PL should be tested in minimum 2 rounds of 10 participants each)
  + 1. Questionnaire
* Is the number of questions \_\_\_\_\_\_\_ sufficient?  yes  no  no information
* Questions cover significant (safety) issues for the PL concerned?

yes  no no information

Comments/further details:

**VIII.4.2 Guidance regarding Questionnaire**

The following points should be taken into consideration when assessing the questionnaire:

* Have the key messages for safe use been identified by the applicant? Is it clear how the questions were selected /drafted? The critical safety issues should be discussed prior to preparing the questionnaire.
* Do the questions cover the key messages and the following areas?
* =>General impressions of package leaflet;

=>“Diagnostic” part of PL (i.e. questions aiming to test whether the participants were able to find specific information quickly and easily in each section of the PL and to verify if they were able to understand this information correctly; the questionnaire should primarily concentrate on safety and correct use of the medicinal product and understanding of the participant to assure safe use –it must be ensured that key safety messages have been addressed);

=>Aspects such as design and layout of PL.

* Is the number of questions sufficient? (too few or too many – e.g. 12- 15)
* Do the questions address “wording” aspects? Can respondents easily understand the text they are reading?
* Is the number of questions sufficient? (too few or too many –
* e.g. 12- 15)
* Do the questions address “wording” aspects? Can respondents easily understand the text they are reading?
* Do the questions provide open or pre-defined answers? Respondents should not be provided with ready-made answers which would increase the possibility of positive results. They should instead answer in their own words in order to check if they understand the information correctly. Questions should be open, should be ordered randomly to see how patients use the PL and should not be leading (however, it is good practice to start with an easy question to ease the participant). Questions that require self-assessment (example: in your opinion, is paragraph X clear?) should not be used. Questions that require a long list of answers to be given (example: “what are the adverse events of this medicinal product?”) should also not be used.
  + 1. **Time aspects**
* Is the time given to answer acceptable?  yes  no  no information
* Is the length of interview acceptable?  yes  no  no information

Comments/further details:

Guidance regarding Time aspects

The following points should be taken into consideration when assessing the time aspects:

* Is it clear how long the test lasted?
* Was the time given for respondents to read and answer the questions adequate? How long did the interview last? [The test should be designed in a way to last no more than 45 minutes, to avoid tiring participants]
* Is it clear at which point would a question be considered “not answered”? E.g. simply because the respondent took too much time to find and / or understand it? (It should not take more than 2 minutes to find the answer).
  + 1. Procedural aspects
* Rounds of testing including pilot \_\_\_\_\_\_\_  yes  no  no information

Comments/further details:

**Guidance regarding Procedural aspects**

The following points should be taken into consideration when assessing the procedural aspects:

* Is the test based on different testing rounds? ( a minimum of two test rounds, each involving 10 participants, is required: As this is an iterative process more rounds may be required in order to satisfy the success criteria; a pilot test (including 2 to 3 persons) could precede to assure the questionnaire is understood and major gaps are precluded. The PL after changes should then be tested on 20 participants in total. However, one single testing round may also be considered sufficient and acceptable on a case-by-case basis)

A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants.

In practice, it means to have 16 out of 20 participants able to find the information and answer each question correctly and act appropriately. However, it need not be the same 16 participants in each case. The success criteria will need to be achieved with each question. Results cannot be aggregated.

* Does it makes use of modification phases in-between the testing rounds in order to maximise readability?
* Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate.
  + 1. Interview aspects
* Was the interview conducted in well structured/organised manner?

yes  no  no information

Comments/further details:

**Guidance regarding Interview aspects**

The following points should be taken into consideration when assessing the interview aspects:

* Is the time given to the participants to read the leaflet before the interview starts clearly stated? (It should not be more than 15 minutes).
* Are there clear instructions for the test instructor(s)? (e.g. instructions on how to get more information from the consumers test, whether or not help should be given, etc.)
* Do interviewers let respondents show where information on the medicinal product can be found in the leaflet?
* Do they ask respondents to give their answer in their own words and not to rely on memory?
* Is there an internal Standard Operative Procedure (SOP) upon which the whole exercise was based?
  1. Evaluation of responses
     1. Evaluation system
* Is the qualitative evaluation of responses acceptable?

yes  no  no information

* Does the evaluation methodology satisfy the minimum prerequisites?

yes  no  no information

Comments/further details:

**Guidance regarding Evaluation system**

The following points should be taken into consideration when assessing the evaluation system:

* Is the assessment based on a check list covering the following 3 basic areas:

1. Whether the respondent was able:

* To find the information (e.g. can a respondent easily find the information on dosage?)
* To understand the information (e.g. can a respondent say in his/her own words what the proper dosage and the instructions for use are?)
* To use the information (e.g. “imagine you are in situation X and Y happens, what must you do?”)

1. Does the report identify difficulties (if any) in finding or understanding certain questions? If so, are these difficulties analysed? And, more importantly, are they addressed in the PL?
2. If the company recorded the body language and behaviour of the participant, it should be described how it will influence the assessment/ results of the user testing.
   * 1. Question rating system

* Is the quantitative evaluation of responses acceptable?

yes  no  no information

Comments/further details:

**Guidance regarding Questions rating system**

The following points should be taken into consideration when assessing the questions rating system:

* How are answers evaluated? (e.g. 1= no answer, 2=wrong answer, 3=incomplete answer, 4=ambiguous answer, 5=complete and correct answer)
  1. Data processing
* Are data well recorded and documented?  yes  no  no information

Comments/further details:

**Guidance regarding Data processing**

The following points should be taken into consideration when assessing the data processing:

* Is it clear how the data are recorded? e.g. videotape, audiotape or in writing.
* Is it clear how long the data are kept for after the end of the study?
* Is the way in which they are recorded satisfactory?
* Have the data been processed satisfactorily? (e.g., is it clear how verbal assessments have been converted into graded answers?)
* Has the assessor been provided with the patient leaflets used during (different rounds of) testing?
* Are the revisions in the PL explained/justified? Is it also clear which comment from the participants were ignored and why?
  1. Quality aspects
     1. Evaluation of diagnostic questions
* Does the methodology follow Readability guideline Annex?

yes  no  no information

* Overall, each and every question meets criterion of 81% correct answers (e.g. 16 out of 20 participants)

yes  no  no information

Comments/further details:

* + 1. Evaluation of layout and design
* Follows general design principles of Readability guideline  yes  no
* Language includes patient friendly descriptions  yes  no
* Layout navigable  yes  no
* Use of diagrams acceptable  yes  no

Comments/further details:

**Guidance regarding Quality aspects**

The following points should be taken into consideration when assessing the quality aspects:

* Is the report complete?
* Does the report clearly distinguish between quantitative and qualitative results?
* Is the medicinal product and the company concerned clearly indicated?
* Based on EC guidelines, are “diagnostic” questions (see 1.2) scoring satisfactorily?
* Do respondents find the layout and design of the package leaflet satisfactory?

Special focus should be given to the following elements:

* Writing style (simple language, short sentences, use of bullets)
* Type face (font size, italics/underlining, lower/upper case)
* Layout (spacing, white space, contrast, left justified, columns)
* Headings (consistent location, stand out)
* Use of colour (present, adequate contrast)
* Pictograms should be subject to user testing as it is well known that these can confuse patients.
* Do respondents encounter difficulties in locating and using correctly (if appropriate) the information provided in the PL?
* Is it clear whether general or specific comments on design and layout have been implemented? If not, has a justification been provided?
  1. Diagnostic quality/evaluation
* Have any weaknesses of the PL been identified?  yes  no
* Have these weaknesses been addressed in the appropriate way?  yes  no

Comments/further details:

**Guidance regarding Diagnostic quality/evaluation**

The following points should be taken into consideration when assessing diagnostic quality/evaluation:

* Are the results (as far as possible) related to actual passages of text?
* Is an attempt made to explain that readers’ problems arose because of certain characteristics of those passages (e.g. something was difficult to find because of a badly chosen heading; or a passage could not be understood because of a double negative; or specific information could not be applied properly because certain terms were unclear)?
* Was a second round revision carried out?
* Have weaknesses of the first round been clearly identified and addressed in the appropriate way? (e.g. questions that scored low led to modifications on the PL => introduction of stylistic changes to improve readability or removal of redundant and confusing information)
* Is it clear which passages have been revised and how and on the grounds of what observations in the first round?
* Is it also clear what observations were ignored in making the revision and why?
* Have modifications been tested and proved to improve readability?
* Is it clear what changes were made in between the different rounds (pilot, 1st and 2nd)? (e.g. summary of PL changes highlighted before and after? Has a new PL with track changes been included in the report reflecting changes between different rounds?)
* Have mock-ups used for each round been submitted? Is the final version the one which has been submitted with the application to be assessed?
  1. Conclusions
* Have the main objectives of the user testing been achieved?  yes  no
* Is the conclusion of applicant accurate? yes  no
* Overall impression of methodology  positive  negative
* Overall impressions of leaflet structure  positive  negative

**CONCLUSION/OVERVIEW**

**Guidance regarding Conclusions**

A general view on the user testing performed and on the overall readability /quality of the PL should be provided here [to be used in the Day 80, Day 150 or Day 180 assessment report as appropriate and the CHMP assessment report – the complete evaluation report of the user testing results should only be included as an Annex of the Day 80 or Day 150 assessment report, as appropriate]

The following points should be taken into consideration when drafting the conclusions:

Objectives:

1. To ensure the final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. The overall quality of the PL should be the absolute focus rather than confirming a successful 81%+ for each and every question.
2. To assess the readability of the PL
3. To identify problems regarding comprehensibility and usefulness of information
4. To describe possible changes in the leaflet in order to improve the readability of the leaflet
5. To ensure that all comments, especially the ones related to design, lay-out, general impression (free text comments), have been taken into account.

* Does the report make it clear on what test results specific conclusions are based?
* Do the conclusions match the results or, given the actual results, is too favourable a picture painted?
* Are the conclusions clear, concise and well organised?
* Have the recommendations and conclusions also been incorporated in any revision of the text?

1. [QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]](https://www.ema.europa.eu/en/documents/template-form/quality-review-documents-qrd-form-submission-and-assessment-user-testing-bridging-proposals_en.doc) [↑](#footnote-ref-2)