<Co>Rapporteur day <60\*><80> critical assessment report

\*in case of accelerated assessment

Quality aspects

<Product name>

International non-proprietary name: <INN> or <Common name>

<Pharmaceutical form and strength>

Procedure No. EMEA/H/C/<XXX>

Applicant:

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

Instructions to Applicants/Rapporteurs for use of this template

In the event that the **Applicant** agrees to pre-fill the factual sections of the template, guidance text for them is provided in blue.

The applicant is expected to pre-fill the factual sections of this template in an objective, data-driven way, without any bias or promotional intent.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. quality overview, 3.2.S parts, 3.2.P parts 3.2.R), references to the literature or other sources.

The use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate. Tables taken from the dossier may also be included in the template. Footnotes should not be forgotten. Tables should be added as MS Word tables and not copy/pasted as pictures or from PDF.

Separate pages have been added in the template to include a list of abbreviations and references, to be completed when necessary.

For multiple active substance sources/manufacturers or where multiple active substances are included in the application, consider to duplicate the sections as required. For example, for multiple active substances, information for 3.2.S should be presented separately for each active substance in the report.

For active substances which may have multiple components or be complexes e.g. radiopharmaceuticals, it should be clearly defined in the report which component or combination of components is considered the subject of module 3.2.S.

If multiple pharmaceutical forms or components are included in the application, consider to duplicate the sections as required in 3.2.P section of the report.

It is recommended that the font used in the main text be Verdana, size 9.

Moreover, in general, the following aspect should be considered when filling in the template:

* For each main section of the assessment report for module 3, the report should describe the data submitted in accordance with Annex I of Directive 2001/83/EC. The types of studies addressed within each section should include all indents as listed in Annex I of Directive 2001/83/EC part 2.
* Justifications should be provided for waiving certain studies or for substituting them with publications.
* If data from publications is used, a direct link as well as clear referencing should be included allowing for clear identification of the publications. Consider the generation of a reference list if a substantial number of publications is used.
* Please introduce aspects of development in the pharmaceutical development programme factually in view of the proposed indication and posology (indicate if there is a paediatric indication or development)and pharmaceutical form. State if the range of studies is in agreement with relevant EU/ICH guidelines.

**NOTE:**

**The guidance in this template is intended to guide the drafting of this assessment report. It should not be understood as guidance for dossier requirements.**

Prior to the submission of the completed template via Eudralink, the Applicant is asked to **remove any Protected Personal Data in the metadata of the document, such as name of author etc**. The applicant is also asked to remove the blue guidance text only (not the green). See the instructions below.

The principle of the template is to make clear distinctions between the presentation of data in the dossier and the judgement (“Rapporteur’s comments”).

Guidance text for **(Co)Rapporteurs** is provided in green. If the Applicant has not agreed to pre-fill the factual sections, this will be done by the Rapporteur, and they can use the blue text as a reference.

This quality assessment report should present and summarise data from the applicant’s dossier, followed by the assessor’s own critical assessment of these data, particularly with respect to control strategy, safety/efficacy consequences and highlighting adherence to specific guidance documents.

In the cases where the Applicant has agreed to complete the factual sections of this report, the Rapporteur may disagree with (some of) its contents. The Rapporteurs can choose to:

* Either amend the sections completed by the Applicant if they consider that the factual data has not been reported accurately.
* Or leave the applicant’s section as-is and comment on disagreements in the commenting boxes.

Assessor’s comments should be differentiated from the applicant’s data; grey shaded boxes (as shown below) are included in the report to achieve this. Specific assessment conclusions should in any case be included in the boxed sections of the report, not in the factual sections.

|  |
| --- |
| (Co)-Rapporteur’s comment(s) on <CTD section>:  In the comment box clearly indicate Questions to be raised as M**ajor Objection** (MO) or **Other Concern**(OC)  <No comments><Text>  Resulting questions:  <None><Text> |

If deemed necessary, the assessor may split its comments depending the subsections (e.g., characterisation/impurities, stability) or to produce a global comment (for 3.2.S.4, 3.2.P.2.1, 3.2.P.2.2).

For multiple active substance sources/manufacturers or where multiple active substances are included in the application, consider to duplicate the sections and assessment comments as required. For example, for multiple active substances, an assessment of 3.2.S for each active substance should be presented.

For active substances which may have multiple components or be complexes, it should be clearly defined in the assessment which component or combination of components is considered the subject of module 3.2.S.

If multiple pharmaceutical forms or components are included in the application, consider to duplicate the sections and assessment comments as required in 3.2.P section of the report.

In general, the following aspects should be considered:

* The data submitted should be assessed based on the legal basis of the application, other legal/regulatory data requirements, applicable guidelines and other scientific criteria.
* The report should be sufficiently detailed to allow for secondary assessment by other CHMP/CAT experts.
* The report should assess salient findings and especially those deficiencies that justify the questions for the applicant. These questions will be listed only in the “CHMP AR/overview”.
* The report should also emphasise findings that need to be reflected in the SmPC.
* For each type of study/data, the report should distinguish between main (pivotal) and supportive data.
* The report should indicate if acceptable justifications have been provided for waiving the need to conduct certain studies, replacing original studies with literature data or when data submitted deviate from the legislation and guidelines requirements. If certain studies are only available as publications, it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in-depth assessment of crucial data.
* If data from publications is used in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generating a reference list if a substantial number of publications is used. If appropriate, ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).

Comments on Quality aspects related to the SmPC, Labelling and Package Leaflet should be introduced directly in the PI document.

The list of Quality questions is to be included only in the CHMP AR/overview document. For reference please consider the following for the classification of the questions raised:

* “Major objections” preclude a recommendation for marketing authorisation. In principle, the major objection should start with a statement concerning the pivotal shortcoming, may entail more than one question and the use of 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.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

* “Other concerns” may affect the proposed conditions for marketing authorisation and product information. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

**NOTE:**

**The guidance in this template is intended to guide the drafting of this assessment report. It should not be understood as guidance for dossier requirements nor as guidance for assessment.**

**How to remove the guidance text:**

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Guidance text – Applicant” or “Guidance text – Rapps” and “Guidance text – black” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

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Administrative information

To be completed by the applicant (if they agreed to pre-fill the template), or by the Rapporteur (in case applicant has not agreed to pre-fill)

|  |  |
| --- | --- |
| Product data |  |
| Product name |  |
| INN or Common Name |  |
| EMA Product Number |  |
| ATC code |  |
| Orphan designation | <Yes/No> (if yes, include ODD number) |
| PRIME scheme | <Yes/No> |

To be completed by the assessment team:

|  |
| --- |
| **Declarations**  The assessment team should tick one or other of the 2 boxes below:  The (co)Rapporteur and/or the assessor confirm(s) that this assessment **does not** include non‑public proprietary information (with the exception of data provided by the applicant), including commercially confidential information provided by a third party (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments, development plans etc), irrespective from which entity was received.  The (co)Rapporteur and/or the assessor confirm(s) that this report **does** include non-public information (as described above), but all relevant paragraphs containing confidential information have been **highlighted in blue**, so that they can be removed before sharing the document with the applicant or other parties |

List of abbreviations

To be completed by the applicant (if they agreed to pre-fill the template).

Rapporteurs to add to applicant’s list if needed, or to complete fully if the applicant has not agreed to pre-fill the template.

|  |  |
| --- | --- |
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Quality critical assessment

GENERAL GUIDANCE

Reference to information, which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product or the restricted part of the ASMF) should be clearly marked as “Confidential” and highlighted using a blue background. These sections will be removed before the assessment is sent to the applicant.

Request for inspection action prior to authorisation

GMP inspections

Pre-approval inspection for human medicinal products may be requested in accordance with Article 8(2) of Regulation (EC) No 726/2004 and Article 111(1) of Directive 2001/83/EC.

<Text>

Introduction

* 1. Type of application

Indicate the type of marketing authorisation application (reference to the legal basis of the application); complete/abridged; whether for conditional approval or under exceptional circumstances. Also indicate whether accelerated assessment was applied for and granted or not granted.

|  |  |
| --- | --- |
| Eligibility to the Centralised Procedure | Only choose 1 and delete the rest  <Article 3(1) and point <1> <3> <4> of Annex of Regulation (EC) No 726/2004.>  <Article 3 (2) <(a)> <(b)> of Regulation (EC) No 726/2004.>  <Article 28 of Regulation (EC) No 1901/2006.>  <Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006.>  <Article 58 of (EC) No Regulation 726/2004 for a scientific opinion in the context of cooperation with the World Health Organisation.> |
| Legal basis | Only choose 1 and delete the rest  <Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.>  <Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well‑established medicinal use supported by bibliographic literature.>  <Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for fixed combination products.>  <Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product. >  <Article 58 of Regulation (EC) No 726/2004, - complete and independent application, by analogy to Article 8(3) of Directive 2001/83/EC.> |
| New Active Substance status claim | The applicant indicates that <INN/common name> is considered to be a <new><known> active substance. |
| Conditional marketing authorisation or authorisation under exceptional circumstances | <Not applicable> <The applicant is applying for a <conditional marketing authorisation><marketing authorisation under exceptional circumstances>.> |
| Accelerated assessment | <Not applicable> <The applicant submitted a request for accelerated assessment for <product name> on <date>. The application was <approved> <rejected> by CHMP at its meeting on <date>.> |

* 1. General background of the product
* Provide a brief description of the product type. The table below may be used. Mention indications, target population, pharmaceutical form, posology (with regard to the ability of the product to deliver this posology, e.g. volume, concentration), method of administration (including the use of a device, if relevant).

|  |  |
| --- | --- |
| Name of the active substance: |  |
| Proposed name of the medicinal product: |  |
| Dosage form and strength: |  |
| Route(s) of administration: |  |
| Therapeutic class : |  |
| Indication: |  |
| Proposed dosage range: |  |

* Highlight if a paediatric formulation was developed. Indicate whether a Paediatric Investigation Plan requiring the development of a paediatric formulation has been agreed with the PDCO Module 1.10.
* State if the active substance is claimed to qualify as a NAS in itself.
* Indicate the Orphan Medicinal Product (OMP) status, if relevant.

Active substance (3.2.S)

**Note:** For multiple active substance sources or where multiple active substances are included in the application, the applicant should duplicate the sections as required. For example, in case of multiple active substances, a separate 3.2.S (with all respective subheadings) for each active substance should be presented.

**Note:** For multiple active substance sources or where multiple active substances are included in the application, the assessor should duplicate the sections and assessment comments as required. For example in case of multiple active substances an assessment of 3.2.S for each active substance should be presented.

General information (3.2.S.1)

*Nomenclature (S.1.1)*

A brief description of the active substance should be provided.

<Text>

Structural formula (S.1.2)

* Present the relevant structural formula (schematic representation of the molecule) and molecular formula and weight.
* Present information on the most important structural features (e.g., glycosylation and other post-translational modifications, cell surface markers, vector components).
* The amino acid sequence or nucleic acid sequence do not need to be copied into the AR.

<Text>

*General properties (S.1.3)*

* Present the main properties such as function, biological activity, vector pathogenicity/virulence, mode of action.
* Aspects regarding e.g. pH, osmolality, protein concentration, primary-, secondary-, tertiary structure, and how they impact the finished product are discussed later in the development section P.2. Cross reference can be done to S.3.1.

<Text>

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| --- |
| (Co)-Rapporteur’s comment(s) on S.1:  Comment on whether the presented general information on the active substance is sufficient.  Make reference to the NAS report when NAS is claimed.  Make reference to the report of orphan similarity, if applicable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Manufacture (3.2.S.2)

*Manufacturer(s) (S.2.1)*

* List the name, address and responsibility of each manufacturer involved in manufacturing and testing, including sites of cell banks manufacture, storage and testing, matching the information in the AF.
* Indicate which evidence of GMP has been provided in M1 e.g. EU GMP certificates, and/or QP declaration as relevant.

|  |  |  |
| --- | --- | --- |
| Manufacturer, address | Responsibility /function | GMP compliance documentation (GMP certificate number, reference to QP declaration, MRA, EudraGMDP etc) |
|  |  |  |
|  |  |  |

<Text>

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| (Co)-Rapporteur’s comment(s) on S.2.1:  Comment on whether the presented information on manufacturers and sites is sufficient.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Description of Manufacturing Process and Process Controls (S.2.2)*

* Provide a summary of the manufacturing process with its process parameters and in-process controls. Where the manufacturing process is relatively standard, copying the manufacturing flow diagram and relevant tables of controls may be sufficient. For unusual or more complicated manufacturing processes, consider including a more detailed description.
* It is not necessary to copy and paste the ranges for every process parameter into the report, however the ranges for the CPPs and IPCs should be clearly described.
* Pooling strategies should be outlined.
* Indicate the proposed commercial batch size.
* If reprocessing is proposed to be registered as part of the manufacturing process, then this should be discussed, including at which steps.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comment(s) on S.2.2:  Comment on whether the manufacturing process is described in sufficient detail, the acceptability of the batch size and if applicable, the acceptability of reprocessing.  If there are questions on some aspects of the manufacturing process, then these aspects of the process should be described in more detail.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Control of Materials (S.2.3)*

* It is not necessary to copy tables of all raw materials into the report, however critical reagents such as chromatography columns and materials of human or animal origin should be included.
* For standard recombinant products, detailed explanations of the development genetics, construct generation and cloning does not need to be copied into the report, a brief summary is sufficient. For certain products such as advanced therapy products (ATMPs) or mRNA-based products, more comprehensive information on the development and testing of starting materials (e.g. autologous/allogeneic cells, vectors) should be included. Tables of master and working cell bank characterisation and/or testing and test panel/protocol for future cell banks should be included or summarised, respectively.

<Text>

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| (Co)-Rapporteur’s comment(s) on S.2.3:  Discuss whether the proposed starting material(s) is/are acceptable or not, including the scientific reasoning for this according to ICH Q11 and its Q&As. Comment on any experiments performed in order to gain additional process knowledge and understanding of input/raw materials, where relevant. Reference could be made to sections S.2.5 or S.2.6.  Comment on the adequacy of proposed specifications for raw material. In particular, mention control aspects which might influence the quality of the active substance, especially if the impurities are not controlled in the active substance specification.  For non-compendial raw materials, confirm whether appropriate in-house specifications are in place.  Comment on the acceptability of any material of biological (animal/human and herbal) origin.  Comment on the proposed re-use of materials if applicable.  Discuss whether proposed protocols for introduction of future cell banks are acceptable.  Make reference to A.2 regarding adventitious agents/viral safety linked to starting materials and raw materials of biological origin; highlight any issues related to TSE risk.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Controls of Critical Steps and Intermediates (S.2.4)*

* A brief summary of the control strategy should be included, preferably including tabulated list of PPs and IPCs. If an enhanced manufacturing approach (e.g. design space, real time release testing, continuous manufacturing) is proposed, it should be clearly described here, cross refer to S.2.6 as needed.
* Provide an overview of the specifications of the intermediates. If non-compendial analytical procedures are used, validation should be discussed.
* If the process parameters and IPCs have already been sufficiently described in S.2.2, they do not need to be duplicated in S.2.4.

<Text>

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| (Co)-Rapporteur’s comment(s) on S.2.4:  Discuss whether the acceptance criteria/ranges for the registered controls (process parameters, in-process controls etc.) are supported by data (e.g. from process validation data, process characterisation studies, prior knowledge etc.). Note, these aspects may also be discussed in S.2.2 or S.2.6, in which case, it does not need to be re-discussed here.  Discuss whether the proposed control strategy is acceptable and supported by appropriate data.  When a proposal for an enhanced manufacturing approach is requested (e.g. design space, real time release testing, continuous manufacturing) indicate whether the proposal can be agreed.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Process Validation and/or Evaluation (S.2.5)*

* The process validation activities should be described so that the reader gains an understanding of the state of validation of the process. In the case of formal PPQ activities, the level of information in the dossier can be extensive. In such cases, the amount of data that needs to be copied and pasted from the dossier is on a case-by-case basis and depends on the complexity of the manufacturing process, the current state of validation etc. However, for extensive datasets, providing a representative example should be considered, rather than including the entire dataset.
* Additional process validation activities should be briefly mentioned as appropriate, including where relevant:
  + Impurity clearance
  + Hold time (or shelf life for intermediates, if applicable) studies
  + Resin/filter lifetimes, sanitation and storage
  + Stability of media and solutions
  + Reprocessing
  + Shipping/transport validation
  + extractable /leachables

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comment(s) on S.2.5:  Discuss whether the commercial process and its control (IPCs and operational process parameters) is supported by the presented information.  Comment on whether the process is sufficiently validated or not.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Manufacturing Process Development (S.2.6)*

* Please provide a table summary of the “genealogy” (origin and use) of the batches used throughout development.

**Comparability**

* The level of comparability data to be included is on a case-by-case basis. When considering what data to include, focus on any data where there are differences between the processes. Where there are multiple comparability exercises, focus on the most critical ones(s), in particular the comparability of the batches used in the pivotal clinical study versus the commercial batches. For comparability studies which are less critical, a very brief summary is sufficient. Present comparability exercises and their outcomes in a tabular format.

<Text>

**Process development and characterisation**

* The process development and process characterisation studies should be described.
* Small scale studies/design of experiments, design space, etc. should be described and it should be confirmed whether they are representative of the commercial scale process. It is not necessary to copy and paste extensive data such as FMEAs or DoEs for every manufacturing step. Illustrative examples can be considered, for example a brief description of the small scale process characterisation data for one of the manufacturing steps could be included, which could serve as an example for the rest of the process characterisation studies.
* If a Design Space is being proposed present how the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the active substance has been established in a multivariate manner.

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| (Co)-Rapporteur’s comment(s) on S.2.6:  Discuss whether comparability has been adequately demonstrated, focussing in particular on the comparability between the pivotal clinical process and the commercial process, where relevant.  Discuss whether the development data supports the manufacturing process description, and the control of the materials and intermediates.  Discuss whether any risk assessment methodology has been used and whether it is appropriate. If applicable, the Design Space should be described and it should be stated if it is accepted or not.  Consider whether appropriate inputs (e.g. process parameters) and outputs (e.g. CQAs) have been considered for each manufacturing step modelled in process characterisation studies. Review any process characterisation studies in the context of the overall control strategy i.e. it should be confirmed that the studies provided in S.2.6 support the ranges for process parameters/IPCs etc. registered in S.2.2 and/or S.2.4.  Discuss whether the development data supports the manufacturing process description, and the control of the materials and intermediates. The Design Space should be discussed and it should be stated if it is accepted or not.  Nonetheless, where issues are identified, these should be discussed in more detail.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Characterisation (3.2.S.3)

*Elucidation of Structure and other Characteristics (S.3.1)*

* Present an overview of how the active substance was characterised. The batches used for the characterisation purposes should be indicated. A comprehensive summary of characterisation data should be included. In all cases, only the most important figures and tables should be copied instead of giving long passages of description. For biosimilars, reference can be given to section 3.2.R, where applicable. Characterisation data do not need to be duplicated in both sections.
* Depending on the type of product in question, the characterisation section could be separated into the following sub-sections. The characterisation studies and their outcomes can be summarised in tabular format see example table below.
  + Physicochemical properties.
  + Primary, secondary and tertiary structure
  + Potency (a clear rationale should be provided for how the potency assay reflects the claimed mechanism of action)
  + Quantity
  + Purity and pattern of heterogeneity, including product – related substances and evaluation of their biological activity where relevant.

Summary of Studies on Elucidation of Structure and other Characteristics

|  |  |  |
| --- | --- | --- |
| Attribute studied | Test method | Test result summary |
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*Impurities (S.3.2)*

* List the relevant impurities, including process-related and product related impurities. Process-related impurities encompass those that are derived from the manufacturing process, e.g. cell substrates (host cell proteins, host cell DNA), cell culture (e.g. inducers, antibiotics, antifoam or media components), or downstream processing impurities. Product-related impurities (e.g., precursors, certain degradation products, aggregates) are molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.
* Adventitious agents should be discussed in Appendix A.2.
* Differentiate between process and product related impurities.
* The characterisation of impurities can be summarised in tabular format, see example table below.
* Provide a summary of the impurity characterisation studies and a summary of the impurity risk assessment.

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| --- | --- | --- |
| Impurity | Test method  (where applicable) | outcome summary |
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| (Co)-Rapporteur’s comment(s) on S.3:  Discuss whether the active substance has been appropriately characterised and whether the company demonstrates a clear understanding of the quality characteristics of their active substance. Indicate whether the batches used for the characterisation purposes are clinically representative. Consider whether the active substance has been sufficiently characterised to conclude on whether the chosen release and stability tests are the most appropriate ones, given the available panel of characterisation tests.  Indicate whether all product- and process -related impurities have been sufficiently addressed. Data on impurity clearance may also be presented in S.2.5 and S.2.6. If this is the case, provide a discussion of the control of impurities in S.3.2.  In particular, for those impurities which are not controlled at batch release, the assessor should indicate whether the overall data package is sufficient to conclude that the clinical risk is acceptable.  The adequacy of the impurity risk assessment should be discussed and particular attention given to the control of such impurities.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Control of active substance (3.2.S.4)

*Specification (S.4.1)*

* Include a table of specifications including reference to Ph. Eur. chapters.

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| (Co)-Rapporteur’s comment(s) on S.4.1:  Consider whether the appropriate parameters and limits have been chosen from the larger panel of characterisation tests to ensure the quality of each batch of active substance; alternatively, this can be discussed in S.4.5.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Analytical Procedures (S.4.2)*

* Where the nature of the method is sufficiently described in the specification table S.4.1, then narrative detail may not be required in the AR. Mention if general Ph. Eur. methods are used for analysis (e.g. pH, solubility, degree of coloration of liquids). If relevant for context e.g. complex or novel methods, the analytical method may be described in more detail. A suitable level of details should be included in the report to facilitate an understanding of the principles and performance of the method.
* For in-house standard methods, a brief description (in tabular format when available in the dossier) is sufficient.
* Analytical procedures used in development which are different from the ones proposed for routine control should be summarised here. Information is also expected why the method was changed and when.
* Describe whether enhanced analytical approaches as per ICH Q14 are requested.

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| (Co)-Rapporteur’s comment(s) on S.4.2:  Discuss whether the analytical methods have been sufficiently described and are appropriate for control of the quality of the AS.  Discuss and conclude on any claims for enhanced analytical approaches.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Validation of Analytical Procedures (S.4.3)*

* Summarise the validation/qualification data for methods e.g. results for accuracy, precision etc.
* Where relevant, the validation results should be summarised in text. In some cases it may be useful to summarise validation results in a table. The example table below can be used if suitable for the analytical procedures used.

<Text>

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Method 1 | Method 2 | Method 3 | Method 4 | Method x |
| Accuracy |  |  |  |  |  |
| Precision: Repeatability |  |  |  |  |  |
| Precision: Intermediate precision |  |  |  |  |  |
| Specificity |  |  |  |  |  |
| Detection limit |  |  |  |  |  |
| Quantitation limit |  |  |  |  |  |
| Linearity |  |  |  |  |  |
| Range |  |  |  |  |  |
| System suitability |  |  |  |  |  |
| other |  |  |  |  |  |

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| (Co)-Rapporteur’s comment(s) on S.4.3:  Discuss whether the methods are adequately validated in accordance with the relevant guidelines to control the substance on a routine basis and whether the stability indicative nature of the methods has been proven.  If enhanced analytical approaches as per ICH Q14, has been proposed comment on whether it is sufficiently supported and acceptable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Batch Analyses (S.4.4)*

* Provide an overview of the batch number, process reference, scale and use (e.g. clinical studies, process validation) for which data are available in the dossier. For clinical batches, specify which clinical trial each batch was used in.
* A table of representative batch data results can be included.

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| (Co)-Rapporteur’s comments comment(s) on S.4.4:  Discuss whether the results are generally consistent from batch to batch and whether the data indicates that the process is under control.  Where relevant, comment on whether the data indicates the proposed commercial process generates an active substance that is in line with earlier clinical batches. If the applicant has presented the data in S.2.6 this may be discussed there, with a cross reference as relevant.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Justification of Specification (S.4.5)*

* Describe the approach used to establish the specifications test procedures and acceptance criteria. Specifications test procedures and acceptance criteria (or absence thereof) should be established and justified in accordance with current guidance.
* Where statistical approaches have been used, describe the methodology.

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| (Co)-Rapporteur’s comment(s) on S.4.5:  Discuss whether the applicant’s proposed justification of the specifications is adequate or whether further justification or revision is required, bearing in mind the intended use of the active substance in the product.  Discuss whether the approach used to establish the specifications is appropriate.  Discuss whether the acceptance criteria are supported by data obtained for lots used in (non-)clinical and stability studies.  Discuss proposals for real time release testing (RTRT) when these are requested by the applicant.  Discuss as necessary the appropriateness of the overall control strategy with regard to the specifications.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Reference standards of materials (3.2.S.5)

* Provide a summary of all reference standards (RS) required by the analytical procedures and state the type of test the standard is used for (e.g. identification, assay or potency assay).
* State whether there are reference standard(s) available from EDQM or if there are other relevant international reference standards (e.g. WHO). If not, describe the in-house reference standard(s) adequately (Refer to Ph. Eur. 5.12 Reference standards).
* Where relevant summarise how in-house working reference material(s) used in the testing of production lots are calibrated against the primary reference material.
* Characterisation, storage conditions and formulation of reference material(s) should also be briefly summarised. Reference could be made to S.3.1., if applicable.
* Mention if a protocol for manufacturing and testing of RS is submitted.

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| (Co)-Rapporteur’s comment(s) on S.5:  Comment whether the quality of the reference standard acceptable for its use.  If a protocol for new reference standards is included in the dossier state whether the protocol (in particular the qualification acceptance criteria) is adequate.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Container closure system (3.2.S.6)

* Briefly summarise the container closure system and justify its selection. Where appropriate, reflect compliance with Ph. Eur. monograph and/or other standards.
* The method of sterilization should be indicated, as appropriate.
* Extractables/leachables studies should be summarised.

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| (Co)-Rapporteur’s comment(s) on S.6:  Comment on the suitability of container closure system and the justification provided, bearing in mind the physical/chemical properties of the active substance .  Reflect whether it provides adequate protection from microbial contamination and where applicable protection from light.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Stability (3.2.S.7)

*Stability summary and conclusion (S.7.1)*

* Provide an overview of the available stability data. The table below can be used (or copied from the dossier). The overview should clearly describe the number of batches tested and the sizes/scale of the batches.

Stability studies

| Study conditions  (Temp °C, RH %) | Study duration | n batches | Batch size /  Manufacturing process (reference) | Intended use of batch | Available data up to y months |
| --- | --- | --- | --- | --- | --- |
| Long-term ( oC/RH) | X months |  | *e.g. Pilot scale (process reference or process ID) /*  *Production scale (process reference or process ID)* | e.g. clinical study (number), process validation, … | Y months |
| Other studies/conditions *(e.g. accelerated, photostability, stress testing)* |  |  |  |  |  |
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* State if the studies were carried out in accordance with current ICH guidelines (including photostability).
* Describe the stability testing parameters applied and make reference to relevant specification limits and analytical procedures in S.4.1 and S.4.2. Justify any alternative analytical procedure used.
* Present the conclusions of the stability studies. Clearly state the proposed shelf life and storage condition.
* Confirm if the containers used in the stability studies are the same or representative of those proposed for routine storage.

<Text>

*Post-approval stability protocol and stability commitments (S.7.2)*

* Provide a high-level summary of the proposed post-approval stability protocol and stability commitments where these are relevant.

<Text>

*Stability data (S.7.3)*

* If not discussed in S.7.1, provide a discussion of the available stability data and discuss whether there are any trends or out-of-specification results.
* There is no benefit in copying tables of stability data into the assessment report.

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| (Co)-Rapporteur’s comment(s) on S.7:  Discuss whether or not the proposed shelf life is justified.  Confirm if bracketing or matrixing approaches are acceptable.  If multiple routes of production are applicable (e.g. for blood derived active substances)and the applicant wishes to bridge stability results, in these instances, include a clear assessment with the rationale on the acceptability of the proposed approach.  Discuss whether the proposed post-approval stability protocol (S.7.2) is appropriate for annual GMP stability testing.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Finished product (3.2.P)

Description and composition of the finished product (3.2.P.1)

* Describe all components of the presentation as intended for marketing, including the dosage form (physical description, available strengths), the container closure system, reconstitution solvent, information about overages/overfill, medical devices, etc. if applicable.
* Where available the applicant should cite the Ph. Eur. nomenclature for excipients in the dossier and this should be consistent with the terminology in the product information.
* Fill in the Table below to indicate the composition or copy a relevant table from the dossier.

Complete composition of XXX

| Ingredient | Reference | XXX  Amount (XXX) | Function |
| --- | --- | --- | --- |
|  |  |  | Active |
|  |  |  |  |
|  |  |  |  |
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| (Co)-Rapporteur’s comment(s) on P.1:  Comment on whether the description and composition information is satisfactory.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Pharmaceutical development (3.2.P.2)

* The objective of the pharmaceutical development should be described and the approach followed to establish the proposed commercial process and its controls should be clarified (minimal, quality by design with or without design space proposal).

<Text>

*Components of the finished product (3.2.P.2.1)*

Active substance (P.2.1.1)

* Identify those physicochemical and biological properties of the active substance that are critical for the formulation and its performance.

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| (Co)-Rapporteur’s comment(s) on P.2.1.1:  Indicate whether the physicochemical and biological properties of the active substance have been adequately discussed, specified and controlled.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Excipients (P.2.1.2)

* The choice, function and quantity of excipients should be justified.

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| (Co)-Rapporteur’s comment(s) on P.2.1.2:  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.  Impact of specific excipients or excipient preparations on the performance of the product should be discussed in more detail in formulation development.  Discuss whether there are excipients of animal/human origin (cross refer to 3.2.A.2 ) or any novel excipients (cross refer to P.4 and 3.2.A.3), as appropriate.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Finished product (3.2.P.2.2)*

Formulation development (P.2.2.1)

* The Quality Target Product Profile (QTPP) of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy, should be presented or copied when available in the MA dossier.
* It is not necessary to describe formulation development studies in detail. The key findings should be summarised, including a discussion on formulation changes during development (if applicable); for information (e.g. comparability) in support of formulation changes, reference can also be made to section 3.2.P.2.3.

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| (Co)-Rapporteur’s comment(s) on P.2.2.1:  The main focus of the assessment should be on whether the proposed formulation, within the proposed specification limits, is appropriate to ensure the quality and stability of the finished product, considering the intended clinical use of the product and the presented QTPP.  Discuss whether the finished product is generally stable (a cross-reference to P.8 can be included). When the stability profile shows no issues and there are no concerns regarding the clinical appropriateness of the formulation, then only limited assessor discussion is needed. In cases where there are noted issues with stability, the formulation development studies may need to be discussed in more detail to provide the reader with an understanding of whether the stability issues are due to sub-optimal formulation development.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Overages (P.2.2.2)

* State if formulation overages are included and provide the justification.

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| (Co)-Rapporteur’s comment(s) on P.2.2.2:  Indicate if the justification for any overage is acceptable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Physicochemical and biological properties (P.2.2.3)

* The physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product should be identified and discussed.

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| (Co)-Rapporteur’s comment(s) on P.2.2.3:  Comment whether the physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product are sufficiently identified and discussed.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Manufacturing process development (P.2.3)*

**Control strategy:**

* Describe the development of the control strategy. List the CQAs. Any risk assessment methodology used should be briefly described. It is not necessary to provide excessive detail on the process development studies.
* If a Design Space is being proposed, present how the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the drug product has been established in a multivariate manner. It is not necessary to copy and paste extensive data such as FMEAs or DoEs for every manufacturing step. Illustrative examples should be considered.

<Text>

**Manufacturing process development:**

* Summarise the manufacturing process development and justify the proposed process. If changes were made to the manufacturing process or formulation during development, describe these changes and discuss the associated comparability studies. More detailed information is required where the process has changed between the pivotal clinical studies and commercial process. Changes during early development may require less details. A tabular format summarising the comparability studies can be copied when provided in the dossier.

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| (Co)-Rapporteur’s comment(s) on P.2.3:  **Control strategy:**  Comment on whether the chosen CQAs are appropriate for the control of the product type. The rationale for the selection of process parameters and in-process controls should be briefly discussed. The data to support the criticality of the process parameters or in-process controls should be described and it should be discussed whether there is data available to support the ranges of the controls process parameters and in-process controls registered in P.3.3 and P.3.4.  Comment on whether the risk assessment methodology used is appropriate.  Discuss whether the development data supports the manufacturing process description, and the control of the materials and intermediates.  If Design Space(s) is/are proposed, comment on whether the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the drug product has been established in a multivariate manner. It should be stated if the Design Space(s) is/are accepted or not.  Comment the results of modelling studies applied to manufacturing process development, if relevant.  Conclude on whether the development of the control strategy is appropriate.  **Manufacturing process development:**  Indicate whether the choice of process has been justified, where necessary. Comment on the relevance of identified critical process parameters to subsequent process validation. Discuss whether process parameter ranges are satisfactorily investigated/supported by pharmaceutical development.  Indicate whether any differences in the manufacturing processes of the commercial product and clinical trial material are adequately explained and discussed.  If the manufacturing process of the product influences the physicochemical properties of the active substance (e.g. polymorphic form), indicate whether the studies carried out on the active substance remain valid.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Container closure system (P.2.4)*

* Outline the selection and choice of the container closure system. The suitability of container closure system should be discussed. Relevant details of container closure may be provided in P.2.4, P.7, and 3.2.R. Therefore (cross reference to other sections can be made, as appropriate).
* Particular consideration should be given to the requirements for medical devices (integral, co-packaged or referenced).
* Important functionality of the container closure system should be described, for example where the closure can impact product delivery and performance.
* Outline any extractable or leachable studies conducted to support the selected container closure.

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| (Co)-Rapporteur’s comment(s) on P.2.4:  Conclude on whether the choice of materials and physical aspects of the container closure are appropriate for the finished product form.  Important functionality of the container closure system should be discussed.  Comment on the results of the presented extractable or leachable studies. Discuss whether there is any risk associated with extractables and leachables and if applicable any additional studies conducted on microbial ingress if not covered under P.2.5.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Microbiological attributes (P.2.5)*

* The use of additives, e.g. preservatives and antioxidants should be justified regarding their concentration and nature. Preservative efficacy test should have been conducted where required.
* Any relevant studies conducted on microbial ingress e.g. for sterile products should be presented.

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| (Co)-Rapporteur’s comment(s) on P.2.5:  Comment on the adequacy of the justification for additives and the results of preservative efficacy test, and if applicable any additional studies conducted on microbial ingress presented here.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Compatibility (P.2.6)*

* Briefly present the results of the compatibility studies with solvents/diluents, mentioned in the SmPC, and relevant administration devices. Cross reference to P.8 for in-use stability is possible.

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| (Co)-Rapporteur’s comment(s) on P.2.6:  Conclude on whether the compatibility data support the proposed administration of the product as described in the SmPC.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Manufacture (3.2.P.3)

*Manufacturer(s) (P.3.1)*

* Provide the name, address, and responsibility of each proposed manufacturing site or facility, including batch release testing sites and primary packaging, (matching the information in the AF), in a tabular format.
* Indicate which evidence of GMP has been provided in M1 e.g., EU GMP certification, as relevant.

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| Manufacturer, address | Responsibility / function | GMP compliance documentation (GMP certificate number, reference to QP declaration, MRA, EudraGMDP etc) |
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| (Co)-Rapporteur’s comment(s) on P.3.1:  Where queries are raised on GMP compliance of specific sites, provide an overview the activities conducted at those sites.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Batch formula (P.3.2)*

* Present the batch formula for the product.

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| (Co)-Rapporteur’s comment(s) on P.3.2:  Where ranges of batch size are proposed for production, blending of batches or the use of sub-batches, the acceptability should be addressed.  Indicate, when relevant, if the ranges proposed are supported by process validation data.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Description of manufacturing process and process controls (P.3.3)*

* Include a flow diagram describing the process and process controls. If the flow diagram is very extensive consider including only a part of it as an illustration and cross refer to the dossier.
* For common manufacturing processes, a summary is sufficient, provided that the manufacturing flow diagram is sufficiently clear. For unusual or more complicated manufacturing processes, a more detailed description is expected.
* The ranges for every process parameter and IPC should be clearly described in the dossier but it is not necessary to copy and paste them all into the report; focus on the CPPs and IPCs.

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| (Co)-Rapporteur’s comment(s) on P.3.3:  Comment on whether the manufacturing process and critical equipment is described in sufficient detail. Where relevant, outline if the applicant has defined required environmental conditions (e.g. moisture, temperature, oxygen, etc) and processing times.  The assessor should comment on CPPs and IPCs if not discussed in the P.3.4.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Controls of critical steps and intermediates (P.3.4)*

* Provide an overview of the IPCs and, if not presented in P.3.3, of the critical process parameters. A tabulated overview is the preferred format.
* If an enhanced manufacturing approach is requested (e.g. design space, real time release testing, continuous manufacturing) is proposed it should be clearly described here.
* For intermediates, provide an overview of the specifications including the justification of the acceptance criteria.
* Claimed bulk storage and holding times should be indicated, with cross reference to other sections of the dossier.

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| (Co)-Rapporteur’s comment(s) on P.3.4:  Discuss whether the acceptance criteria/ranges for the controls (process parameters, in-process controls etc.) are supported by data (note this may also be discussed in P.3.3, in which case, it does not need to be re-discussed in P.3.4).  If intermediate or bulk holding times are claimed, discuss whether the data provided support these.  When a proposal for an enhanced manufacturing approach is requested (e.g. design space, real time release testing, continuous manufacturing) indicate whether the proposal can be agreed.  Discuss whether the proposed control strategy is acceptable and supported by appropriate data.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Process validation and/or evaluation (P.3.5)*

* The process validation activities should be described and the outcomes summarised so that the reader gains an understanding of the state of validation of the process. The amount of data should be commensurate with the complexity of the manufacturing process.
* Specific process validation activities should be summarised as appropriate, including where relevant (e.g. media fills, formulation robustness/homogeneity, hold times studies, sterile filter validations, transport validation, continuous process verification approaches).

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| (Co)-Rapporteur’s comment(s) on P.3.5:  Conclude whether the presented validation data is sufficient and outline whether further process validation data are needed.  Comment on whether formulation robustness/homogeneity has been addressed and whether the results support the proposed specifications (e.g. release specification for polysorbate content).  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Control of excipients (3.2.P.4)

*Specifications (P.4.1)*

* Include the specifications for non compendial excipients. For Ph. Eur. excipients, reference to the Ph. Eur. is generally sufficient.
* Where Functionality-related characteristics (FRCs) are identified they should be discussed in 3.2.P.2.1. In such cases FRCs should be included in the specifications.

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| (Co)-Rapporteur’s comment(s) on P.4.1:  Confirm whether the proposed specifications are acceptable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Analytical procedures (P.4.2)*

* For Ph. Eur. methods, in most cases it is sufficient to state that they are carried out according to the monograph.
* For in-house methods, a suitable level of detail should be included in the report to facilitate an understanding of the principles and performance of the method.

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| (Co)-Rapporteur’s comment(s) on P.4.2:  Conclude whether the analytical procedures are sufficiently described.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Validation of analytical procedures (P.4.3)*

* For Ph. Eur. excipients, no details of method validation are needed when the method is described in the monograph.
* For non-compendial excipients, provide a summary of the validation activities for the analytical procedures, preferably in a tabular format.

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| (Co)-Rapporteur’s comment(s) on P.4.3:  Conclude whether the analytical procedures are sufficiently validated.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Justifications of specifications (P.4.4)*

* For Ph. Eur. excipients, no detailed justification of specifications is required where the parameters are covered by the monograph.
* For non-compendial excipients and those excipients with functionality related characteristics, provide a brief overview of the justification of specifications.

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| (Co)-Rapporteur’s comment(s) on P.4.4:  Comment on the adequacy of the justification provided for the control of the excipients.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Excipients of human and animal origin (P.4.5)*

* For excipients of human or animal origin, provide relevant information. Cross-reference to 3.2.R or 3.2.A.2 can be included as appropriate.

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| (Co)-Rapporteur’s comment(s) on P.4.5:  For excipients of human or animal origin, discuss whether there is sufficient information, for example on the risk adventitious agents, a cross-reference to 3.2.R or 3.2.A.2 can be included as appropriate.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Novel excipients (P.4.6)*

* For excipient(s) used for the first time in a finished product or by a new route of administration, reference should be made to section 3.2.A.3.

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| (Co)-Rapporteur’s comment(s) on P.4.6:  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Control of finished product (3.2.P.5)

*Specification(s) (P.5.1)*

* Include a table of specifications (release and shelf life). Clearly state in the specification if reduced testing or RTRT is proposed.

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| (Co)-Rapporteur’s comment(s) on P.5.1:  Discuss whether appropriate parameters and limits are in place to ensure the quality of each batch of finished product. Reference can be made to P.5.6.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Analytical procedures (P.5.2)*

* Where the nature of the method is sufficiently described in the specification table P.5.1, then narrative detail may not be required in the AR.
* For Ph. Eur. methods, in most cases it is sufficient to state that they are carried out according to the monograph.
* For in-house methods, a suitable level of detail should be included in the report to facilitate an understanding of the principles and performance of the method.
* Analytical procedures used in development which are different from the ones proposed for routine control should be summarised here. Information is also expected why the method was changed and when.
* Describe whether enhanced analytical approaches as per ICH Q14 are requested.

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| (Co)-Rapporteur’s comment(s) on P.5.2:  Comment on the adequacy of the analytical procedures to control the quality of the finished product.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Validation of analytical procedures (P.5.3)*

* State if the methods are validated in accordance with ICH Q2, and mention any deviation.
* The validation results should be summarised. It may be useful to summarise validation results in a table, example below.
* State/summarise whether the suitability/qualification of certain Ph. Eur. methods (e.g. microbial contamination, endotoxins) has been performed.
* If the analytical procedure control strategy includes elements based on enhanced development, appropriate information from analytical procedure risk assessment and development studies to support the proposed lifecycle management strategy should be summarised. Validation protocols should be referenced where relevant.

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| --- | --- | --- | --- | --- |
|  | Method 1 | Method 2 | Method 3 | Method 4 |
| Accuracy |  |  |  |  |
| Precision:  Repeatability |  |  |  |  |
| Precision:  Intermediate precision |  |  |  |  |
| Specificity |  |  |  |  |
| Detection limit |  |  |  |  |
| Quantitation limit |  |  |  |  |
| Linearity |  |  |  |  |
| Range |  |  |  |  |
| System suitability |  |  |  |  |
| Other parameters |  |  |  |  |

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| (Co)-Rapporteur’s comment(s) on P.5.3:  Discuss whether the methods are adequately validated in accordance with the relevant guidelines to control the finished product on a routine basis and whether the stability indicative nature of the methods has been proven. If enhanced analytical approaches as per ICH Q14, have been proposed comment on whether it is sufficiently supported and acceptable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Batch analyses (P.5.4)*

* Provide an overview of the batches for which data are available in the dossier. The scale, number of batches, use of the batches e.g. in the clinical programme should be described as relevant. For clinical batches, specify which clinical trial each batch was used in.
* An example table of representative batch data results can be included.

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| (Co)-Rapporteur’s comment(s) on P.5.4:  Discuss whether the batch results confirm consistency & uniformity of the finished product. Discuss whether the data indicates that the process is under control.  Where relevant, comment on whether the data indicates the proposed commercial process generates a finished product that is in line with earlier clinical batches. If the applicant has presented the data in 3.2.P.2 this may be discussed there, with a cross reference as relevant.  If more than one manufacturing site of the finished product is proposed, include a clear assessment as to whether the quality of the finished product from each of the sites can be considered comparable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Characterisation of impurities (P.5.5)*

* Impurities which have not already been addressed in the active substance section should be discussed here.
* Active substance related impurities (i.e. degradation products) which may arise during product manufacture and/or storage should be discussed here.
* Also include the cumulative presence of other organic and inorganic impurities (e.g. residual solvents, elemental impurities), mutagenic impurities and nitrosamine impurities from active substance, excipients, and finished product manufacturing process, in accordance with relevant Guidances.

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| (Co)-Rapporteur’s comment(s) on P.5.5:  Comment on the adequacy of the characterisation of impurities relevant to the finished product.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

*Justification of specification(s) (P.5.6)*

* Release and shelf life acceptance criteria/limits should be established, justified, and if needed qualified in accordance with relevant ICH guidelines, applicable Ph. Eur. monographs, and relevant EMA guidelines.
* The approach used to establish the specification test procedures and acceptance criteria or omit certain criteria from the specifications should be described. Where statistical approaches have been used, describe the methodology.

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| (Co)-Rapporteur’s comment(s) on P.5.6:  Discuss whether the applicant’s proposed justification of the specifications is adequate or not, bearing in mind the intended use of the finished product.  Discuss whether the approach used to establish the specifications is appropriate.  Discuss whether the acceptance criteria are supported by data obtained for lots used in (non-)clinical and stability studies.  Discuss proposals for real time release testing (RTRT) when these are requested by the applicant.  Discuss as necessary the appropriateness of the overall control strategy with regard to the specifications.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Reference standards or materials (3.2.P.6)

* Where relevant, cross-refer to 3.2.S.5.
* State whether there are reference standard(s) available from EDQM or if there are other relevant international reference standards (e.g. WHO). If not, describe the in-house reference standard(s) adequately (Refer to Ph. Eur. 5.12 Reference standards).
* At the time of submission, the manufacturer should have established an appropriately characterised in-house primary reference material, prepared from lot(s) representative of production and clinical materials. Summarise how in-house working reference material(s) used in the testing of production lots are calibrated against the primary reference material.
* Mention if a protocol for manufacturing and testing of future reference standards is submitted.

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| (Co)-Rapporteur’s comment(s) on P.6:  Comment on whether the quality of the reference standards is acceptable for their use.  If a protocol for new reference standards is included in the dossier, state whether the protocol including the qualification acceptance criteria is acceptable.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Container closure system (3.2.P.7)

* Describe the Container closure system and provide its specification. Reflect compliance with standards such as the Ph. Eur. Monograph or ISO standards.
* If pre-sterilised containers are used, the method of sterilisation of the final container and compliance with compendial requirements for sterilisation or applicable ISO standards should be mentioned.
* Where required by guidance, provide supplier details (i.e. name and address) of primary packaging components.

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| (Co)-Rapporteur’s comment(s) on P.7:  Confirm that the description and specification of the containers proposed for routine storage are acceptable. Confirm compliance with appropriate standards such as the Ph. Eur. Monograph. Where relevant the compliance with ISO standards should be confirmed.  Where relevant, discuss the acceptability of pre-sterilised container closure components.  Particular consideration should be given to the requirements for medical devices.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Stability (3.2.P.8)

*Stability summary and conclusion (P.8.1)*

* Present the conclusions of the stability studies. Clearly outline the shelf life period and storage condition.
* Provide an overview of the available stability data. The table below can be used (or copied from the dossier).
* The overview should clearly describe the number of batches tested and the sizes/scale of the batches. Any modelling studies (using statistical approaches) applied to stability data should be described and justified.
* If bracketing or matrixing approaches have been used, these should be described.

Stability studies

| Study conditions  (Temp °C, RH %) | Study duration | n batches | Batch size /  Manufacturing process (reference) | Intended use of batch | Available data up to y months |
| --- | --- | --- | --- | --- | --- |
| Long-term (°C / RH) | x months |  | e.g. Pilot scale (process reference or process ID) /  Production scale (process reference or process ID) | e.g. clinical study (number), process validation, … | y months |
| Other conditions (e.g. accelerated, photostability, in-use, stress testing) |  |  |  |  |  |
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* Describe the stability testing parameters applied and make reference to relevant specification limits and analytical procedures in P.5.1 and P.5.2. Justify any alternative analytical procedure used.
* Provide a discussion of the main findings, trends, out of specifications, etc results of the stability studies.
* Describe any in-use stability studies and conclusions thereof.
* Confirm if the containers used in the stability studies are the same as those proposed for routine storage.

<Text>

*Post-approval stability protocol and stability commitment (P.8.2)*

* Provide a high-level summary of the proposed post-approval stability protocol and stability commitments where these are relevant.

<Text>

*Stability data (P.8.3)*

* If not discussed in P.8.1., provide a summary of the available stability data and discuss whether there are any trends or out-of-specification results.
* There is no benefit in copying tables of stability data into the assessment report.

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| (Co)-Rapporteur’s comment(s) on P.8:  Discuss whether or not the proposed shelf life and storage conditions are justified or cross refer to P.8.1.  State if the studies are carried out in accordance with current ICH guidelines (including Photostability). If bracketing or matrixing approaches have been used, it should be confirmed if they are acceptable. If applicable, comment on the acceptability of the modelling studies applied to stability data.  Confirm, where applicable, whether the proposed in-use shelf life and other conditions listed in the SmPC are supported by data.  Discuss whether the proposed post-approval stability protocol and stability commitments are appropriate.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Appendices (3.2.A)

A.1. Facilities and equipment

Information from this section is not required to be included in the assessment report.

Information from this section is not required to be included nor to be commented in the assessment report.

A.2. Adventitious agents safety evaluation

* Information in this section may be present in other sections of the dossier, cross reference to Sections 3.2.S.2.3. Control of Materials, and 3.2.P.4.5. Excipients of Human or Animal Origin can be made as relevant to avoid repetition

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*A.2.1. Non-viral adventitious agents*

* Information on non-viral adventitious agents should include the risk of contamination with TSE, mycoplasma, bacteria and fungi. Cross-references to other parts of the assessment report could be included, as appropriate.
* Materials which fall within the scope of the TSE Note for Guidance should be identified. TSE compliance should be demonstrated either by providing a TSE certificate and/or via scientific documentation.

<Text>

*A.2.2. Adventitious viruses*

* A viral risk assessment should be provided.
* Identification of materials of biological origin:

A short description or listing of materials of biological origin which are introduced, or come into contact with, the product during production, should be provided. The characteristics of the materials with regard to the possibilities for virus contamination should be summarised. Cell substrates, cultivation media, reagents used or introduced directly or indirectly (e.g. affinity chromatography materials), as well as excipients should be considered.

* Testing at Appropriate Stages of Production

Controls on donors, donated tissues, and cell banks. (Products derived from human cell tissue) should be summarized.

The viral testing carried out on the relevant cell substrates (e.g. MCB, WCB, EOP) should be included in this section or a cross-reference to S.2.3 made, as appropriate.

For plasma derived products, include a reference to the European Plasma Master File, if necessary.

* Routine testing on unprocessed bulk (if applicable):

Summarize any routine testing of unprocessed bulk, as appropriate.

* Viral clearance studies

An overview of the viral clearance studies should be provided.

Use of prior knowledge should be justified (i.e. are data applicable to process/product).

Representativeness of the scale down viral clearance studies should be demonstrated.

A table of log reduction factors (LRFs) should be included.

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| (Co)-Rapporteur’s comment(s) on A.2:  It should be confirmed whether testing is in accordance with ICH Q5A and discussed whether the analytical methods used for viral testing are sufficiently qualified as appropriate.  Discuss whether testing of the unprocessed bulk is appropriate.  As regards the viral validation studies, it should be discussed whether the choice of model viruses is appropriate to capture the relevant risks of viral contamination. Discuss whether the choice of process steps for virus clearance are appropriate and whether the commercial manufacturing process is adequately represented in the laboratory-scale experiments.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

A.3. Novel excipients

* For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the active substance format.

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| (Co)-Rapporteur’s comment(s) on A.3:  Discuss whether the presented information on the manufacture, characterisation, and controls of the novel excipients(s) is satisfactory; this may alternatively be discussed under P.4.6.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Biosimilarity

* Summarize and compare the proposed formulation and packaging configuration of the biosimilar product and reference medicinal product (preferable in tabular format).
* Summarize information on the biosimilar (e.g. development phase/scale, age) and reference medicinal product batches (e.g. source (region), age), number of batches, batch numbers, quality target product profile (QTPP), formulation/dosage form.
* Summarize the comparability approach, e.g. QA criticality risk ranking, statistical approaches, pooling strategies, 2-way/3-way analytical similarity.
* Summarize comparability testing results, the analytical procedures used and the main conclusion for the evaluated QA’s. Include a table, presenting the quality attributes compared, analytical method used and key findings (see example below).

| *Molecular parameter* | *Attribute* | *Methods for control and characterization* | *Key findings* |
| --- | --- | --- | --- |
| Primary structure | e.g. Amino acid sequence | e.g. Reducing peptide mapping (MS) | e.g. Identical primary sequence |
| Higher order structure | e.g. Secondary and tertiary structure | e.g. CD spectroscopy | e.g. Comparable higher order structure |
| … etc |  |  |  |

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| (Co)-Rapporteur’s comment(s) on Biosimilarity:  Discuss the Applicant´s approach for demonstrating analytical similarity. Discussion should focus on:  - whether the comparability testing includes the relevant QAs as identified in the quality profile of the chosen reference medicinal product,  - whether the biosimilar drug product batches used in the comparability study are representative for commercial manufacture, as well as representativeness of the reference product batches (age),  - whether qualitative and quantitative comparability acceptance criteria are pre-defined and justified (based on sound statistics, as appropriate),  - whether sensitive and orthogonal methods were used to determine not only similarities but also potential differences in QA’s.  Conclude whether (or not) analytical similarity between the proposed biosimilar and reference medicinal product has been demonstrated.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Regional information

Post approval change management protocols (PACMPs)

* Details of any PACMPs should be included in this section.

<Text>

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| (Co)-Rapporteur’s comment(s):  Confirm if the protocol is acceptable and if it includes all the relevant study plans with a clear description of the planned changes and data requirements (acceptance criteria) to support the future variation. The reporting category for the future implementing variation should be stated.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Process validation scheme for the finished product

* If applicable, outline and summarise the process validation scheme for the proposed finished product(s). Include reference to the number and scale of batches to be validated. If additional testing or controls will be applied to the process validation batches, make reference to this.

<Text>

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| (Co)-Rapporteur’s comment(s):  Confirm the acceptability of the proposed process validation scheme, this may alternatively be discussed under P.3.5.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc Avoid “nice-to-have” questions.  <None><Text> |

Medical device aspects

* Where relevant, the applicant should confirm how compliance with the GSPRs of the Medical Devices Regulation (EU) 2017/745 has been demonstrated, for example CE mark or NB opinion for the intended use.

<Text>

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| (Co)-Rapporteur’s comment(s):  Discuss the acceptability of the medical device aspects, where covered elsewhere, this may alternatively be discussed in those sections e.g. P.2, P.7 etc.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

TSE aspects

* Include a summary of the available TSE certification to support the suitability of the medicinal product.

<Text>

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| (Co)-Rapporteur’s comment(s) on TSE aspects:  Discuss the acceptability of the presented information, where covered elsewhere, this may alternatively be discussed in those sections e.g. P.4.5.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the **CHMP AR/Overview**. Mark the question as **MO or OC** as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

Assessor’s overall conclusions on quality

This section is to be filled by the (Co)Rapporteurs only, not the Applicant.

This section should simply state the main conclusions; the text in the “**Overview and D120 LOQ template**” should be elaborated on separately. The following text can my used.

The presented information on development, manufacture and control of the active substance <is> <is not> satisfactory at this stage. Major Objections have <not> been identified<, pertaining to: ….. >.

The presented information on development, manufacture and control of the finished product <is> <is not> satisfactory at this stage. Major Objections have <not> been identified<, pertaining to: …..>.

In addition a number of Other Concerns have been identified related to <the active substance> <and> <the finished product>. <The issues raised as Other Concerns are expected to be addressed and resolved prior to approval.>

Highlight those issues impacting the Benefit-Risk balance. With respect to a paediatric formulation, indicate if there is a need to request an Opinion from the PDCO.

Annex 1 (as appropriate)

Not applicable for Biological products.

Annex 2 (For centrally – submitted product)

Proposals for post-authorisation Sampling and Testing

Selection of parameters for testing during post authorisation surveillance for centrally authorised products

EMA manages annual sampling and testing programmes for centrally authorised products in accordance with Art. 57r of Regulation (EC) 2004/726 in conjunction with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Official Medicines Control Laboratories of the EU/EEA Member States.

The (co)rapporteur’s recommendations for the parameters to be tested should be included on the attached form. Recommendations should be focused on the finished product and should be as precise as possible. Whenever several methods are applicable to a parameter, the method(s) used should be clearly specified. Assessors are recommended to discuss the selection of parameters to be tested with colleagues from the OMCL of the (Co)rapporteur’s country.

Parameters indicative of the overall quality of the product such as appearance, weight or volume, dissolution, pH, moisture content particle counts, osmolality and disintegration are readily performed by OMCLs.

Usually active substance-specific assays and impurity tests provide sufficient information on the identity of the active substance and the need for additional specific identity testing should be justified.

When bioassays are requested, it should be noted that these are often very challenging for OMCLs to repeat in a proficient manner but should normally be requested when it is the only means to verify the concentration of the active, or where there is other justification.

It should also be noted that occasionally the use of laboratory animals is required.

Owing to the limitations of the test itself and the non-availability of appropriate samples, requests for sterility testing is not recommended as part of routine post-authorisation surveillance.

The form allows to record also recommendations for the testing of the active substance. However, testing of active substances should only be requested where justified e.g.:

potential safety problems with impurities arising from the process;

stability problems (if this cannot be covered adequately by the testing of the finished medicinal product);

the active ingredient is too diluted in the finished medicinal product so that an important parameter cannot be tested;

matrix problems that prevent testing an important parameter in the finished medicinal product.

The selection of products for inclusion in any annual sampling and testing programme is largely driven through a risk based approach as agreed by CHMP in January 2008 (EMEA/INS/S&T/81176/2007). The second page of the attached form allows the assessor to assign weightings based on his/her detailed assessment of the quality part of the dossier which will then be used by EMA in the risk ranking model used for the selection of products for testing in any one annual programme.

The intention is to give the assessor the opportunity to influence the weighting assigned to the product in the context of the sampling and testing scheme should it be felt appropriate. Each box checked will assign a weighting value. Any number of boxes can be checked as appropriate.

Doc. Ref: EMEA/INS/3924/02 Proposals from the Rapporteur / Co-Rapporteur[[1]](#footnote-2) on “Essential Quality Parameters to be tested for the Control of Marketed Centrally Authorised Product”

|  |  |
| --- | --- |
| **NAME OF MEDICINAL PRODUCT**  **- - - - - - - - - - - - - - - - - - - - -** | Application number:  EMEA/ / / |
| Authorisation number:  EU/ / |
| **Active substance**  **- - - - - - - - - - - - - - - - - - - - -** | NCE  Other |
| **Active substance**  **(please see guidance given above)**  No control  Identity  Assay / activity  Purity (Main impurities - Manufacturing)  Other parameters | |
| Following a critical review the following quality test parameters have been selected for testing by OMCLs during post-authorisation surveillance | |
| Medicinal Product Identity  Assay / activity  Purity (main impurities - stability)  Dissolution  Uniformity of dosage units  Moisture Content  Other parameters | |
| **Recommendation, when applicable, on pharmaceutical form / strength / presentation to be tested** | |

|  |  |  |
| --- | --- | --- |
| **Please record below the name, organisation and telephone number of a contact person** | | |
| Name: |  |  |
| Organisation: |  |  |
| Telephone Nr.: |  |  |
|  |  |  |

Assessor-identified weighting factors to be taken into account in the risk-based selection of products for testing

An inherent variability in the production process

Inherent difficulties foreseen with the testing methodology

Novel manufacturing or control technology[[2]](#footnote-3)

Potential presence of toxic impurities

A particular risk of bioavailability problems

A particular risk inherent in the manufacturing or control methodology not covered by any of the above(explanatory comments may be made below).

…………………………………………………………………………………….

…………………………………………………………………………………….

None of the above weighting factors apply

1. Delete as appropriate [↑](#footnote-ref-2)
2. Note: PAT or new ICH approaches to quality are expected to lead to enhanced product and process knowledge and improved quality assurance rather than increased risk but it is accepted that assessors may wish to express caution in some cases until there is greater experience and confidence. [↑](#footnote-ref-3)