



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance document on the content of the <Co- >Rapporteur day <60* ><80> critical assessment report

**in case of accelerated assessment for procedures starting from
September 2016 onwards*

Quality aspects

<Invented name>

<(Active substance)>

EMA/H/C/<xxx>

Applicant:

Rapporteur:	
Co-rapporteur:	
EMA PTL:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	



Table of contents

1. Request for inspection action prior to authorisation	8
2. Introduction.....	10
3. Drug substance (CTD module 3.2.S)	11
3.1. General information (CTD module 3.2.S.1).....	11
3.2. Manufacture (CTD module 3.2.S.2)	14
3.3. Characterisation (CTD module 3.2.S.3).....	18
3.4. Control of drug substance (CTD module 3.2.S.4)	20
3.5. Reference standards of materials (CTD module 3.2.S.5).....	23
3.6. Container closure system (CTD module 3.2.S.6)	24
3.7. Stability (CTD module 3.2.S.7)	25
4. Drug product (CTD module 3.2.P)	26
4.1. Description and composition of the drug product (CTD module 3.2.P.1)	26
4.2. Pharmaceutical development (CTD module 3.2.P.2).....	27
4.3. Manufacture (CTD module 3.2.P.3).....	30
4.4. Control of excipients (CTD module 3.2.P.4)	32
4.5. Control of drug product (CTD module 3.2.P.5)	34
4.6. Reference standards or materials (CTD module 3.2.P.6).....	36
4.7. Container closure system (CTD module 3.2.P.7).....	36
4.8. Stability (CTD module 3.2.P.8)	37
5. Appendices (CTD module 3.2.A).....	38
6. Regional information	42
7. Assessor's comments on the SmPC, labels and package leaflet	42
8. Assessor's overall conclusions on quality	43
9. List of questions as proposed by the <co>rapporteur.....	44
10. Annex 1 (as appropriate).....	46
11. Annex 2 (For centrally – submitted product)	47
12. Annex 3 (Draft).....	50

Administrative information

Invented name of the medicinal product:	
INN (or common name) of the active substance(s):	
Applicant:	
Applied Indication(s):	
Pharmaco-therapeutic group (ATC Code):	
Pharmaceutical form(s) and strength(s):	
Rapporteur contact person:	Name: Tel: Fax: Email:
Co-Rapporteur contact person:	Name: Tel: Fax: Email:
EMA Product Lead:	Name: Tel: Fax: Email:
Procedure Manager:	Name: Tel: Fax: Email:
Names of the Rapporteur assessors (internal and external):	Quality: Name(s) Tel: Fax: Email: Non-clinical: Name(s) Tel: Fax: Email: Clinical : Name(s) Tel: Fax: Email:

Names of the Co-Rapporteur assessors (internal and external):	Quality: Name(s) Tel: Fax: Email: Non-clinical: Name(s) Tel: Fax: Email: Clinical: Name(s) Tel: Fax:
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Declarations

- The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, unless there are previous contracts and/or agreements with the third party(ies).
- The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

List of abbreviations

GENERAL GUIDANCE

In general the following aspects should be considered:

The report should be sufficiently detailed to allow for secondary assessment by other CHMP experts.

The report should describe salient findings and those deficiencies that justify the questions intended for the applicant. These questions will be listed in the "overview module" of the assessment.

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. overview, summary, study reports), references to the literature or other sources.

The report should also emphasise those findings that need to be reflected in the SPC.

The use of tables is encouraged; examples are given in the template and are to be used as appropriate. Tables taken from the dossier may also be appended to the assessment. Don't forget footnotes!

A separate page has been added in the template for the inclusion of a list of abbreviations, to be completed when necessary.

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

Link to specific CHMP or CHMP/ICH Notes for guidance as a general framework for guidance:

(<http://www.emea.eu.int/index/indexh1.htm>)

Quality critical assessment

GENERAL GUIDANCE

The following structure for the quality assessment report keeps basically to the CTD structure of the dossier, apart from some preliminary sections, e.g. an Introduction section to put the product in context.

Whilst this guidance is relevant for both NCE, known chemical active substances and Biotech/Biological products, in some cases specific additional guidance is given for either NCE or Biotech/Biological products.

Please also refer to the CTD guidance text for the applicant - it is not considered necessary to repeat this here, but rather to highlight some additional aspects not specifically detailed in the CTD, for the benefit of assessors. Note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the 'main'

headings. Assessors may add more, or less, depending upon the complexity of the product. In addition, note also that the CTD terms 'Drug Substance' and 'Drug Product' are synonymous with the EU legislative terms 'Active Substance' and 'Finished Product' respectively.

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

This quality assessment report should be 'self-standing'. This may be achieved in two ways:

1) Presenting or copying data which are taken from the applicant's dossier, followed by the assessor's own critical assessment of these data, particularly with respect to safety/efficacy consequences and highlighting adherence to specific guidance documents. The heading 'Assessor's Comments' should be introduced as a separator in this case, to avoid confusion.

2) Alternatively, this report may consist largely* of the assessor's own views with references to the applicant's own data and/or Quality Overall Summary (QOS). In this case, the assessor's views are intended to be read in conjunction with the QOS which must be attached. The additional headings for assessor's comments would not be needed.

See specific CHMP or CHMP/ICH Notes for guidance as a general framework for quality assessment,

e.g.: The Rules Governing Medicinal Products in the EU, volume 3A

<http://www.emea.eu.int/index/indexh1.htm>: The Notice to Applicants revision incorporating the CTD.

In addition, other multidisciplinary guidelines not indexed under 'quality' may also be relevant, and certain 'technical' legislation may also be relevant, e.g. Directive 89/343/EEC relating to radiopharmaceuticals.

In general, assessors should try to relate quality matters to efficacy and safety consequences as much as possible. Matters arising from the scientific evaluation below, which have a bearing on the product information, should also be mentioned (comments on the SPC, Labels & Package Leaflet.).

Note that for generic applications (chemicals) a special template for the Day 80 AR is developed.

In the case of an application for a similar biological medicinal product an extensive comparability exercise will be required to

demonstrate that the similar biological and reference products already authorised in the community have similar profiles in terms of quality, safety and efficacy.

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorisation in EU will be checked by EMA during validation. In addition to these details the batch number and country of origin of the batches used in the comparability exercise (quality, non-clinical and clinical) should be confirmed by the assessor and need to be provided in tabular format in the quality part (Product: Reference Standards or Materials, CTD Module 3.2.P.6).

For similar biological medicinal products the relevant guidelines (EMA/CHMP/437/04 Guideline on similar biological medicinal products, EMA/CHMP/49348/2005 Guideline on similar biological medicinal products containing biotechnology derived medicinal products as active substances: quality issues) should be taken into consideration. Other guidance for biotechnology derived medicinal products in general is also applicable.

The quality comparability exercise for a similar biological medicinal product is an additional element to the CTD dossier. Applicants should provide distinct sections where appropriate on these comparisons for ease of assessment and this should be done on the basis of concluding in a concise summary in the CHMP AR as to whether comparability has been demonstrated for both the active substance and finished product.

For Post Approval Change Management Protocols Annex 3 should be used to summarise what has been agreed upon. These protocols may be found under Regional Information, e.g. under "Comparability Protocols".

Indicate whether a Paediatric Investigation Plan requiring the development of a paediatric formulation has been agreed with the PDCO.

Finally, in the case of centrally-submitted applications, assessors are encouraged to complete the proforma for sampling and testing attached to the end of this template (Annex 2) to assist in the post-authorisation sampling and testing scheme coordinated by the EMA Inspections function.

* a limited amount of the applicant's data such as flow diagrams, specifications etc. may be copied in, to facilitate the reading of the report.

1. Request for inspection action prior to authorisation

Where a site has already been inspected, such requests are expected to be uncommon. However, when quality issues requiring a future inspection are identified during the dossier assessment phase, they should be

notified as soon as possible to the relevant Inspections authority. Because on-site Inspection takes time to organise, it is not necessary to wait until day 80 if the assessor considers such action is necessary prior to authorisation. The relevant Inspection authority (e.g. EMEA in the case of centrally-authorized products) should be notified; if possible, in advance of the day 80 assessment report, and this request should be highlighted in this part of the assessment report at day 80. It is important to note that such requests may be made to resolve questions in any part of the quality dossier, and the reasons for the request should be briefly described here and in more detail in the relevant section of the report which follows, e.g. S.2, P.3, etc, for either GMP-compliance and/or product-process specific inspections:

- Active substance manufacturing site:

Since 30 October 2005, the Directive 2004/27/EC introduces a requirement for manufacturing authorisation holders to use only active substances which have been manufactured according to GMP in the manufacture of medicinal products. The GMP Basic Requirements for Active Substances used as Starting Materials have been introduced as a Part II to the GMP guide. It is the responsibility of the manufacturing authorisation holders using the active substance as a starting material to ensure the GMP compliance of their suppliers of active substances. However, inspections by EU GMP inspectors may be requested on when there are causes for concern raised during the assessment for any site.

Ad hoc GMP Inspection Services has adopted a guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances and this document is incorporated into the Compilation of Community Procedures on Inspections and Exchange of Information and can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf. It should be particularly noted that inspections should be triggered automatically in the case of a biological substance or for the sterilisation step of a sterile active substance when there is no evidence that the site in question is subject to routine inspection by a National Competent Authority of the EEA (in some Member States a manufacturing authorisation is required for these activities and in these cases the guidance given below for finished product manufacturing sites applies).

- Finished product manufacturing site

This includes all stages of manufacture of the medicinal product including intermediate stages and quality control. For sites located in the EEA, importation and batch release (certification) are also included):

- Site located in the EEA:

The Supervisory Authority of the Member State on a routine basis inspects this site for GMP. An inspection is requested only if there are specific issues connected with assessment of the application.

- Site outside the EEA:

* GMP:

An inspection of the site is not requested, unless product or process related issues arise in the assessment (see below), if a valid GMP certificate (or entry in EudraGMDP database) issued by an EEA or MRA authority is available for the same category of product.

The validity date does not mean that the certificate is expired. The issuing authority will confirm the validity.

* Product/process:

An inspection may always be requested to cover product or process specific issues. In which case, a list of questions/items should be provided to the inspectorate, which should be addressed during the inspection.

If you are recommending an inspection, please also consider any recommendations for the composition of the inspection team.

A question should be raised to the applicant in order to be able to conduct the inspection during the clock stop.

TESTING:

If testing is recommended for applications under the centralised procedure, please define the testing protocol (type of samples: active, bulk, finished product / tests to be carried out / number of samples / number of batches / Official testing laboratory / deadline for reporting of the results) and summarise the results for the Committee as soon as possible. If assistance is needed to identify a laboratory, please contact EMA (Manufacturing and Quality Compliance Service) who can provide assistance within the framework of the EMA sampling and testing programme.

2. Introduction

General background of the product.

- Brief description of the product type (active substance {e.g. NCE, known chemical active substances, Biotech/Biological) radiopharmaceutical, herbal}, pharmaceutical form, container). Highlight if a paediatric formulation was developed.
- Orphan Medicinal Product (OMP) status, if relevant.

- *Mention any potential structural similarity conflicts with pan-EU authorised OMPs, if detected. (Note that a detailed report on structural similarity conflicts will be prepared separately, as part of the general report of similarity, at day 90 according to the current procedural guidance)*
- *Indications, target population, posology (with regard to the ability of the product to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device).*
- *Mention relationship of drug substance to others in the same therapeutic class.*
- *Preparation/reconstitution of product (e.g. radiopharmaceuticals, lyophilisate).*
- *Other special features of the product such as delivery or administration systems, medical devices etc.*
- *Linked or related applications (e.g. drug of a pro-drug, line-extension, simultaneous or 'double' applications).*

The information provided here is intended to provide a brief description of the main critical features of the product. The amount of information provided will depend on the nature of the particular product. The clinical context of use should also be briefly mentioned.

Name:	
Dosage form and strength:	
Procedure:	
Therapeutic class or indication:	
Proposed dosage range:	

3. Drug substance (CTD module 3.2.S)

Note that if information on the active substance is presented in the form of an ASMF with a confidential/closed part this should be stated here. The assessment of this closed or restricted part dealing with information which is protected by intellectual property rights or which is otherwise sensitive should be done in a separate report, together with a separate list of questions arising from this report, attached as an Annex. Note ASMFs are not applicable for biological medicinal products.

3.1. General information (CTD module 3.2.S.1)

Under this heading, the following CTD Headings would be discussed:

S.1.1 Nomenclature

S.1.2 Structure

S.1.3 General Properties

Nomenclature: At least one sentence to mention the name. Confirm whether the name is rINN, pINN, Common Name, etc.

Structure: Include this and link to similar compounds, by description or by structure.

General properties: Also specify the properties relevant to the performance of the product in the clinic and give values, e.g., pKa, solubility, polymorphism, isomers, particle size distribution etc. where relevant.

For biotech/ biological substances, S.1 should also include a description of the active substance. The name and description of the molecule should be given. This should include features such as glycosylation/post-translational modifications, "artificial" modifications (amino-acid substitutions, pegylation), molecular size. Information on secondary and tertiary structure should be given if appropriate. Highlight and discuss elements of structure important for mechanism of action. Identify those issues not adequately covered and which need to be addressed in the LoQ (with reference to question number, if wanted). Identify 'Major' issues.

NOTES:

- It should be mentioned whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used.

In case the ASMF procedure is used it should be mentioned that the assessment of the Active Substance Master File (ASMF) is provided in a separate ASMF Assessment Report with a confidential annex on the Restricted Part.

- Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF

- Letters of Access in relation to specific drug products should be described for the product in question.

- When a CEP or ASMF is used, only section III.4 Control of Drug Substance and III.5 Reference Standards or Materials relating to the product manufacturer need completing, unless the applicant has provided additional data e.g. 3.2.S.7 stability data to support a longer re-test period

- The questions to the restricted part of the ASMF reports will not be sent to the MAH but only to the relevant ASM/holder of the ASMF

- Where ASMF or CEP is applicable, clarify the source (applicant or ASMF holder or CEP holder) and level of details to be drafted in the assessment report.

- The assessment of the drug substance in this AR should only address additional information provided by the applicant, which is not included in the open part as provided by the ASMF holder. In case a full dossier for the Active Substance is provided by the applicant the full assessment of the active substance should be included in the day 80 AR.

Nomenclature (CTD section: S.1.1)

International non-proprietary name (INN):	
United States Adopted Name (USAN):	
Chemical names:	
Other name:	
CAS registry number:	
Laboratory code:	
Molecular formula:	
Relative molecular mass:	

Structural Formula (CTD section: S.1.2):

General Properties (CTD section: S.1.3)

Physical characteristics:	
Solubility:	
pK _a -value:	
Partition coefficient:	
Hygroscopicity:	
Stereochemistry:	
Polymorphism	

Assessor's comments on S.1 General Information

3.2. Manufacture (CTD module 3.2.S.2)

Under this heading, the following CTD Headings would be discussed:

S.2.1 Manufacturer(s)

S.2.2 Description of Manufacturing Process and Process Controls

S.2.3 Control of Materials

S.2.4 Controls of Critical Steps and Intermediates

S.2.5 Process Validation and/or Evaluation

S.2.6 Manufacturing Process Development

NCE/Known chemical active substances

- *Manufacturer(s): The name, address and responsibility of each manufacturer, including contractors, involved in the manufacturing and testing should be provided..*
- *A QP declaration for EU GMP compliance should always be provided, and include all relevant sites. Normally, the use of the template EMA/334808/2014 is expected. Any deviations from the requirements on QP declarations should be commented on.*
- *Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps. • Relevant process parameters and amounts of materials, reagents and solvents should be laid down in the process description with set points or ranges. The set points and ranges should be justified by process development. Alternatively, the set points used during process validation could be accepted without further justification. Are significant process parameters missing from the description? Has the applicant justified the proposed ranges? "Ranges" only defined by an upper or a lower limit should also be considered. Comment on any other elements of the control strategy, i.e. in-process controls that supplement the process description to assure active substance quality.*

- *Mention if the proposed starting material(s) is acceptable or not including the scientific reasoning for this. Comment on any experiments performed in order to gain additional process knowledge and understanding, e.g. purge studies.*
- *Indicate proposed commercial batch size and discuss batch size from batches provided, if necessary.*
- *Alternate processes - if mentioned, include comment.*
- *Reprocessing - if mentioned, include comment (e.g., when could this occur). Comment on any reasoning why reprocessing should be described in the dossier instead of handled under GMP.*
- *Catalysts and solvents - include comment if not in the main application (but in ASM Restricted part of an ASMF).*
- *Control of materials: State adequacy/extent of proposed specifications with particular mention of control of all impurities (including solvents), which might influence the quality of the active substance, especially if the impurities are not controlled in the ASS. Comment if of biological origin.*
- *Controls of critical steps and intermediates. Discuss the adequacy of the proposed process control.*
- *Process validation - brief summary of the extent of data and results, where relevant. [Process validation data and/or evaluation studies for aseptic processing and sterilisation should be provided.](#)*
- *Manufacturing process development - brief summary of the extent of data and results with reference to substance used preclinical/clinical studies if applicable.*
- *Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the active substance been established in a multivariate manner? If a Design Space is proposed please consult Annex III.*

In general, critical statements are needed on the adequacy of the description of the synthesis, of the control of the materials and intermediates, reproducibility of the manufacturing process identifying those issues not adequately covered and which need to be addressed in the LoQ (with reference to number if wanted). Identify 'Major' issues.

BIOTECH

S.2.1 Manufacturer(s)

- *List of manufacturers. Identify manufacturers for which comparability issues or other quality issues have been raised.*

Highlight potential GMP issues (e.g. transportation between sites...).

S.2.2 Description of Manufacturing Process and Process Controls

- Provide summary of manufacturing process and in-process controls (specially those related to the safety of the product, e.g. tests for adventitious agents, RT activity); highlight any re-processing.
- Provide summary for lifetime and sanitization procedures for chromatographic columns used during the purification process; assessment in relation to any impact on product safety.
- Critical assessment of the adequacy of the development, consistency and control.
- For a similar biological medicinal product attention should be drawn to major differences with the process of the reference product, which could affect quality attributes, as appropriate.

S.2.3 Control of Materials

- Information on the development genetics including origin of the gene, description of the gene construction, rationale behind the gene construct, genetic stability (specify state of the recombinant gene and copy number).
- Description of the producer strain /cell line (type, origin), history of establishment and identification. Highlight any issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin).
- Cell banks: Establishment of the MCB/WCB, adequacy of tests performed, cell bank stability, phenotypic and genotypic characterisation, protocol for the establishment of future WCB.
- For of biological materials (e.g. monoclonal antibody purification columns, blood/plasma derivatives) used in the manufacture of the drug substance, the assessment of the source, manufacture, characterisation and control should be provided. For biological materials (e.g. blood/plasma derivatives such as human albumin) used in the manufacture of the drug substance, the assessment of the source, manufacture, characterisation and control should be provided. The note for guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95 rev.3) indicates that for plasma products such as human albumin that whenever it is used in the manufacture of medicinal products, it should comply with the note for guidance and should have the same documentation, including the origin of donations, the same quality and specifications as that of albumin for therapeutic use.

- *Make reference to A2 regarding adventitious agents/viral safety linked to source materials; highlight any issues related to TSE risk evaluation.*

S.2.4 Controls of Critical Steps and Intermediates

- *End of production / cultivation criteria /definition of a batch.*
- *Proposed intervals of set-point specifications and limits of IPC specifications in relation to the results of process validation.*
- *Include description of storage conditions/shelf life of intermediates.*
- *Highlight any specific step aimed/validated for virus removal/inactivation (e.g. low pH treatment).*

S.2.5 Process Validation and/or Evaluation

- *Critical assessment of the adequacy of the validation of the manufacturing process; specify parameters tested and their relevance for the product concerned.*
- *Re-processing should be specifically included or excluded.*
- *Make reference to A2 regarding adventitious agents/viral safety linked to source materials.*
- *Removal of impurities (process and product-related): assessment of the adequacy.*

S.2.6 Manufacturing Process Development

- *Assessment of history of development of manufacturing process and discuss impact on comparability (e.g. batches used for clinical trials vs commercial batches...) making reference to S.4.4.*
- *Description of changes and reasons for changes (justification) with respect to the impact on quality.*
- *Critical assessment of the significance of changes.*

Manufacturer(s) (CTD section: S.2.1) GMP

Description of manufacturing process and process controls (CTD section: S.2.2)

Control of materials (CTD section: S.2.3)

Control of critical steps and intermediates (CTD section: S.2.4)

Process validation and/or evaluation (CTD section: S.2.5)

Manufacturing process development (CTD section: S.2.6)

Assessor's comments on S.2 Manufacture:

3.3. Characterisation (CTD module 3.2.S.3)

Under this heading, the following CTD Headings would be discussed:

S.3.1 Elucidation of Structure and other Characteristics

S.3.2 Impurities

NCE/ Known chemical active substances

- Elucidation of structure and other characteristics: Summary of methods used to elucidate the structure and characterise properties of the active substance, e.g., chirality, polymorphism, etc.*
- In the case of radiopharmaceuticals, it should be made clear what the active substance is considered to be, i.e. unlabelled ligand, radiolabelled substance, or radiolabel for labelling of another 'carrier' molecule. (In this latter case information is normally included in the 'carrier' dossier).*
- In general, critical statements are especially needed on the issue of whether or not methods used for elucidation of structure are adequate.*
- Impurities, including process-related impurities & degradation products & solvents, reagents, etc - refer to text in QOS for this summary of data.*

Link to stability data & S.4.

For radiopharmaceuticals, mention also radiochemical purity and radionuclidic purity.

- Differentiate, when possible, between process related impurities and impurities resulting from the degradation of the API.*
- Conclusion on the adequacy of the company's approach to the control and qualification of impurities, with particular reference to non-clinical (toxicology) and clinical studies.*

BIOTECH

For a similar biological medicinal product a fundamental part of the comparability exercise for quality will be the comparison of characterisation data. This should consider structural identity and impurity profiles versus the reference product as appropriate.

Under S.3.1 include:

- Physicochemical properties.*
- Determination of the composition, physical properties, and primary structure, information on higher-order structure.*
- Pattern of heterogeneity (regarding product - related substances) and demonstration of its consistency biological activity.*
- Validity of the assay to measure the biological activity should be demonstrated.*
- Correlation between the biological assay and the clinical response should be established.*
- Potency (expressed in units).*
- Results of biological assays should be expressed in units of activity calibrated against an international or national or in house reference material.*
- Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass immunochemical properties.*
- When the product itself is an antibody, its immunological properties should be fully characterised.*
- For proteins, immunocochemical properties may serve to establish its identity, homogeneity or purity or serve to quantify it.*
- Quantity*

Quantity expressed in mass is a physicochemical measure of protein content.

- Purity (including product-related substances)*

The drug substance can include several molecular entities or variants which are considered product-related substances: individual and/or collective acceptance criteria for product-related substances should be set as appropriate.

Under S.3.2 (impurities) include the following:

- Impurities should be characterised to the extent possible and, where possible, their biological activities should be evaluated.
- Acceptance criteria for impurities (individual and/or collective) should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.
- Process-related

Process-related impurities encompass those that are derived from the manufacturing process, i.e., cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g. inducers, antibiotics, or media components), or downstream processing.

- Product-related

Product-related impurities (e.g., precursors, certain degradation products) 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.

(Note: Contaminants include all adventitiously introduced agents not intended to be part of the manufacturing process and as such should be discussed in Appendix A.2.).

- Comparability

Elucidation of structure and other characteristics (CTD section: S.3.1)

Impurities (CTD section: S.3.2)

Assessor's comments on S.3 Characterisation:

3.4. Control of drug substance (CTD module 3.2.S.4)

Under this heading, the following CTD Headings would be discussed:

S.4.1 Specification

S.4.2 Analytical Procedures

S.4.3 Validation of Analytical Procedures

S.4.4 Batch Analyses

S.4.5 Justification of Specification

NCE/ Known chemical active substances

- *Specification: Table of specification to be inserted. Provide a compiled specification when there are more than one sources of the active substance having different specifications.*
- *Analytical procedures: Combine in above table – just refer to method. If relevant for the context the principle may be described in more detail. Is any analytical method flexibility described?*
- *Validation of analytical procedures: State if in accordance with ICH or not, and mention any deviation. If necessary, e.g. in order to highlight significant deviations or to highlight validation results, a table may be used (see D80 AR template).*
- *Are the methods adequate to control the substance on a routine basis?*
- *Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?*
- *Is the applicant's proposed justification of the specification adequate or not, bearing in mind the intended use of the drug substance in the product.*
- *If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate models are used to predict the active substance quality attributes or for online process monitoring see Annex III.*

BIOTECH

Under S.4.1 include:

Appearance and description

A qualitative statement describing the physical state (e.g., solid, liquid) and colour of a drug substance should be provided.

Identity

The identity test(s) should be highly specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical,

biological and/or immunochemical) may be necessary to establish identity.

Purity and impurities

The absolute purity of biotechnological and biological products is difficult to determine and the results are method-dependent. Consequently, the purity of the drug substance is usually estimated by a combination of methods. The choice and optimisation of analytical procedures should focus on the separation of the desired product from product-related substances and from impurities. The impurities observed in these products are classified as process-related and product-related.

Potency

A relevant, validated potency assay should be part of the specifications for a biotechnological or biological drug substance and/or drug product. When an appropriate potency assay is used for the drug product, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage. In some cases, the measurement of specific activity may provide additional useful information.

Quantity

The quantity of the drug substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be independent of a reference standard or material. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

The drug substance specification should be included in or appended to the AR.

Under S4.3 include:

Adequacy of the validation of analytical methods.

Under S4.4 include:

Information on batch-to-batch consistency.

Consistency of the pattern of heterogeneity (e.g. glycoforms, isoforms) should be demonstrated.

Discussion of differences, if any, in impurity levels in pre-clinical, clinical and production batches.

Under S.4.5 include:

The rationale used to establish the acceptable range of acceptance criteria should be described, taking into account the overall manufacturing and purification process and the analytical procedures utilised. Acceptance criteria should be established and justified based

on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.

In some cases, testing at production stages rather than at the drug substance or drug product stages may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and included in the specification of drug substance or drug product in accordance with the requirements of the regional regulatory authorities.

The evaluator should assess whether the MAA has chosen the appropriate set of test methods to be routinely applied to drug substance specifications out of the larger number of methods used during the development and characterisation phases.

Specification (CTD section: S.4.1)

Table S. 4-1. Specifications

Specification parameter	Test method	Test limits

Analytical procedure (CTD section: S.4.2)

Validation of analytical procedure (CTD section: S.4.3)

Batch analyses (CTD section: S.4.4)

Justification of specification (CTD section: S.4.5)

Assessor's comments on S.4 Control of Drug Substance:

3.5. Reference standards of materials (CTD module 3.2.S.5)

NCE/ Known chemical active substances

Are reference standard(s) available from EDQM? If not, are in-house reference standard(s) adequately described? (Refer to EP 5.12 Reference standards).

Make a list of all reference standards required by the analytical procedures and state the type of test the standard is used for (e.g. identification, assay or related substances test). Is the quality of the reference standard acceptable for its use?

BIOTECH

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available.

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. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material.

Where an international or national standard is available and appropriate, reference materials should calibrate against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary.

Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established.

When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterisation, storage conditions and formulation supportive of reference material(s) stability should also be provided.

For a **similar biological medicinal product** comparison at the level of the active substance is required. Confirmation should be given that active substance from the reference products as stated in Section 3.2.P.6, was used as appropriate.

Assessor's comments on S.5 Reference Standards or Materials:

3.6. Container closure system (CTD module 3.2.S.6)

Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the drug substance?

Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period (ref. S.7).

Assessor's comments on S.6 Container Closure System:

3.7. Stability (CTD module 3.2.S.7)

Under this heading, the following CTD Headings would be discussed:

S.7.1 Stability Summary and Conclusions

S.7.2 Post-approval Stability Protocol and Stability Commitment

S.7.3 Stability Data

- State if the studies are carried out in accordance with current ICH/CPMP guidelines. Are there deviations? Are the deviations justified in this case?*
- Stability summary and conclusions: Reference to any differences in manufacturing. Processes used, with comments on whether or not this has a significant effect on the stability profile.*
- Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.*
- Confirm that the analytical methods are stability-indicating (ref. S.4). Stability indicating tests should be chosen, which are able to detect significant changes in the quality of the product.*
- Particularly for NCE's or known chemical active substances, confirm that the containers used in the stability studies are the same as those proposed for routine storage (ref. S.6).*
- Are there any trends? A brief summary should be given for the stability data.*
- Final conclusion on whether or not the proposed re-test period is justified.*

Stability summary and conclusion (CTD section: S.7.1)

Table S. 7-1. Stability studies

Temp °C, RH %	n batches x months	Batch size	Package
25 °C / 60% RH		Production scale / Pilot scale	Intended for marketing
40 °C / 75% RH			

Post-approval stability protocol and stability commitments (CTD section: S.7.2)

Stability data (CTD section: S.7.3)

The stability data on which the summary and conclusion in S.7.1 is based, is included in the dossier.

Assessor's comments on S.7 Stability:

4. Drug product (CTD module 3.2.P)

4.1. Description and composition of the drug product (CTD module 3.2.P.1)

- *Self-explanatory. All components of the presentation as intended for marketing, including reconstitution diluents, medical devices, etc. should be clearly stated.*
- *In particular where the product presentation includes a medical device, it is important to cross-refer to the details of the device in 3.2R, Regional Information. Check that any medical devices are CE-marked prior to submission of the dossier for the medicinal product. Has the CE mark been attributed for the intended use?*
- *Whilst the composition may be obvious, it may be necessary to pay particular attention to the details of the container/closure system, especially for labile or sterile products.*
- *For a similar biological medicinal product attention should be drawn to major differences in composition of the reference product as appropriate.*

The composition of {drug product} is presented in Table P.1-1 below.

Table P.1-1. Complete composition of XXX

Ingredient	Reference	XXX Amount (XXX)	XXX Amount (XXX)	Function
				Active

Assessor's comments on P.1 Description and Composition of the Drug Product:

4.2. Pharmaceutical development (CTD module 3.2.P.2)

Under this heading, the following CTD Headings would be discussed:

P.2.1 Components of the Drug product

P.2.1.1 Drug Substance

P.2.1.2 Excipients

P.2.2 Drug Product

P.2.2.1 Formulation development

P.2.2.2 Overages

P.2.2.3 Physicochemical and biological Properties

P.2.3 Manufacturing Process Development

P.2.4 Container Closure System

P.2.5 Microbiological Attributes

P.2.6 Compatibility

Components of the Drug Product:

- Drug Substance: Has the company identified those physico-chemical properties of the drug substance that are clinically relevant for the patient?*
- Have these properties been adequately specified and are they adequately controlled?*
- On what basis have the limits been justified?*
- The identification of the drug substance attributes that may impact the finished product critical quality attributes may be performed on an empirical level or through systematic evaluation*

using risk assessment methodologies and statistically designed experimentation. In the later case please consult Annex III

- Where potentially key parameters are not controlled, is the justification for their omission acceptable?
- Use of materials of animal or human origin - have these been justified?

Excipients:

- Have important, novel or unusual excipients been identified regarding their impact on product performance?

The applicant's choice and function of key excipients should be mentioned, e.g. those modifying release or disposition of the drug substance. In some cases (e.g. gas dispersions for diagnostic ultrasound investigations) the total formulation or system is responsible for the clinical efficacy of the product and these cases should be discussed in detail.

- Is the quantity of the excipients used justified? (preservatives, buffers, etc)
- The identification of the drug substance attributes that may impact the finished product performance may be performed on an empirical level or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the later case please consult Annex III

Assessors should also refer to section V of this report (CTD Appendix 3.2.A.3, Novel Excipients), where a more detailed evaluation of the excipient per se may be given. Note that 'new' excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc.

Drug Product:

- *Formulation Development:* Has the applicant presented the Target Product Profile of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy? Is the formulation development supported by clinical development? Discussion of Bioequivalence between commercial formulation and clinical trial formulations, if different. Discuss if possible differences in finished product quality attributes (e.g. impurity and dissolution profile) in case of different strengths or a line extension. Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties. Results of studies to establish IVIVC, if relevant. Early development formulations for pre-clinical and clinical studies should be

highlighted where relevant, and comments made relating to the findings of these studies. Additional details should be given if the development encompasses an age specific formulation including information for which age group this is intended, if appropriate.

- In case of scored tablets, has relevant testing of the efficacy of the break-mark(s) according to Ph. Eur. Tablets; Subdivision of tablets been performed?

Overages:

- On which basis are overages justified?

Physico-chemical and Biological properties:

- Are key parameters identified and adequately controlled?

The CTD-Q gives an adequate list of parameters that need to be discussed with regard to their impact on the performance of the product, where relevant, e.g. for tablets - the particle size and polymorphism of an active substance with low aqueous solubility may need to be discussed with reference to their effects on dissolution and bioavailability. In this example the pH-solubility profile would also be relevant basic information having an impact on the choice of dissolution test methodology.

Manufacturing Process Development:

- If the manufacturing process of the product influences the physicochemical properties of the drug substance (e.g. polymorphic form), check that the studies carried out on the drug substance remain valid.
- Has the choice of process been justified, where necessary? Are critical process parameters, relevant for subsequent process validation, identified? Are process parameter ranges satisfactorily investigated/supported by pharmaceutical development? Are differences in the manufacturing processes of the commercial product and clinical trial material adequately explained and discussed? Does the process compensate for the variability in the material attributes? The identification of the critical process parameters may be performed on an empirical basis or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the later case please consult Annex III.

Container Closure System:

- Is the choice of materials for the container and closure adequate to support the stability and use of the product with its targeted patient group (e.g. elderly, child resistant)?

- *If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions which, as far as possible, simulate the use of the product.*
- *Technical properties of the container closure system with respect to patient use should be considered, e.g. nasal sprays, inhalers, prefilled syringes.*
- *Microbiological Attributes: Is the use of additives, e.g. preservatives and antioxidants justified regarding their concentration and nature?*

Compatibility:

- *Do the compatibility studies support the instructions for use and handling in the SPC?*

Components of the drug product (CTD section: P.2.1)

Drug substance (CTD section: P.2.1.1)

Excipients (CTD section: P.2.1.2)

Drug product (CTD section: P.2.2)

Formulation development (CTD section:P.2.2.1)

Bioequivalence study and reference product / Clinical formulation

Overages (CTD section: P.2.2.2)

Physicochemical and biological properties (CTD section: P.2.2.3)

Manufacturing process development (CTD section: P.2.3)

Container closure system (CTD section: P.2.4)

Microbiological attributes (CTD section: P.2.5)

Compatibility (CTD section: P.2.6)

Assessor's comments on P.2 Pharmaceutical Development:

4.3. Manufacture (CTD module 3.2.P.3)

Under this heading, the following CTD Headings would be discussed:

P.3.1 Manufacturer(s)

P.3.2 Batch Formula

P.3.3 Description of Manufacturing Process and Process Controls

P.3.4 Controls of Critical Steps and Intermediates

P.3.5 Process Validation and/or Evaluation

- *The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing and testing should be provided.*
- *Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.*
- *Relevant process parameters should be laid down in the process description with set points or ranges. The set points and ranges should be justified by pharmaceutical development. Alternatively, the settings used during process validation could be accepted without further justification. Are significant process parameters missing from the description? Has the applicant justified the proposed ranges? "Ranges" only defined by an upper or a lower limit should also be considered. Comment on any other elements of the control strategy, i.e. in-process controls that supplement the process description to assure product quality.*
- *Has the applicant introduced controls to monitor real time the critical material attributes and critical process parameters? Do the controls reduce the risks identified during formulation and process development? Are there feedback loops in place that allow adjustment of the process to compensate for the variability observed?*
- *Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes been established in a multivariate manner? If a Design Space is proposed please consult Annex III.*
- *Where the product consists of the active substance without excipients details of the manufacturers should also be referred to here and should be accordingly licensed.*
- *Where ranges of batch size are proposed for production, blending of batches or the use of sub batches, the acceptability should be addressed. Discuss the bath size(s) of the data provided.*
- *The assessor should discuss any specialised processes that may need to be inspected (see preamble to this report).*

- Confirm that process holding times and transport arrangements are relevant and have been justified / validated.

The assessor should comment here on whether process validation data are needed in the dossier (i.e. whether it is needed prior to authorisation). Where non-standard methods are used these validation data would normally be expected. For standard processes the process validation scheme referred to in 3.2.R Regional Information should be evaluated.

- Any proposals for continuous process verification should be supported by adequate development data and an appropriate control strategy that allows real time monitoring of the critical process parameters and material critical quality attributes.
- Any requests for 'real time release testing' need to be fully evaluated and commented on here, with a comment from the GMP Inspectors, where necessary, in accordance with the CHMP NfG.
- Where relevant, the safety of the product in respect of transmission of 'adventitious agents' should be considered under Appendix A.2 Note: This is perhaps more relevant for biotech/biological products.

Manufacturer(s) (CTD section: P.3.1)

Batch formula (CTD section: P.3.2)

Description of manufacturing process and process controls (CTD section: P.3.3)

Controls of critical steps and intermediates (CTD section: P.3.4)

Process validation and/or evaluation (CTD section: P.3.5)

Assessor's comments on P.3 Manufacture:

4.4. Control of excipients (CTD module 3.2.P.4)

Under this heading, the following CTD Headings would be discussed:

- P.4.1 Specifications
- P.4.2 Analytical Procedures
- P.4.3 Validation of Analytical Procedures
- P.4.4 Justification of Specifications
- P.4.5 Excipients of Human or Animal Origin
- P.4.6 Novel Excipients

- *If PhEur monograph exists, mention may be brief and should be enough in most cases.*
- *If non-PhEur, is the specification adequate?*
- *Do the specifications and tests reflect the functionality in a relevant way? Especially in novel delivery systems, some ingredients may have a special function, and should be described and controlled in more detail, especially with regard to functionality testing.*
- *For biological materials (e.g. blood/plasma derivatives such as human albumin) used in the manufacture of the drug product, the assessment of the source, manufacture, characterisation and control should be provided. The note for guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95 rev.3) indicates that for plasma products such as human albumin that whenever it is used in the manufacture of medicinal products, it should comply with the note for guidance and should have the same documentation, including the origin of donations, the same quality and specifications as that of albumin for therapeutic use.*
- *Make reference to A2 regarding adventitious agents/viral safety linked to excipients; highlight any issues related to TSE risk evaluation.*
- *Note that 'new' excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed under section V of this report, CTD-Q Appendix A3 below).*

Specifications (CTD section: P.4.1)

Analytical procedures (CTD section: P.4.2)

Validation of analytical procedures (CTD section: P.4.3)

Justifications of specifications (CTD section: P.4.4)

Excipients of human and animal origin (CTD section: P.4.5)

Novel excipients (CTD section: P.4.6)

Assessor's comments on P.4 Control of Excipients:

4.5. Control of drug product (CTD module 3.2.P.5)

Under this heading, the following CTD Headings would be discussed:

P.5.1 Specification(s)

P.5.2 Analytical Procedures

P.5.3 Validation of Analytical Procedures

P.5.4 Batch Analyses

P.5.5 Characterisation of Impurities

P.5.6 Justification of Specification(s)

- Specification: Release and shelf life specifications should be presented side by side in tabular form, with brief reference to the method used.*
- If relevant for the context the principle may be described in more detail. Is any analytical method flexibility described?*
- If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate models are used to predict finished product quality attributes or for online process monitoring see Annex III.*
- Specification summary, important tests, particularly relating to bioavailability/efficacy (e.g. dissolution, particle size, polymorphism if relevant.) and safety (impurities or sterility,*

pyrogens etc. for sterile products). The general relevance of the release specification should be discussed considering the method of manufacture and clinical use, route of administration etc.

- Validation of analytical procedures: State if in accordance with ICH or not, and mention any deviations. (All control methods, regardless of whether they are applicable to control at release or to the shelf life should be discussed here, under P.5). If necessary, e.g. in order to highlight significant deviations, a table may be used.
- Note that the tests for impurities in the product specification should focus on degradation products arising from the manufacturing process and those expected during storage, rather than manufacturing process-related impurities carried over in the drug substance if these are controlled in the drug substance and do not change in the product during storage.
- Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?
- For radiopharmaceuticals, a discussion of radiochemical purity of reconstituted 'cold' kits should be discussed, where relevant.
- For biotechnological products, the important key elements described for specification of drug substance are also in many cases applicable for the drug product.

Specification(s) (CTD section: P.5.1)

Table P. 5-1. Release and shelf-life specifications

Specification parameter	Test method	Test limits

Analytical Procedures (CTD section: P.5.2)

Validation of analytical procedures (CTD section: P.5.3)

Batch analyses (CTD section: P.5.4)

Characterisation of impurities (CTD section: P.5.5)

Justification of specification(s) (CTD section: P.5.6)

Assessor's comments on P.5 Control of Drug Product:

4.6. Reference standards or materials (CTD module 3.2.P.6)

(See S5 where relevant)

NCE / Known chemical active substances

Are reference standard(s) available from EDQM? If not, are in-house reference standard(s) adequately described? (Refer to EP 5.12 Reference standards).

Make a list of all reference standards required by the analytical procedures and state the type of test the standard is used for (e.g. identification, assay or related substances test). Is the quality of the reference standard acceptable for its use?

For a similar biological medicinal product, the following information regarding the reference product should be provided in a table: Name, strength, pharmaceutical form, MAH, batch number and country of origin of the batches used in the comparability exercise (the reference product must be from an EU source).

Assessor's comments on P.6 Reference Standards or Materials:

4.7. Container closure system (CTD module 3.2.P.7)

Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the product?

Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life. (ref. CTD.3.2.P.8).

Assessor's comments on P.7 Container Closure System:

4.8. Stability (CTD module 3.2.P.8)

Under this heading, the following CTD Headings would be discussed:

P.8.1 Stability Summary and Conclusion

P.8.2 Post-approval Stability Protocol and Stability Commitment

P.8.3 Stability Data

- State if the studies are carried out in accordance with current ICH/CPMP guidelines. Are there deviations? Are the deviations justified in this case?*
- Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies. Bracketing & Matrixing designs - acceptable?*
- Are the methods used the same as or different to those described in P.5? Are they well validated and shown to be stability indicating?*
- Confirm that the containers used in the stability studies are the same as those proposed for routine storage.*
- Note that the qualification of impurities carried out on the active substance may not necessarily address degradants induced by the product matrix or product manufacturing process. In addition, other product characteristics may change on storage and these need to be justified with reference to the preclinical and clinical results.*
- Are there any trends? A brief summary should be given for the stability data including findings that could be useful as a basis for the EPAR. Since limited information is included in the SPC, other relevant stability information should be included in the EPAR (including any in-use stability studies).*
- Confirm if the proposed shelf life and storage conditions are adequate.*

In-Use stability:

- Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc. Are an in-use shelf life and storage conditions necessary? Are the applicant's proposals in line with the current guidelines? If not, are they still justified?*

- *For radiopharmaceuticals, a discussion of user-reconstitution methods for 'cold' kits may be discussed here, together with a discussion of post-reconstitution stability.*

General:

- *Are all of the above considerations correctly reflected in the SPC/package leaflet? Conclusions on whether or not all shelf lives and storage conditions defined in the SPC are justified.*

Stability summary and conclusion (CTD section: P.8.1)

Table P.8-1. Major stability studies

Temp °C, RH %	n batches x months	Batch size	Package
25 °C / 60% RH		Production scale / Pilot scale	Intended for marketing
40 °C / 75% RH			

Post-approval stability protocol and stability commitment (CTD section: P.8.2)

Stability data (CTD section: P.8.3)

The stability data on which the summary and conclusion in P.8.1 is based, is included in the dossier.

Assessor's comments on P.8 Stability:

5. Appendices (CTD module 3.2.A)

A.1. Facilities and equipment

A.2. Adventitious agents safety evaluation

A.2.1. Non-viral adventitious agents

1.1. Control of mycoplasma, bacteria and fungi

1.2. Risk of contamination with animal TSE

1.1 Control of mycoplasma, bacteria and fungi:

- *Cross-references to other parts of the assessment report (manufacturing process etc.) should be provided.*

- *If non-pharmacopoeial methods are used for bacterial, mycoplasma and fungal testing, these methods should be assessed.*
- *If, for specific reagents or substances problems with respect to sterility have been identified, a detailed assessment should be conducted.*

1.2. Risk of contamination with animal TSE:

- *Materials which fall within the scope of the TSE Note for Guidance, should be identified (reference to Table A) and TSE compliance should be demonstrated by the applicant, by TSE certification and/or via scientific documentation. (It may be useful to present a summary of the most important information in a table).*
- *Assessment of documentation for compliance with the TSE guideline, if necessary.*
- *Conclusion.*

A.2.2. Adventitious viruses

2.1 Identification of materials of biological origin

2.2 Testing of the source materials

2.3 Routine testing on unprocessed bulk (if applicable)

2.4. Testing of purified bulk (if applicable)

2.5 Viral clearance studies

2.1. Identification of materials of biological origin:

- *The assessment report should include a short description or listing of materials of biological origin which are introduced, or come into contact with, the product during production, summarising the characteristics of the materials with regard to the possibilities for virus contamination. Cell substrates, reagents used or introduced directly or indirectly (e.g. affinity chromatography materials), as well as excipients should be considered. (Some of the required information may be found in the dossier under 3.2.S.2.3. Control of Materials, and under 3.2.P.4.5. Excipients of Human or Animal Origin)*

2.2. Testing of source materials:

- *Cell line characterisation. The tests conducted should be tabulated. Tables should indicate which tests have been performed on which cells (MCB, WCB, EOP). Cell lines used for in-vitro testing on adventitious viruses should be identified, MAP/HAP tests need not to be described in detail, but in-vivo testing should indicate the animals used and, if relevant, the route of*

administration. Were three batches of unprocessed bulk tested for the presence of adventitious viruses?

- Reference to European Plasma Master File or assessment of the plasma master file data, if necessary. (Plasma derivatives)
- The assessment report should address controls on donors, donated tissues, and cell banks. (Products derived from human cell tissue).
- Are all relevant European Pharmacopoeia and WHO tests and controls intended to exclude contamination with specific and non-specific extraneous agents applied? (Virus vaccines)
- In the light of the information provided in point 2.1, has the applicant done an appropriate investigation of viral contamination?

2.3. Routine testing on unprocessed bulk (if applicable):

- Is a routine testing of unprocessed bulk required? Is the testing regime appropriate and adequate? (Cell derived products).
- In the light of the information provided in point 2.2, has the applicant developed an appropriate strategy for routine testing?

2.4. Testing of purified bulk (if applicable):

- Has the applicant provided an acceptably justified regime for routine/not-routine testing the purified bulk?

2.5. Viral clearance studies

- General remarks to the design of the study
- Are virus clearance steps required for the product?
- Is the choice of process steps for virus clearance appropriate and sufficient?
- Is the choice of viruses acceptable?
- In principle, are the studies performed according to the recommendations of the guidelines?

2.5.1 Assessment of the validation studies according to the different stages of manufacture which have been studied:

1) Is the manufacturing process adequately represented in the laboratory-scale experiments?

- Are the important process parameters compared and convincingly reproduced in the down scale process?
- Is appropriate down scaling confirmed by the analytical data of the intermediate products/fractions used?

- *In the case of chromatographic steps, are the parameters (bed height, loading, flow rates (cm/min) for all steps during the process, loading, elution profiles) comparable?*

Is the post-elution fraction (wash) as well as the high salt fraction, if appropriate, tested for virus content? Are the parameters reported for each run?

- *If columns are proposed for re-use, are the conditions of sanitisation and re-use of column reported and validated?*
- *In the case of filtration steps, are the parameters (volume/filter area, flow rates or pressure and/or transmembrane pressure) identical to the manufacturing process? Do the clearance studies adequately reflect the different stages of the filtration process during manufacture (filtration/ultra filtration or washing out of the product) and are these stages appropriately investigated?*
- *Deficiencies should be identified.*

2) Are the virus clearance experiments convincing?

- *Are the possibilities for material cytotoxicity, and interference with the virus assays, tested?*
- *If filtration processes are evaluated, are virus aggregates tested for, and excluded by appropriate procedures?*
- *Are raw data provided and taken into account in the calculation of the reduction factors?*

Any deficiencies should be identified.

3) Assessment of claimed virus reduction factors (Rf)

- *Are claimed Rf values convincing and adequately supported by the data?*
- *A table summarising the reduction factors should be included (amended values, if necessary).*
- *Is the robustness (influence of important procedural parameters) of the manufacturing step investigated?*
- *Has it been demonstrated that the validated virus clearance steps are able to eliminate substantially more virus than is potentially present in a single-dose equivalent of unpurified bulk.*

Summary of A.2.2.5

A table of the reduction factors for the whole process should be provided (amended values, if necessary).

The assessment should be summarised.

A.2.3. Conclusion of 5.2

Overall summary and conclusion should be provided on:

- Sterility (bacterial, fungal, mycoplasmal)
- TSE safety
- Viral safety

A.3. Novel excipients

Note that 'new' excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed here).

6. Regional information

Process validation scheme for the drug product

Medical device issues

Where the presentation of the medicinal product includes elements which are classified as medical devices (e.g. needles, catheters, etc.), these must be CE-marked prior to submission of the dossier and a statement on compliance with the relevant medical devices legislation is required. Otherwise, to complete the evaluation of the product as a whole, the medicines competent authority has to consult with a medical devices competent authority in order to verify the acceptability of the device element with regard to EU requirements. In addition, for those cases where the device may not be so simple, but may in fact be a complex delivery system (e.g. transdermal iontophoretic delivery system included in the total presentation) an evaluation report on the device aspects in relation to the clinical performance of the product as a whole would also be necessary.

TSE issues

7. Assessor's comments on the SmPC, labels and package leaflet

Please, comment on following sections if appropriate

2. Qualitative and Quantitative Composition	
3. Pharmaceutical Form	

<i>4.2 Posology and method of administration (e.g. terminology used for oral liquids)</i>	
<i>4.4 Special warnings and precautions for use (i.e. warnings necessary for excipients or residues)</i>	
<i>6.1 List of excipients</i>	
<i>6.2 Incompatibilities</i>	
<i>6.3 Shelf life</i>	
<i>6.4 Special precautions for storage</i>	
<i>6.5 Nature and contents of the container</i>	
<i>6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product</i>	
<i>11. Dosimetry (if applicable)</i>	
<i>12. Instructions for preparation of radiopharmaceuticals (if applicable)</i>	

8. Assessor's overall conclusions on quality

The content of this paragraph could be carried forward to the "Overview module" of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In relation to the Quality aspects impacting the Benefit-Risk balance, indicate if there is any quality aspect either in the active substance or in the finished product which could lead to impact on the Benefit-Risk Balance.

Indicate if a paediatric formulation has been developed or is to be developed. Indicate in which paediatric age groups the formulation would be used.

As an alternative this section could simply state the main conclusions, in which case the text in the "Overview module" has to be elaborated on separately.

Highlight any areas of agreement/disagreement with the "quality overall summary" in the submitted dossier. With respect to a paediatric

formulation, indicate if there is a need to request an Opinion from the PDCO.

9. List of questions as proposed by the <co>rapporteur

Definitions of questions:

"Major objections", preclude a recommendation for marketing authorisation. In principle, one major objection 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 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 resolve other concerns may render the application un-approvable.

In general, subheadings should be used where necessary throughout the list, to collect objections and concerns in relevant groups.

This list should be carried forward to the "overview module".

Quality aspects

Major objections

Drug substance [related to additional data provided by applicant only]

Drug substance [applicant's part as provided by ASMF holder]

Note: In case the ASMF procedure is used the following should be stated in case Major Objections are being raised on the restricted part of the ASMF:

"For Major Objections on the restricted part of the ASMF see separate AR on the ASMF"

In addition, it should as far as possible be mentioned what these Major Objections concern without revealing any details.

Drug product

Other concerns

Drug substance [related to additional data provided by applicant only] In addition, mention if there are additional concerns on the drug

substance concerning the confidential / closed part of an ASMF. These will be detailed in an annex to the main Quality Report.

Note: When applicable: "For other concerns on the restricted part of the ASMF see separate AR on the ASMF"

Drug product

10. Annex 1 (as appropriate)

Active Substance Master File (ASMF) Assessment Report(s) – in separate document(s).

11. 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-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 you 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.

It is understood that if any of these risk factors are deemed to apply that the assessor will nevertheless have satisfied himself, if necessary by seeking further information from the applicant, that the product meets the necessary quality standards for the grant of a marketing authorisation. The intention is simply 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-Rapporteur¹ 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 -----	<input type="checkbox"/> NCE <input type="checkbox"/> Other
Active substance (please see guidance given above)	Rationale for testing² (specification and test method, when appropriate)
<input type="checkbox"/> No control <input type="checkbox"/> Identity <input type="checkbox"/> Assay / activity <input type="checkbox"/> Purity (Main impurities - Manufacturing) <input type="checkbox"/> Other parameters
Following a critical review the following quality test parameters have been selected for testing by OMCLs during post-authorisation surveillance	
Medicinal Product	Comments (specification and test method, if several methods are possible for a parameter please specify which method(s) should be applied)
<input type="checkbox"/> Identity <input type="checkbox"/> Assay / activity <input type="checkbox"/> Purity (main impurities - stability) <input type="checkbox"/> Dissolution <input type="checkbox"/> Uniformity of dosage units <input type="checkbox"/> Moisture Content <input type="checkbox"/> 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.: _____

¹ Delete as appropriate

² A (short) rationale should be provided for each test selected for the active substance.

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 technology³
- 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

³ 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.

12. Annex 3 (Draft)

The purpose of this Annex is to highlight issues that should be reflected in the assessment report concerning the evaluation of risk assessment methodologies and statistical tools that are used in the context of ICH Q8, ICH Q9 and Q11 (draft) Guidelines. Assessors are encouraged to read this annex in conjunction with any related Guidelines.

1. Risk assessment methodologies

Risk assessment tools can be used in many situations. For instance it may be used to rank and select material quality attributes and /or process parameters that should be within appropriate ranges to ensure the desired product quality. Such tools could also be used to select process parameters that may potentially impact product quality based on prior knowledge and experimental data. Issues that need to be taken into account in the evaluation include:

- Has a summary of all material quality attributes and process parameters that based on previous knowledge and/or experimental data may have an impact on product quality been presented?*

For FMEA analyses:

- Have all the relevant known risk factors been included? e.g. known risk factors of the finished product (e.g. degradation, solubility etc)*
- Has the effect of unit operations and material properties been included?*
- Has the applicant explained how the risk ranking and scoring has been performed?*
- Has the applicant justified how the threshold has been set in order to select, which parameters will be further studied?*
- Do you agree with the proposed risk ranking?*
- Is the result of the FMEA in accordance with existing scientific knowledge? If not has it been justified?*
- Are the identified risks managed by the Design Space or the proposed control strategy?*

2. Design of Experiments

Design of Experiments (DoEs) is a strategy for experimentation, whereby all factors under study are varied at the same time in accordance to rigorously formulated mathematical protocols. The goal is to generate representative and informative experiments that maximise the information provided with the minimum number of experiments. The factors to be studied in a DoE should come out of the risk assessment

exercise. A full statistical evaluation of DoEs performed at early development stages (e.g. for screening) is not necessary. A narrative description of the factors and levels studied and the conclusions reached is adequate.

However for DoEs used for the establishment of CQAs, CPPs and / or a Design Space:

The following data should be considered:

- Type of experimental design used and justification of its appropriateness (e.g. some screening designs are not appropriate since they cannot identify interactions). The power of the design should be stated. (Experimental error compared to the differences in the responses that have to be shown)
- Factors under study and their ranges (in a tabular format if possible)
- The list of design runs clearly stating the batch or study number and the scale of the batch involved in each run. The number of replicated runs should be mentioned.
- Reference to the analytical methods used for the evaluation of the data and demonstration of their suitability for their intended use.
- Statistical results (e.g. Pareto diagrams or a simple list of the sizes of effects and interactions) showing the relative significance of the factors under study as well as of the interactions between them (where applicable) should be provided
- Ensure that the predictions made from a DoE study are appropriate for the ranges studied and scale/equipment differences.

3. Multivariate Data Analysis (MVDA) for Multivariate Statistical Process Control (MSPC)

Multivariate data analysis (MVDA) including Principal Components Analysis (PCA) and Partial Least Squares (PLS) can be used to model pharmaceutical processes. PCA is often used for data overview e.g. for detecting groups and trends among observations, for evaluating relationships between variables and between observations and variables. While PLS is used for linking input and response variables together with the aim of predicting one or more components. Issues that need to be taken into account, when MVDA models are used for MSPC include:

- Are the spectral sample preparation and the reference analytical method used to analyse the sample fit for purpose? For online or in-line control where there is no sampling: what is the repeatability and the reproducibility of the sampling in combination with the analytical method?

- *Are the validation (training) and calibration (test) datasets representative of the expected process variability? Has the applicability of the model been demonstrated across all the variation allowed by the Design Space? In the cases that this is difficult to show, the results of the risk assessment could be used. The influence of all important risk factors should be checked and included in the calibration, validation and test set.*
- *Does the variability of the calibration (test) set adequately represent most of the variability of the validation (training) set?*
- *Have outliers been identified in the original dataset and if yes, is the justification for (non)- omission of data valid? Please note that if the dataset used to develop the model is generated from a DoE, the omission of data may have a greater impact on the predictive power of the model compared to historical datasets.*
- *Is the information concerning the pre-treatment of data (if any) adequately described and consistently applied for all datasets used for creation, optimization and validation of the model?*
- *Are the MVDA modelling techniques adequately described including a brief justification for the selection of the selected algorithm?*
- *Do you agree with the selection of the variables that have been included in the model? Compare with the results of the risk assessment. Are there any relevant sources of variation not included in the model and if yes, is this justified?*
- *For PLS models, is the model fit for purpose? Is the complexity of the model optimal? Note: the PLS model complexity usually corresponds to the number of PLS (latent) factors resulting in the lowest RMSECV. The model complexity (number of PLS factors used to build the model) should be presented in a graph showing the regression coefficients for each variable*
- *Can the weightings (high/ low) of the variables in the model be explained with the existing scientific knowledge or rational concerning that variable and/or manufacturing process?*
- *Is the MVDA model statistically evaluated for fitting and predictive ability? The standard error for prediction should be discussed against the precision of the reference analytical method precision.*
- *Has a model verification scheme been proposed for the product lifecycle? Has it been defined which criteria would trigger an update of the model and are they adequate?*

4. *Design Space (DS)*

Aspects that may be considered when a DS has been proposed include:

- *Has the applicant provided adequate data to support the DS applied for? (Risk assessment, experimental data, models that have been statistically evaluated and verified at full scale)*
- *In case that the Design Space has been developed at lab or pilot scale, has the applicant demonstrated its validity at production scale through the use of scaling factors or independent experiments, or otherwise has it been demonstrated that the parameters are scale independent? Scaling factors might be supported by literature or prior knowledge. Has the applicant discussed the potential risks in the scale-up operation and is there an appropriate control strategy in place to manage these risks?*
- *Has the applicant considered all CQAs, when developing a DS? (See risk assessment and DoE results)*
- *Does the control strategy support the DS?*
- *Are all critical parameters identified in the unit operation part of the Design Space? If not, is there an appropriate justification?*

Design space and change management protocols (if applicable)

This Annex is an extract of the main body of the AR and its purpose is to summarise all aspects agreed upon in the dossier that result to post approval regulatory flexibility. This annex may be used by Inspectors and could be a basis for the evaluation of post-approval variation applications.

1. Active substance

1.1. Design space for the active substance

(Presentation of the Design Space (attributes and their ranges) in a tabular format

1.2. Change management protocols for the active substance

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change)

2. Finished product

1.3. Design space for the finished product

(Presentation of the Design Space (attributes and their ranges) in a tabular format

1.4. Change management protocols for the finished product

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change)