MODULE 2.3

QUALITY OVERALL SUMMARY: PRODUCT DOSSIER (QOS-PD)

1. **Summary of product information:**

|  |  |
| --- | --- |
| **Non-proprietary name of the finished pharmaceutical product (FPP)** |  |
| **Proprietary name of the finished pharmaceutical product (FPP)** |  |
| **International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)** |  |
| **Applicant name and address**  |  |
| **Dosage form** |  |
| **Application Number(s)** |  |  |  |
| **Strength(s)** |  |  |  |
| **Route of administration** |  |
| **Proposed indication(s)** |  |
| **Contact information** | Name:Phone:Fax:Email:  |

1. **Other Introductory information:**

**Related dossiers (e.g. FPP(s) with the same API(s) submitted to the MRA by the applicant):**

|  |  |  |  |
| --- | --- | --- | --- |
| **Registration Number (e.g. BOT14000XX)** | **Registered (Y/N)** | **API, strength, dosage form**(eg. Abacavir (as sulphate) 300 mg tablets) | **API manufacturer**(including address) |
|  |  |  |  |
|  |  |  |  |

**Identify available literature references for the API and FPP:**

|  |  |  |
| --- | --- | --- |
| **Publication(s)** | **Most recent edition/volume****in which API/FPP appears** | **Most recent edition/volume****consulted** |
| **API status in pharmacopoeia and forum:** |
| Ph.Int. |  |  |
| Ph.Int. monographdevelopment (through www.who.int) | <e.g. monograph under development or draft/final published> |  |
| USP |  |  |
| PharmacopeialForum |  |  |
| Ph.Eur. |  |  |
| Pharmeuropa |  |  |
| BP |  |  |
| Other (e.g. JP) |  |  |
| **FPP status in pharmacopoeia and forum:** |
| Ph.Int. |  |  |
| Ph.Intmonographdevelopment (through www.who.int) | <e.g. monograph under development or draft/final published> |  |
| USP |  |  |
| PharmacopeialForum |  |  |
| BP |  |  |
| Other (e.g. JP) |  |  |
| **Other reference texts (e.g. public access reports):** |
|  |  |  |

|  |
| --- |
| **SUMMARY OF QUALITY ASSESSMENT OF LABELLING AND SAMPLES** ***(MRA 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. FPP, device)**<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 API information:**

|  |  |
| --- | --- |
| **Name of API:** |  |
| **Name of API manufacturer:** |  |
| □  | Confirmation of API Prequalification document |
| □ | Certificate of suitability to the European Pharmacopoeia (CEP) |
| □  | Full details in the PD |

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

Information from 3.2.S.1 should be included.

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

1. (Recommended) International Non-proprietary name (INN):
2. Compendial name, if relevant:
3. Chemical name(s):
4. Company or laboratory code:
5. Other non-proprietary name(s) (e.g. national name, USAN, BAN):
6. Chemical Abstracts Service (CAS) registry number:

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

1. Structural formula, including relative and absolute stereochemistry:
2. Molecular formula:
3. Relative molecular mass:

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

1. Physical description (e.g. appearance, colour, physical state):
2. Solubilities:

In common solvents:

 Quantitative aqueous pH solubility profile (pH 1 to 6.8):

|  |  |
| --- | --- |
| **Medium (e.g. pH 4.5 buffer)** | **Solubility (mg/ml)** |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

 Dose/solubility volume calculation:

1. **Physical form (e.g. polymorphic form(s), solvate, hydrate):**

 Polymorphic form:

 Solvate:

 Hydrate:

1. **Other:**

|  |  |
| --- | --- |
| **Property** |  |
| pH |  |
| pKa |  |
| Partition coefficients |  |
| Melting/boiling points |  |
| Specific optical rotation (specify solvent) |  |
| Refractive index (liquids) |  |
| Hygroscopicity |  |
| UV absorptionmaxima/molar absorptivity |  |
| Other |  |

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

Information from 3.2.S.2 should be included:

* Information on the 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 and address****(includingblock(s)/unit(s))** | **Responsibility**  | **CEP number (if applicable)** |
|  |  |  |
|  |  |  |
|  |  |  |

1. Manufacturing authorization for the production of API(s) and certificate of GMP compliance (GMP information should be provided in Module 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;
* *A flow diagram, as provided in 3.2.S.2.2;*

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

 (a) Flow diagram of the synthesis process(es):

 (b) Brief narrative description of the manufacturing process(es):

 (c) Alternate processes and explanation of their use:

 (d) Reprocessing steps and justification:

* A description of the Source and Starting Material and raw materials of biologicalorigin used in the manufacture of the drug substance, as described in 3.2.S.2.3;

***2.3.S.2.3 Control of Materials (name, manufacturer) – Option 3 only***

 **(a)** Summary of the quality and controls of the starting materials used in the manufacture of the API:

| **Step/starting material** | **Test(s)/method(s)** | **Acceptance criteria** |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

 (b) Name and manufacturing site address of starting material manufacturer(s):

 (c) Where the API(s) and the starting materials and reagents used to manufacture the API(s) are *without* risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

* A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;

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

 (a) Summary of the controls performed at critical steps of the manufacturing process and on intermediates:

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

* A description of process validation and/or evaluation, as described in 3.2.S.2.5.

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

 (a) Description of process validation and/or evaluation studies (e.g. for aseptic processing and sterilization):

* A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

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

 (a) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, stability, scale-up, pilot and, if available, production scale batches:

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

**For NCE:** A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

**For Biotech:** 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), as described in 3.2.S.3.1, should be included.

**For NCE and Biotech:** 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. A tabulated summary of the data provided in

3.2.S.3.2, with graphical representation, where appropriate should be included.

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

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

 (a) List of studies performed (e.g. IR, UV, NMR, MS, elemental analysis) and conclusion from the studies (e.g. whether results support the proposed structure):

 (b) Discussion on the potential for isomerism and identification of stereochemistry (e.g. geometric isomerism, number of chiral centres and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:

 (c) Summary of studies performed to identify potential polymorphic forms (including solvates):

 (d) Summary of studies performed to identify the particle size distribution of the API:

 (e) Other characteristics:

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

1. Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:
2. List of API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure and origin:

| **API-related impurity (chemical name or descriptor)** | **Structure** | **Origin** |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

 (ii) List of process-related impurities (e.g. residual solvents, reagents), including compound names and step used in synthesis:

| **Process-related impurity (compound name)** | **Step used in synthesis** |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

 **(b) Basis for setting the acceptance criteria for impurities:**

 **(i)** Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding to ICH Reporting/Identification/Qualification Thresholds for the API-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

| **Maximum daily dose for the API:** | **<x mg/day>** |
| --- | --- |
| **Test** | **Parameter** | **ICH threshold or concentration limit** |
| API-related impurities | Reporting Threshold |  |
| Identification Threshold |  |
| Qualification Threshold |  |
| Process-related impurities | <solvent 1> |  |
| <solvent 2>, etc. |  |
|  |  |

 (ii) Data on observed impurities for relevant batches (e.g. comparative bioavailability or biowaiver, stability batches):

| **Impurity****(API-related and process-related)** | **Acceptance****Criteria** | **Results (include batch number\* and use\*\*)** |
| --- | --- | --- |
|  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

\* include strength, if reporting impurity levels found in the FPP (e.g. for comparative studies)

\*\* e.g. comparative bioavailability or biowaiver studies, stability

 (iii) Justification of proposed acceptance criteria for impurities:

**2.3.S.4 Control of Drug Substance (name, manufacturer)**

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

**2.3.S.4 Control of the API (name, manufacturer)**

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

1. **API specifications *of the FPP manufacturer*:**

| **Standard (e.g. Ph.Int.,Ph.Eur., BP, USP, House)** |  |
| --- | --- |
| **Specification reference number and version** |  |
| **Test** | **Acceptance criteria** | **Analytical procedure****(Type/Source/Version)** |
| Description |  |  |
| Identification |  |  |
| Impurities |  |  |
| Assay |  |  |
| etc. |  |  |
|  |  |  |
|  |  |  |

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

 **(a) 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 and validation information (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

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

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

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

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

 **(a) Description of the batches:**

| **Batch number** | **Batch size** | **Date and****site of production** | **Use (e.g. comparative bioavailability or biowaiver, stability)** |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

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

| **Test** | **Acceptance****Criteria** | **Results** |
| --- | --- | --- |
| **<batch x>** | **<batch y>** | **etc.** |
| Description |  |  |  |  |
| Identification |  |  |  |  |
| Impurities |  |  |  |  |
| Assay |  |  |  |  |
| etc. |  |  |  |  |
|  |  |  |  |  |

 **(c)** 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)***

 **(a)** Justification of the API specification (e.g. evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

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

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

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

 (a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int.,Ph.Eur., BP, USP, in-house):

1. Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis):
2. Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard) :

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

A brief description and discussion of the information, from 3.2.S.6 should be included.

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

1. Description of the container closure system(s) for the shipment and storage of the API (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)**

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

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

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

 **(a) 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 is observed)** |
| --- | --- | --- |
| Heat |  |  |
| Humidity |  |  |
| Oxidation |  |  |
| Photolysis |  |  |
| Acid |  |  |
| Base |  |  |
| Other |  |  |
|  |  |  |

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

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

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

| **Test** | **Results** |
| --- | --- |
| Description |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| etc. |  |
|  |  |

 **(c) Proposed storage statement and re-test period (or shelf-life, as appropriate):**

|  |  |  |
| --- | --- | --- |
| **Container closure system** | **Storage statement** | **Re-test period\*** |
|  |  |  |
|  |  |  |

\* indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

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

 (a) 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 |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| etc. |  |
|  |  |
| Testing frequency |  |
| Container closure system(s) |  |
|  |  |

 (b) 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 |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| etc. |  |
|  |  |
| Testing frequency |  |
| Container closure system(s) |  |
|  |  |

 (c) 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 |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| etc. |  |
|  |  |
| Testing frequency |  |
| Container closure system(s) |  |
|  |  |

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

 (a) The actual stability results should be provided in *Module 3*.

 (b) 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 Drug Product (name, dosage form)**

Information from 3.2.P.1 should be provided. Composition from 3.2.P.1 should be provided.

**2.3.P.1 Description and Composition of the FPP**

 (a) Description of the FPP:

 (b) Composition of the FPP:

 (i) Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

| **Component and quality standard (and grade, if applicable)** | **Function** | **Strength (label claim)** |
| --- | --- | --- |
|  |  |  |
| **Quant. per unit** | **%** | **Quant. per unit** | **%** | **Quantity per unit** | **%** |
| <complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection> |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Subtotal 1 |  |  |  |  |  |  |  |
| <complete with appropriate title e.g. Film-coating> |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Subtotal 2 |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |

 (ii) Composition of all *components purchased as mixtures* (e.g. colourants, coatings, capsule shells, imprinting inks):

 (c) Description of accompanying reconstitution diluent(s), if applicable:

1. Type of container closure system used for the FPP and accompanying reconstitution diluent, if applicable:
2. ***2.3.P.4.5 Excipients of Human or Animal Origin***

 (a) For FPPs using excipients *without* risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

**2.3.P.2 Pharmaceutical Development (name, dosage form)**

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

**2.3.P.2 Pharmaceutical Development**

***2.3.P.2.1 Components of the FPP***

 ***2.3.P.2.1.1 Active Pharmaceutical Ingredient***

 (a) Discussion of the:

 (i) compatibility of the API(s) with excipients listed in 2.3.P.1:

 (ii) key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API(s) that can influence the performance of the FPP:

 (iii) for fixed-dose combinations, compatibility of APIs with each other:

 ***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 FPP performance):

***2.3.P.2.2 Finished Pharmaceutical Product***

***2.3.P.2.2.1 Formulation Development***

 (a) Summary describing the development of the FPP (e.g. route of administration, usage, optimization of the formulation, etc.):

 (b) Summary of results for comparative *in vitro* studies (e.g. dissolution):

 ***2.3.P.2.2.2 Overages***

 (a) Justification of overages in the formulation(s) described in 2.3.P.1:

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

 (a) Discussion of the development of the manufacturing process of the FPP (e.g. optimization of the process, selection of the method of sterilization):

 (b) Discussion of the differences in the manufacturing process(es) for the batches used in the comparative bioavailability or biowaiver studies and the process described in 2.3.P.3.3:

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

 (a) 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 FPP (e.g. choice of materials, protection from moisture and light, compatibility of the materials with the FPP):

1. 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):

**2.3.P.3 Manufacture**

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

 (a) 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** |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |

 (b) Manufacturing authorization, marketing authorization and, where available, WHO-type certificate of GMP:

***2.3.P.3.2 Batch Formula***

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

| **Strength (label claim)** |  |  |  |
| --- | --- | --- | --- |
| **Master production document****reference number and/or 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 title e.g. Core tablet, Contents of capsule, Powder for injection> |
|  |  |  |  |
|  |  |  |  |
| Subtotal 1 |  |  |  |
| <complete with appropriate title e.g. Film-coating> |
|  |  |  |  |
|  |  |  |  |
| Subtotal 2 |  |  |  |
| Total |  |  |  |

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

 (a) Flow diagram of the manufacturing process:

 (b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

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

 (a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

| **Step****(e.g. granulation, compression, coating)** | **Controls** |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |

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

 (a) 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):

**2.3.P.5 Control of FPP**

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

 (a) Specification(s) for the FPP:

| **Standard (e.g. Ph.Int., BP, USP, House)** |  |
| --- | --- |
| **Specification reference number and version** |  |
| **Test** | **Acceptance criteria****(release)** | **Acceptance criteria****(shelf-life)** | **Analytical procedure****(type/source/version)** |
| Description |  |  |  |
| Identification |  |  |  |
| Impurities |  |  |  |
| Assay |  |  |  |
| etc. |  |  |  |
|  |  |  |  |
|  |  |  |  |

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

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

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

**2.3.P.7 Container Closure System**

 **(a)** Description of the container closure systems, including unit count or fill size, container size or volume:

|  |  |  |  |
| --- | --- | --- | --- |
| **Description****(including materials of construction)** | **Strength** | **Unit count or fill size** | **Container size** |
|  |  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |  |
|  |  |  |
|  |  |  |

 **(b)** Summary of specifications of each primary and functional secondary (e.g. foil pouches) packaging components:

|  |  |
| --- | --- |
| **Packaging component** | **Specifications** **(list parameters e.g. identification (IR))** |
| HDPE bottle |  |
| PP cap |  |
| Induction sealed liners |  |
| Blister films (PVC, etc) |  |
| Aluminum foil backing |  |
| etc. |  |
|  |  |

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

**2.3.P.8 Stability (name, dosage form)**

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in- use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included. The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

**2.3.P.8 Stability**

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

 (a) Summary of stress testing and results (e.g. photostability studies, cyclic studies, freeze-thaw studies):

 (b) 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 the stability results observed for the above accelerated and long-term studies:

| **Test** | **Results** |
| --- | --- |
| Description |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| etc. |  |
|  |  |

 (c) 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.R.1 Production Documentation**

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

 (a) List of batches (including strengths) for which executed production documents have been provided (e.g. comparative bioavailability or biowaiver batches):

***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*.

**3.2.R.3 Bioequivalence trial information form (BTIF)**

3.2.R.3.1 A completed BTIF should be submitted both in hard copy and electronic (word format)

3.2.R.3.2 Biowaiver requests in relation to conducting comparative bioavailability study

A completed Biowaiver Application Form should be submitted both in hard copy and electronic (word format)

Requirements for biopharmaceutic studies are described in the Botswana Bioavailability/Bioequivalence Guideline. [3]

Notes to the Assessor

BIOEQUIVALENCE ASSESSMENT

Copy filled BTIF / Biowaiver-BCS Application Form / Biowaiver-Additional Strength Form here and assess it here

Points to be communicated to the Manufacturer

Please copy all relevant observation and information to be communicated to the manufacturer in the corresponding letter and save it accordingly

Active Pharmaceutical Ingredient(s) (Inn)

Finished Pharmaceutical Product (Inn .mg pharmaceutical form)

bioequivalence / biowaiver-BCS / biowaiver-additional strength

Overall recommendation

Please fill in the relevant recommendation (registration/rejection), based on the review of the data on quality and bioequivalence.

The dossier can be proposed for registration only, if minor issues are pending.

Outstanding commitments

Please list the outstanding commitments, which should be answered before the product can be listed on the registration list.

Recommendations for inspection

|  |  |
| --- | --- |
| **Evaluator:** | **Date:** |
| **Reviewer:** | **Date:** |