MODULE 2.3

QUALITY OVERALL SUMMARY: PRODUCT DOSSIER (QOS-BTP)

See sections 1.5, 3 and 4 of “WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab” for general and detailed instructions on the completion of this template.

# INTRODUCTION

## Summary of product information:

|  |  |  |  |
| --- | --- | --- | --- |
| Non-proprietary name(s) of Drug Product (DP) |  | | |
| **Proprietary name(s) of the Drug Product (DP)** |  | | |
| **International non-proprietary name(s) of the Drug Substance (DS).** |  | | |
| **Applicant name and address** |  | | |
| **Dosage form** |  | | |
| **Reference Number(s)** |  |  |  |
| **Strength(s)** |  |  |  |
| **Route of administration** |  | | |
| **Proposed indication(s)** |  | | |
| **Primary Contact person responsible for this application[[1]](#footnote-1)** | Title:  First name:  Family Name: | | |
| **Contact person's job title** |  | | |
| **Contact person's postal address** | | | |
| **Unit** |  | | |
| **Building/PO Box number** |  | | |
| **Road/Street** |  | | |
| **Plant/Zone** |  | | |
| **Village/suburb** |  | | |
| **Town/City** |  | | |
| **District and Mandal** |  | | |
| **Province/State** |  | | |
| **Postal code** |  | | |
| **Country** |  | | |
| **Contact person's email address** |  | | |
| **Contact person's phone number** |  | | |

If there are other contacts who should be routinely copied into correspondence for this application they should also be listed below.

|  |  |
| --- | --- |
| Additional contact person | Title:  First name:  Family name: |
| Contact person's job title |  |
| **Contact person's postal address** | |
| **Unit** |  |
| **Building/PO Box number** |  |
| **Road/Street** |  |
| **Plant/Zone** |  |
| **Village/suburb** |  |
| **Town/City** |  |
| **District and Mandal** |  |
| **Province/State** |  |
| **Postal code** |  |
| **Country** |  |
| **Contact person's email address** |  |
| **Contact person's phone number** |  |

|  |  |
| --- | --- |
| Additional contact person | Title:  First name:  Family name: |
| **Contact person's job title** |  |
| **Contact person's postal address** | |
| **Unit** |  |
| **Building/PO Box number** |  |
| **Road/Street** |  |
| **Plant/Zone** |  |
| **Village/suburb** |  |
| **Town/City** |  |
| **District and Mandal** |  |
| **Province/State** |  |
| **Postal code** |  |
| **Country** |  |
| **Contact person's email address** |  |
| **Contact person's phone number** |  |

## Other Introductory information:

Related dossiers (e.g. DP(s) with the same DS submitted to the Prequalification Team: medicines (PQTm) by the applicant):

|  |  |  |  |
| --- | --- | --- | --- |
| Reference number  (eg HA998) | Prequalified (Y/N) | DP, strength, dosage form  (eg. Trastuzumab powder for injection 440 mg) | DS and DP manufacturer  (including address if same  manufacturer as current dossier) |
|  |  |  |  |
|  |  |  |  |

|  |
| --- |
| SUMMARY OF QUALITY ASSESSMENT OF LABELLING AND SAMPLES (*WHO Use Only*) |
| **Discussion/comments on the quality components of:** |
| **Summary of product characteristics**  <insert assessment observations, comments, etc.> |
| **Labelling (outer and inner labels)**  <insert assessment observations, comments, etc.> |
| **Package leaflet (patient information leaflet)**  <insert assessment observations, comments, etc.> |
| **Samples (e.g. DP, resuspension solution)**  <insert assessment observations, comments, etc.> |

**2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)**

Complete the following table for the option that applies for the submission of DS information:

|  |  |  |
| --- | --- | --- |
| Name of DS: | |  |
| **Name of DS manufacturer:** | |  |
| □ | Full details in the PD:   * Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the PQTm guideline. * Document version number/identifier of current module 3.2.S: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ * If an earlier Module 3.2.S document was provided with a previous DP submission: * a) list document number/identifier of the most recent submission to aid comparison: Document version:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ submitted with DP \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_, and, * b) provide a summary of changes document comparing the current and most recent version of the Module 3.2.S. | |

**2.3.S.1 General Information (name, manufacturer)**

## *2.3.S.1.1 Nomenclature (name, manufacturer)*

(Information from 3.2.S.1 should be included)

1. **(Recommended) International Non-proprietary name (INN):**
2. **The nomenclature of the DS:**
3. **Information of the structure of the DS:**

## *2.3.S.1.2 Structure (name, manufacturer)*

**(a) Structural formula:**

**(b) Molecular formula:**

**(c) Relative molecular mass:**

## *2.3.S.1.3 General Properties (name, manufacturer)*

**(a) Physico-chemical properties:**

**(b) Biological properties (including bioidentity, bioassay):**

## 2.3.S.2 Manufacture (name, manufacturer)

## *2.3.S.2.1 Manufacturer(s) (name, manufacturer)*

1. **Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:**

|  |  |  |
| --- | --- | --- |
| Name | Address  (including block(s)/unit(s)) | Responsibility |
|  |  |  |
|  |  |  |
|  |  |  |

**Note: In the absence of identified block numbers, all blocks producing the ds at this site will be considered as part of the inspection.**

1. **Manufacturing authorization for the production of DS and, where available, certificate of GMP compliance (GMP information should be provided in Module 1):**

## *2.3.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)*

1. **A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality** [*The explanation of the batch numbering system, information regarding any pooling of harvests or intermediates, information on the batch size or scale, fermentation scale and purification scale . The description of the manufacturing process, controls, tolerance and critical ranges for critical parameters, reprocessing procedures (e.g. filter integrity test failure), and any transfer of materials, , purification and modification reactions, filling, information on the container closure system, storage and transportation (shipping), in this order.*]:
2. **Flow diagram** [Insert either the overall process diagram or the flow diagrams of cell culture and harvest and purification]

***2.3.S.2.3 Control of Materials***

1. **A description of the source of the starting material and raw materials of biological origin used in the manufacture** [*Insert the summary (e.g. tabulated summary) of the biological raw material(s) used; a brief description of the source and generation (flow chart of the successive steps) of the cell substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the expression of the relevant gene is promoted and controlled in production, information on the cell banking system, quality control activities and cell line stability*]

## *2.3.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)*

1. **A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria** [*A summary of critical manufacturing steps, process controls, and acceptance criteria; a discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria*]
2. **Summary of the controls performed at critical steps of the manufacturing process and on intermediates:**

|  |  |  |
| --- | --- | --- |
| Step/materials | Test(s)/method(s) | Acceptance criteria |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

## *2.3.S.2.5 Process Validation and/or Evaluation (name, manufacturer)*

1. **A brief description of process validation and/or evaluation** [To *document that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes (identification and scale of validation batches)*]

## *2.3.S.2.6 Manufacturing Process Development (name, manufacturer)*

1. **A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, stability, scale-up, pilot and, if available, production scale batches** [*The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes to allow a clear identification of the process versions used to produce each batch used in non-clinical and clinical studies, in order to establish an appropriate link between pre-change and post-change batches; brief summary of major manufacturing changes made through development and conclusions from the assessment used to evaluate product consistency; A cross-reference to the location of nonclinical and clinical studies provided in other modules of the submission, in which drug substance batches that were affected by a significant manufacturing change had been used;* summary of *development studies conducted to establish and validate the dosage form, formulation, and container closure system (including integrity to prevent microbial contamination) and usage instructions*]

## 2.3.S.3 Characterisation (name, manufacturer)

**The characterization should include the determination of physicochemical properties, primary and higher-order structure, post-translational modifications (including but not limited to glycoforms), biological activity, purity, impurities, product-related (active) substances (variants), and immunochemical properties and immunochemical properties.**

## *2.3.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)*

1. **A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data** (for example, primary and higher order structure and biological activity)
2. **List of studies performed and a summary of conclusion from the Physicochemical characterisation program** [*determination of the class, subclass, light chain composition (kappa and/or lambda chain), primary and higher order structure (secondary/tertiary/quaternary) of the monoclonal antibody, deduced and confirmed aminoacid sequence, free sulphydryl groups and disulfide bridges, carbohydrate content and characterization, glycan structures characterization, higher-order structure of the DS*]
3. **List of studies performed and a summary of conclusion from the immunological properties studies** [specificity, affinity, avidity, binding kinetics and immunoreactivity, cross reactivity with other structurally homologous proteins, unintentional reactivity/cytotoxicity, ability for complement binding and activation, and/or other effector functions]
4. **List of studies performed and a summary of conclusion from the biological activity studies** [biological activity - quantity, mechanism of action]

## *2.3.S.3.2 Impurities (name, manufacturer)*

**Summary of studies performed to characterize purity, impurity and contaminants and a summary of conclusion.** [*The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified. [Insert the discussion of results which are close to or outside limits, and the rationale for the choice of tests, the proposed limits and their qualification] The QOS should also include a description of the potential contaminants, which include all adventitiously introduced materials not intended to be part of the manufacturing process (e.g. microbial species, endotoxins) and the control strategy to minimise them.]*

## 2.3.S.4 Control of the DS (name, manufacturer)

## *2.3.S.4.1 Specification (name, manufacturer)*

**The DS standard declared by the company responsible for routine release testing, should be specified**

1. **DS specifications of the DP manufacturer.**

|  |  |  |
| --- | --- | --- |
| Specification reference number and version | |  |
| **Test** | **Acceptance criteria** | **Analytical procedure**  **(Type/Source/Version)** |
| Description |  |  |
| Identity |  |  |
| Impurities |  |  |
| Potency |  |  |
| Quantity |  |  |
| Etc. |  |  |
|  |  |  |

## *2.3.S.4.2 Analytical Procedures (name, manufacturer)*

1. **Summary of the analytical methods referenced in the specification (e.g. key method parameters, conditions, system suitability testing):**

See *2.3.R Regional Information* for the expected summaries of the analytical procedures (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

Summarized tabulated methods and validation may be provided in a separate file <provide reference>.

## *2.3.S.4.3 Validation of Analytical Procedures (name, manufacturer)*

**All analytical methods referenced in the specification should be validated**

1. **Summary of the analytical methods referenced in the specification validation information (e.g. validation parameters and results):**

See *2.3.R Regional Information* for the expected summaries of the validation information (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

Summarized tabulated methods and validation may be provided in a separate file <provide reference>.

## *2.3.S.4.4 Batch Analyses (name, manufacturer)*

**A tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided [***written summary of the batch analyses, the tabulated summary (or graphical representation where appropriate) of results (other than impurities) from in vivo study batches and recent production batches.*

1. **Description of the batches:**

|  |  |  |  |
| --- | --- | --- | --- |
| Batch number | Batch size | Date and  site of production | Use (e.g. non-clinical studies, clinical trials, commercial batches, stability) |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

1. **Summary of batch analyses release results *of the DS manufacturer* for relevant batches (e.g. non-clinical studies, clinical trials, commercial batches, stability):**

| **Test** | **Acceptance**  **Criteria** | **Results** | | |
| --- | --- | --- | --- | --- |
| **<batch x>** | **<batch y>** | **etc.** |
| Description |  |  |  |  |
| Identity |  |  |  |  |
| Impurities |  |  |  |  |
| Potency |  |  |  |  |
| Quantity |  |  |  |  |
| Etc. |  |  |  |  |

1. **Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g. historical analytical procedures):**

## *2.3.S.4.5 Justification of Specification (name, manufacturer)*

1. **A summary of the justification of the specification(s), the analytical procedures, and validation, should be included [***The QOS should include a summary of the rationale used to establish the acceptable range of acceptance criteria established and justified taking into account data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, data from stability studies and relevant development data***]**

## 2.3.S.5 Reference Standards or Materials (name, manufacturer)

1. **Information on the reference standards or reference materials used for testing of the drug substance should be included.** [Insert the *Information regarding the manufacturing process used to establish the reference material. If more than one reference standard has been used during the clinical development, a qualification history should be provided describing how the relationship between the different standards was maintained*].

## 2.3.S.6 Container Closure System (name, manufacturer)

1. **Description of the container closure system(s) for the shipment and storage of the DS (including the identity of materials of construction of each primary packaging component and a brief summary of the specifications):**

|  |  |  |
| --- | --- | --- |
| Packaging component | Materials of construction | Specifications (list parameters e.g. identification (IR)) |
|  |  |  |
|  |  |  |
|  |  |  |

**(b) Other information on the container closure system(s) (e.g. suitability studies):**

## 2.3.S.7 Stability (name, manufacturer)

## *2.3.S.7.1 Stability Summary and Conclusions (name, manufacturer)*

**A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions should be inserted.**

1. **Summary of stress testing (e.g. heat, humidity, oxidation, photolysis, acid/base): and results:**

|  |  |  |
| --- | --- | --- |
| Stress condition | Treatment | Results (e.g. including discussion whether mass balance and peak purity are observed) |
| Light |  |  |
| Heat |  |  |
| Etc. |  |  |

1. **Summary of accelerated and long-term testing parameters (e.g. studies conducted):**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Storage condition  (◦C, % RH) | Batch number | Batch size | Process version | Container closure system | Completed (and proposed) testing intervals |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Summary of the stability results observed for the above accelerated and long-term studies:**

|  |  |
| --- | --- |
| Test (limits) | Results |
| Description |  |
| Impurities |  |
| Potency |  |
| Quantity |  |
| Etc. |  |
|  |  |

1. **Proposed storage statement and shelf-life [***shelf-life of the active substance under the proposed storage conditions should be stated.***]**

|  |  |
| --- | --- |
| Container closure system | Storage statement |
|  |  |
|  |  |

## *2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)*

**Description of the post-approval stability protocol and stability commitment**

1. **Stability protocol for *Primary stability batches* (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Batch number(s) / batch size(s) |  | |
| Tests and acceptance criteria | Description |  |
| Impurities |  |
| Potency |  |
| Quantity |  |
| Etc. |  |
|  |  |
| Testing frequency |  | |
| Container closure system(s) |  | |
|  |  | |

1. **Stability protocol for *Commitment batches* (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Batch number(s) / batch size(s) | *<not less than three production batches>* | |
| Tests and acceptance criteria | Description |  |
| Impurities |  |
| Potency |  |
| Quantity |  |
| Etc. |  |
|  |  |
| Testing frequency |  | |
| Container closure system(s) |  | |
|  |  | |

1. **Stability protocol for *Ongoing batches* (e.g. storage conditions (including tolerances), batch sizes and annual allocation, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Annual allocation | *<at least one production batch per year (unless none is produced that year) in each container closure system >* | |
| Tests and acceptance criteria | Description |  |
| Impurities |  |
| Potency |  |
| Quantity |  |
| etc. |  |
|  |  |
| Testing frequency |  | |
| Container closure system(s) |  | |
|  |  | |

## *2.3.S.7.3 Stability Data (name, manufacturer)*

1. **The actual stability results should be provided in *Module 3*.**
2. **Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g. analytical procedures used only for stability studies):**

## 2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

## 2.3.P.1 Description and Composition of the DP

**The qualitative and quantitative composition of the DP should be stated**

1. **Description of the DP (in signed specifications) [description of accompanying diluents(s), if any should be detailed]:**
2. **Composition of the DP:**
3. **Composition [list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer’s specifications)]:**

| **Component and quality standard (and grade, if applicable)** | **Function** | **Strength (label claim)** | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | |  | |
| **Quant. per unit or per mL** | **%** | **Quant. per unit or per mL** | **%** | **Quantity per unit or per mL** | **%** |
| <complete with appropriate titles e.g. Powder for injection, solution for injections | | | | | | | |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Subtotal 1 |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |

1. **Description of accompanying reconstitution diluent(s), if applicable:**
2. **Type of container closure system used for the DP and accompanying reconstitution diluent, if applicable** [a summary of the type of container and closure*]***:**

## 2.3.P.2 Pharmaceutical Development

## Summary of information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application

## *2.3.P.2.1 Components of the Drug Product*

## *2.3.P.2.1.1 Drug Substance*

1. **Discussion of the:**
2. **Compatibility of the DS with excipients listed in 2.3.P.1:**

## *2.3.P.2.1.2 Excipients*

1. **Discussion of the choice of excipients listed in 2.3.P.1 (e.g. their concentrations, their characteristics that can influence the DP performance, their function and quality grade):**

## *2.3.P.2.2 Drug Product*

## *2.3.P.2.2.1 Formulation Development*

**Information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified**

1. **Discussion of the:**
2. **Formulation development, including justification of any new excipient**
3. **For products requiring additional preparation (e.g. reconstitution, dilution, mixing), compatibility with the used materials (e.g. solvents, diluents) the method of preparation should be summarized:**
4. **Development of the drug product taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed.**
5. **A discussion of the information and data from 3.2.P.2 should be presented [combined summary of the information and data from the completed module 3.2.P.2.1. to 3.2.P.2.6.:**
6. **Summary of the batch numbers and composition of the formulations used in non-clinical and clinical trials, and the batches affected from the completed module 3.2.P.2.2.1.:**

|  |  |  |  |
| --- | --- | --- | --- |
| Batch number(s) of the DP used in | | | |
| **Non - clinical batches** | **<e.g. non clinical batch n..>** | | |
| **Clinical batch** | **<e.g. clinical trial batch n..>** | | |
| **Stability studies (primary batches)** | | | |
| ‹packaging configuration I› |  |  |  |
| ‹ packaging configuration II› |  |  |  |
| *‹Add/delete as many rows as necessary›* |  |  |  |
| **Stability studies (production batches)** | | | |
| ‹ packaging configuration I› |  |  |  |
| ‹ packaging configuration II› |  |  |  |
| *(Add/delete as many rows as necessary)* |  |  |  |
| **Validation studies (primary batches) if available** | | | |
| ‹ packaging configuration I› |  |  |  |
| ‹ packaging configuration II› |  |  |  |
| *(Add/delete as many rows as necessary)* |  |  |  |
| **Validation studies (at least the first three consecutive production batches)**  **or code(s)/version(s) for process validation protocol(s)** |  |  |  |

1. **Summary of formulations and discussion of any differences:**
2. **Add column for clinical batches below**

| **Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)** | **Clinical** | | | **Non-clinical** | | **Stability** | | **Process validation** | | **Commercial (2.3.P.1)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **<Batch nos. and sizes>** | | | **<Batch nos. and sizes>** | | **<Batch nos. and sizes>** | | **<Batch nos. and sizes>** | | **<Batch nos. and sizes>** | |
|  | **Theor.**  **quantity per batch** | | **%** | **Theor.**  **quantity per batch** | **%** | **Theor.**  **quantity per batch** | **%** | **Theor.**  **quantity per batch** | **%** | **Theor.**  **quantity per batch** | **%** |
|  | | <complete with appropriate title e.g. Powder for injection, solution for injection> | | | | | | | | | |
|  |  | | |  |  |  |  |  |  |  |  |
|  |  | | |  |  |  |  |  |  |  |  |
|  |  | | |  |  |  |  |  |  |  |  |
|  |  | | |  |  |  |  |  |  |  |  |
| Total |  | | |  |  |  |  |  |  |  |  |

1. **Description of changes in the manufacturing process including changes in formulation and dosage form compared to previous clinical trials** [*conclusions from the assessment used to evaluate product consistency; A cross-reference to the location of nonclinical and clinical studies provided in other modules of the submission, in which DP batches that were affected by formulation changes had been used*]**:**
2. **Summary of *development studies conducted to establish and validate the dosage form, formulation, and container closure system (including integrity to prevent microbial contamination) and usage instructions*]**

## *2.3.P.2.2.2 Overages*

1. **Justification of overages in the formulation(s) described in 2.3.P.1, if any:**

## *2.3.P.2.2.3 Physicochemical and Biological Properties*

1. **Brief discussion of the parameters relevant to the performance of the FPP (e.g. physicochemical, biological aspects):**

## *2.3.P.2.3 Manufacturing Process Development*

1. **Brief discussion on the development studies conducted to establish the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instructions (e.g. optimization of the process, selection of the method of sterilization):**
2. **Brief discussion on the identification and description of the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality**
3. **Discussion of the differences in the manufacturing process(es) for the batches used in the clinical and non-clinical studies and the process described in 2.3.P.3.3:**

## *2.3.P.2.4 Container Closure System*

1. **Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping) and use of the DP (e.g. choice of materials, protection from moisture and light, compatibility of the materials with the DP):**
2. **For a device accompanying a multi-dose container, a summary of the study results demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume for the lowest intended dose):**

## *2.3.P.2.5 Microbiological Attributes*

1. **Discussion of microbiological attributes of the DP (e.g. preservative effectiveness studies):**

## *2.3.P.2.6 Compatibility*

1. **Discussion of the compatibility of the DP (e.g. with reconstitution diluent(s) or dosage devices, extractables and leachables):**

## 2.3.P.3 Manufacture

## *2.3.P.3.1 Manufacturer(s)*

1. **Name, address and responsibility (e.g. fabrication, packaging, labelling, testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:**

|  |  |
| --- | --- |
| Name and address  (include block(s)/unit(s)) | Responsibility |
|  |  |
|  |  |
|  |  |
|  |  |

1. **Manufacturing authorization, marketing authorization and, where available, WHO-type certificate of GMP (GMP information should be provided in *Module 1*):**

## *2.3.P.3.2 Batch Formula*

Largest intended commercial batch size:

Other intended commercial batch sizes:

<information on all intended commercial batch sizes should be in the QOS-BTP>

1. **List of all components of the DP to be used in the manufacturing process and their amounts on a per batch basis (including individual components of mixtures prepared in-house and overages, if any):**

|  |  |  |  |
| --- | --- | --- | --- |
| Strength (label claim) |  |  |  |
| **Master production document**  **reference number and version** |  |  |  |
| **Proposed commercial batch size(s) (e.g. number of dosage units)** |  |  |  |
| **Component and quality standard**  **(and grade, if applicable)** | **Quantity per batch (e.g. kg/batch)** | **Quantity per batch (e.g. kg/batch)** | **Quantity per batch (e.g. kg/batch)** |
| <complete with appropriate titles e.g. Powder for injection, solution for injection | | | |
|  |  |  |  |
|  |  |  |  |
| Total |  |  |  |

## *2.3.P.3.3 Description of Manufacturing Process and Process Controls*

1. **Flow diagram of the manufacturing process:**
2. **Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:**
3. **Describe and justify any reprocessing during manufacture of the drug product (e.g. filter integrity test failure):**

## *2.3.P.3.4 Controls of Critical Steps and Intermediates*

1. **Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:**

|  |  |
| --- | --- |
| Step  (e.g. compounding, filtration, filling, sealing etc) | Controls (parameters/limits/frequency of testing) |
|  |  |
|  |  |
|  |  |
|  |  |

1. **A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria** [*discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria*]:
2. **Discussion and information on the quality and control of intermediates isolated during the process.**
3. **Proposed/validated holding periods for intermediates (including bulk product):**

## *2.3.P.3.5 Process Validation and/or Evaluation*

1. **Summary of the process validation and/or evaluation studies conducted (including product quality review(s) where relevant) and/or a summary of the proposed process validation protocol for the critical steps or critical assays used in the manufacturing process (e.g. protocol number, parameters, results):**

**Document code(s) for the process validation protocol(s) and/or report(s) (including reference number/version/date):**

## 2.3.P.4 Control of Excipients

## *2.3.P.4.1 Specifications*

1. **Summary of the specifications:**

## *2.3.P.4.2 Analytical Procedures*

1. **Summary of the analytical procedures for supplementary tests:**

## *2.3.P.4.3 Validation of Analytical Procedures*

1. **Summary of the validation information for the analytical procedures for supplementary tests (where applicable):**

## *2.3.P.4.4 Justification of Specifications*

1. **Justification of the specifications (e.g. evolution of tests, analytical procedures and acceptance criteria, exclusion of certain tests, differences from officially recognized compendial standard(s)):**

## *2.3.P.4.5 Excipients of Human or Animal Origin*

1. **For DP using excipients *without* risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:**
2. **CEP(s) demonstrating TSE-compliance can be found in:**

## *2.3.P.4.6 Novel Excipients*

Novel excipients are not accepted in PQTm. See quality guideline for definition.

## 2.3.P.5 Control of DP

## *2.3.P.5.1 Specification(s)*

1. **Specification(s) for the DP:**

|  |  |  |  |
| --- | --- | --- | --- |
| Standard (e.g. Ph.Int., BP, USP, in-house) | | |  |
| **Specification reference number and version** | | |  |
| **Test** | **Acceptance criteria**  **(release)** | **Acceptance criteria**  **(shelf-life)** | **Analytical procedure**  **(type/source/version)** |
| Description |  |  |  |
| Identity |  |  |  |
| Impurities |  |  |  |
| Potency |  |  |  |
| Quantity |  |  |  |
| Etc. |  |  |  |
|  |  |  |  |

## *2.3.P.5.2 Analytical Procedures*

1. **Summary of the analytical procedures (e.g. key method parameters, conditions, system suitability testing):**

*See 2.3.R Regional Information* for summaries of the analytical procedures (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

Summarized tabulated methods and validation may be provided in a separate file <provide reference>.

## *2.3.P.5.3 Validation of Analytical Procedures*

1. **Summary of the validation information (e.g. validation parameters and results):**

*See 2.3.R Regional Information* for summaries of the validation information (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

Summarized tabulated methods and validation may be provided in a separate file <provide reference>.

## *2.3.P.5.4 Batch Analyses*

1. **Description of the batches:**

|  |  |  |  |
| --- | --- | --- | --- |
| Strength and  batch number | Batch size | Date and  site of production | Use (e.g. non-clinical studies, clinical trials, commercial batches, stability) |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

1. **Summary of batch analyses release results for relevant batches (e.g. comparative bioavailability or biowaiver, stability):**

| **Test** | **Acceptance**  **criteria** | **Results** | | |
| --- | --- | --- | --- | --- |
| **<batch x>** | **<batch y>** | **etc.** |
| Description |  |  |  |  |
| Identity |  |  |  |  |
| Impurities |  |  |  |  |
| Potency |  |  |  |  |
| Quantity |  |  |  |  |
| Etc. |  |  |  |  |

1. **Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5.2 and 2.3.P.5.3 (e.g. historical analytical procedures):**

## *2.3.P.5.5 Characterization of Impurities*

1. **Summary of the characterization of impurities:**
2. **Basis for setting the acceptance criteria for impurities:**
3. **Data on observed impurities for relevant batches (e.g. non-clinical, clinical):**

| **Impurities** | **Acceptance**  **criteria** | **Results** | | |
| --- | --- | --- | --- | --- |
| <batch no., strength, use> |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

1. **Justification of proposed acceptance criteria for impurities:**

## *2.3.P.5.6 Justification of Specification(s)*

1. **Justification of the DP specification(s) (e.g. evolution of tests, analytical procedures and acceptance criteria,):**

## 2.3.P.6 Reference Standards or Materials

1. **information on the reference standards or reference materials used for testing of the drug product** [*Information regarding the manufacturing process used to establish the reference material. If more than one reference standard has been used during the clinical development, a qualification history should be provided describing how the relationship between the different standards was maintained*].

## 2.3.P.7 Container Closure System

1. **Description of the container closure systems, including fill size, container size or volume:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Description**  **(including materials of construction)** | **Strength** | **fill size** | **Container size**  **(e.g. 5 ml, 100 ml etc.)** |
|  |  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |  |
|  |  |  |
|  |  |  |

1. **Summary of specifications of each primary and functional secondary packaging components:**

|  |  |
| --- | --- |
| Packaging component | Specifications  (list parameters e.g. identification (IR)) |
| Glass vial |  |
| Rubber stopper |  |
| Aluminium cap |  |
| etc. |  |
|  |  |

1. **Other information on the container closure system(s):**

## 2.3.P.8 Stability

## *2.3.P.8.1 Stability Summary and Conclusions*

1. **Summary of stress testing and results (e.g. photostability studies, cyclic studies, freeze-thaw studies, demonstration of stability-indication of purity/assay method(s)):**
2. **Summary of accelerated and long-term testing parameters (e.g. studies conducted):**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Storage conditions (◦C, % RH) | Strength and batch number | Batch size | Container closure system | Completed (and proposed) test intervals |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

**Summary of additional stability studies, if applicable (with reference to data location)** *<e.g. studies at intermediate conditions, holding period studies for intermediates and bulk product, transport studies, in-use studies>:*

**Summary of the stability results observed for the above accelerated and long-term studies:**

|  |  |
| --- | --- |
| Test | Results |
| Description |  |
| Identity |  |
| Impurities |  |
| Potency |  |
| Quantity |  |
| Etc. |  |

1. **Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):**

|  |  |  |
| --- | --- | --- |
| Container closure system | Storage statement | Shelf-life |
|  |  |  |
|  |  |  |

## *2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment*

1. **Stability protocol for *Primary stability batches* (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Batch number(s) / batch size(s) | *<primary batches>* | |
| Tests and acceptance criteria | Description |  |
| Identity |  |
| Impurities |  |
| Potency |  |
| etc. |  |
|  |  |
| Testing frequency |  | |
| Container closure system(s) |  | |

1. **Stability protocol for *Commitment batches* (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Batch number(s) / batch size(s) | *<not less than three production batches in each container closure system>* | |
| Tests and acceptance criteria | Description |  |
| Identity |  |
| Impurities |  |
| Potency |  |
| Etc. |  |
| Testing Frequency |  | |
| Container Closure System(s) |  | |

1. **Stability protocol for *Ongoing batches* (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):**

| **Parameter** | **Details** | |
| --- | --- | --- |
| Storage condition(s) (◦C, % RH) |  | |
| Batch size(s), annual allocation | *<at least one production batch per year (unless none is produced that year) in each container closure system >* | |
| Tests and acceptance criteria | Description |  |
| Identity |  |
| Impurities |  |
| Potency |  |
| Etc. |  |
| Testing frequency |  | |
| Container closure system(s) |  | |

## *2.3.P.8.3 Stability Data*

1. **The actual stability results should be provided in *Module 3*.**
2. **Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):**
3. **Bracketing and matrixing design and justification for *Commitment* and/or *Ongoing stability batches*, if applicable:**

## 2.3.A APPENDICES

## 2.3.A.1 Facilities and Equipment (name, manufacturer)

**(a) Summary of information on facilities and equipment, in addition to the information provided in other sections of the submission:** Not applicable.

## 2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

**Summary of measures implemented to control endogenous and adventitious agents in production:**

1. **A summary of the measures used to avoid and control non-viral adventitious agents during production**
2. **A summary of the measures used to test, evaluate, and eliminate the potential risks of viral adventitious agents during production**
3. **A summary of the measures used to select, test, evaluate, and eliminate the potential risks of adventitious agents in any materials of animal or human origin that are used**
4. **A brief summary of the virological test(s) conducted during manufacturing, at which step(s) and intermediate(s), and the conclusion of the testing results**
5. **A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results**
6. **The rationale and action plan for assessing viral clearance, the results and evaluation of the viral clearance studies**
7. **Tabulated summary of the reduction factors for viral clearance**
8. **A calculation of the estimated particles /dose, where relevant, should be provided.**

## 2.3.A.3 Excipients

**(a) Summary of the details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:** Not applicable. Novel excipients are not accepted in PQTm. See quality guideline for definition.

## 2.3.R REGIONAL INFORMATION

## 2.3.R.1 Production Documentation

## *2.3.R.1.1 Executed Production Documents*

**(a) List of batches (including strengths) for which executed production documents have been provided (e.g. batch(es) used in the comparability study):**

## *2.3.R.1.2 Master Production Documents*

**(a)** **The blank master production documents for each strength, proposed commercial batch size and manufacturing facility should be provided in *Module 3*.**

**Discussion of differences between the proposed commercial batch size master production documents compared to the biostudy batch records with respect to the formulation (2.3.P.2.2.1 b) (ii)) and the manufacturing process (2.3.P.2.3 b)):**

<include a tabulated discussion for all differences, including processes, equipment (model/make/capacity), settings and operating parameters >

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter (e.g. process, equipment, process parameter) | Comparability study batch(es)  <indicate batch number(s)> | Proposed production batches  <indicate proposed batch size> | Discussion of the relevance of the differences |
| <Main processes and associated equipment (make, model, capacity, settings)> |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

**2.3.R.1.3 Summary of comparability exercise**

## 2.3.R.2 Analytical Procedures and Validation Information

|  |  |  |  |
| --- | --- | --- | --- |
| ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES | | | |
|  | | | |
| **ATTACHMENT NUMBER:** | |  | |
|  | | | |
| **HPLC Method Summary** | | **Volume/Page:** |  |
| **Method name:** |  | | |
| **Method code:** |  | **Version and/or Date:** |  |
| Column(s) / temperature (if other than ambient): | |  | |
| Mobile phase (specify gradient program, if applicable): | |  | |
| Detector (and wavelength, if applicable): | |  | |
| Flow rate: | |  | |
| Injection volume: | |  | |
| Sample solution preparation and concentration  (expressed as mg/ml, let this be termed “A”): | |  | |
| Reference solution preparation and concentration  (expressed as mg/ml and as % of “A”): | |  | |
| System suitability solution concentration  (expressed as mg/ml and as % of “A”): | |  | |
| System suitability tests (tests and acceptance criteria): | |  | |
| Method of quantification (e.g. against API or impurity reference standard(s)): | |  | |
| Other information (specify): | |  | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ATTACHMENT NUMBER: | |  | | | | |
|  | | | | | | |
| **Validation Summary** | | **Volume/Page:** | |  | | |
| **Analytes**: | |  |  | |  |  |
| Typical retention times (RT) | |  |  | |  |  |
| Relative retention times (RTImp./RTAPI or Int. Std.): | |  |  | |  |  |
| Relative response factor (RFImp./RFAPI): | |  |  | |  |  |
| **Specificity:** | |  | | | | |
| **Linearity / Range:** | Number of concentrations:  Range (expressed as % “A”):  Slope:  Y-intercept:  Correlation coefficient (r2) : |  |  | |  |  |
| **Accuracy:** | Conc.(s) (expressed as % “A”):  Number of replicates:  Percent recovery (avg/RSD): |  |  | |  |  |
| **Precision /**  **Repeatability:**  (intra-assay precision) | Conc.(s) (expressed as % “A”):  Number of replicates:  Result (avg/RSD): |  | | | | |
| **Precision /**  **Intermediate Precision:**  (days/analysts/equipment) | Parameter(s) altered:  Result (avg/RSD): |  | | | | |
| **Limit of Detection (LOD):** (expressed as % “A”) | |  | | | | |
| **Limit of Quantitation (LOQ):** (expressed as % “A”) | |  | | | | |
| **Robustness:** | Stability of solutions:  Other variables/effects: |  | | | | |
| **Typical chromatograms or spectra may be found in:** | |  | | | | |
| **Company(s) responsible for method validation:** | |  | | | | |
| **Other information (specify):** | |  | | | | |

1. *Please note that the contact listed in this form will be the primary contact for email and mail communication for this specific application.* [↑](#footnote-ref-1)