# SUMMARY OF CRITICAL REGULATORY ELEMENTS (SCoRE)

## ADMINISTRATIVE INFORMATION OF THE PRODUCT

|  |  |  |
| --- | --- | --- |
| Applicant (company) |  | |
| Application number | Master | Duplicate |
|  |  |
| Product (proprietary) name | Master | Duplicate |
|  |  |
| Approved name (INN or INNM) |  | |
| Pharmaceutical form & Strength |  | |
| Date of initial application |  | |
| Date of current submission  (SCoRE amendment) |  | |
| FPP manufacturer(s) used for developmental batches (name, address) |  | |
| FPP manufacturer(s) applied for (name, address) |  | |
| API manufacturer(s) used for developmental batches (name, address) |  | |
| API manufacturer(s) applied for (name, address) |  | |

### General:

* The Summary of Critical Regulatory Elements (SCoRE), is required for all new registration and variation applications, to facilitate evaluation by SAHPRA, and should be submitted with applications at the time of submission
* When updating a SCoRE for a variation, any changes should be marked in track changes, however, the document submitted to SAHPRA must be highlighted in yellow. Information should be included for all strengths. The following is applicable:
* For variations to applications registered with a SCoRE, the complete SCoRE should be submitted
* For variations to applications registered without a SCoRE, a partial SCoRE: (completing only the relevant sections affected by the change), should be submitted
* Please note that the SCoRE does not replace the Quality Overall Summary (QOS), nor does it replace the requirements outlined in the relevant guidelines
* The PDF version of the document should be included in Module 3.2.R.8 (Other) of the CTD submission
* An additional MS Word text version (i.e. editable) of SCoRE should be included in the working documents folder
* Font used in the main text must be Arial, size 11. Tables may be Arial size 10.
* As per revised SAHPRA APIMF[[1]](#footnote-1) Procedure, if information is in the closed part of the APIMF, reference to the closed part should be made (where applicable) with the understanding that the API manufacturer submits the closed part directly to SAHPRA
* Please delete all light grey text in square brackets ([ ]) (guides and examples) when submitting the SCoRE
* Do not change or delete the titles and the numbering (add “Not applicable” if necessary)
* Add additional rows to tables where required
* Please duplicate Module 3.2.S and Module 3.2.P for multiple API and FPP in the product
* Please note that hyperlinking or referencing sections of the dossier is **not acceptable**; information should be summarised in the SCoRE

## SCoRE AMENDMENT HISTORY

The SCoRE version should start with V001 for the first submission. Each resubmission of the SCoRE should incrementally increase the version by 1 (i.e. V002 for the second version, or first resubmission of an amended SCoRE). This version number should be included in the footer of the document, as well as the document name.

The ‘reason for update’ should reference key amended sections by their number in order to aid the evaluator.

An example has been included in grey text and italicised below – please delete this text before submitting the SCoRE to SAHPRA.

|  |  |  |  |
| --- | --- | --- | --- |
| **Date** | **Pre-registration/ post-registration** | **Reason for update** | **Version** |
| *[2019/01/01]* | *[Pre-registration]* | *[Initial submission]* | *[V001]* |
| *[2019/01/31]* | *[Pre-registration]* | *[Module 3.2.P.5 (Section 2.5.9 of SCoRE) updated in response to recommendation from P&A committee on 2019/01/15]* | *[V002]* |
| *[2019/03/25]* | *[Post-registration]* | *[Variation Type II (Description)]* | *[V003]* |
| *[2020/07/30]* | *[General]* | *[Removal of duplicated sections and examples, inclusion of headings as guidance]* | *[V004]* |
|  |  |  |  |

*[Please add additional rows as required]*

## TABLE OF CONTENTS

[SUMMARY OF CRITICAL REGULATORY ELEMENTS (SCoRE) 1](#_Toc87978457)

[ADMINISTRATIVE INFORMATION OF THE PRODUCT 1](#_Toc87978458)

[General: 2](#_Toc87978459)

[SCoRE AMENDMENT HISTORY 3](#_Toc87978460)

[TABLE OF CONTENTS 4](#_Toc87978461)

[LIST OF ABBREVIATIONS 5](#_Toc87978462)

[FOREIGN REGISTRATION / COLLABORATIVE PROCEDURE 6](#_Toc87978463)

[MODULE 1 6](#_Toc87978464)

[Module 1.7 Good manufacturing practice 6](#_Toc87978465)

[MODULE 3: QUALITY 7](#_Toc87978466)

[3.2.S Active Pharmaceutical Ingredient *(name, manufacturer)* 7](#_Toc87978467)

[3.2.S.1 General Information (name, manufacturer) 8](#_Toc87978468)

[3.2.S.2 Manufacture(s) (name, manufacturer) 9](#_Toc87978469)

[3.2.S.3 Characterisation (name, manufacturer) 10](#_Toc87978470)

[3.2.S.4 Control of the API (name, manufacturer) 10](#_Toc87978471)

[3.2.S.5 Reference standard (name, manufacturer) 12](#_Toc87978472)

[3.2.S.6 Container closure system (name, manufacturer) 12](#_Toc87978473)

[3.2.S.7 Stability (name, manufacturer) 12](#_Toc87978474)

[3.2.P Finished Pharmaceutical Product (FPP) (name, dosage form) 13](#_Toc87978475)

[3.2.P.1 Description and Composition of the pharmaceutical product (name, dosage form) 13](#_Toc87978476)

[3.2.P.2 Pharmaceutical Development (name, dosage form) 13](#_Toc87978477)

[3.2.P.3 Manufacture (name, dosage form) (refer to table 1.7-2) 15](#_Toc87978478)

[3.2.P.5 Control of pharmaceutical product (name, dosage form) 16](#_Toc87978479)

[3.2.P.6 Reference standards or materials (name, dosage form) 17](#_Toc87978480)

[3.2.P.7 Container closure system (name, dosage form) 18](#_Toc87978481)

[3.2.P.8 Stability (name, dosage form) 18](#_Toc87978482)

[3.2.R.1 PHARMACEUTICAL AND BIOLOGICAL AVAILABILITY AND MODULE 5 19](#_Toc87978483)

[Biostudies for generics 19](#_Toc87978484)

[Bioequivalence for the X mg tablets 20](#_Toc87978485)

[Biowaiver for the Y mg tablets: 20](#_Toc87978486)

[Signed Attestation 21](#_Toc87978487)

[UPDATE HISTORY 22](#_Toc87978488)

## LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| API | Active Pharmaceutical Ingredient |
| APIMF | Active Pharmaceutical Ingredient Master File |
| ASMF | Active Substance Master File |
| BCS | Biopharmaceuticals Classification System |
| BP | British Pharmacopoeia |
| CAS | Chemical Abstracts Service |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| cGMP | Current Good Manufacturing Practices |
| CMC | Chemistry, Manufacture and Control |
| CoA | Certificate of Analysis |
| CPQ | Confirmation of WHO API Prequalification |
| CRO | Contract Research Organisation |
| CTD | Common Technical Document |
| DMF | Drug Master File |
| DSMF | Drug Substance Master File |
| eCTD | Electronic Common Technical Document |
| EMA | European Medicines Agency |
| EU | European Union |
| FPP | Finished Pharmaceutical Product |
| GCP | Good Clinical Practices |
| GMP | Good Manufacturing Practice |
| HCR | Holder of Certificate of Registration |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| INN | International Non-proprietary Name |
| INNM | International Non-proprietary Name Modified |
| MHRA | Medicines and Healthcare products Regulatory Agency (UK) |
| MRP | Mutual Recognition Procedure |
| PD | Product Dossier |
| Ph. Eur | European Pharmacopoeia |
| Ph.Int | International Pharmacopoeia |
| PQ | Pre-qualification |
| PSD | Particle size distribution |
| QOS | Quality Overall Summary |
| RM | Regulatory Manager |
| RP | Responsible Pharmacist |
| RRA | Recognised Regulatory Authority |
| RSA | Republic of South Africa |
| SADC | Southern African Development Community |
| SAHPRA | South African Health Products Regulatory Authority |
| SCoRE | Summary of Critical Regulatory Elements |
| TGA | Therapeutic Goods Administration (Australia) |
| US FDA | United States of America Food and Drug Administration |
| USP | United States Pharmacopeia |

[Please include additional abbreviations if you use them in your SCoRE submission.]

## FOREIGN REGISTRATION / COLLABORATIVE PROCEDURE

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of Recognised Regulatory Authority (RRA)[[2]](#footnote-2)** | **Date of registration** | **Unredacted/Redacted assessment reports?** | **Letter of access?**[[3]](#footnote-3) |
| {Name of RRA 1} | {YYYY.MM.DD} | <Y/N/Not applicable> | <Y/N/Not applicable> |
|  |  |  |  |
|  |  |  |  |

[Add/delete additional rows as required]

# MODULE 1

### Module 1.7 Good manufacturing practice

Table 1.7-1: API manufacturer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Name of API** | **ASMF/DMF/CEP/CPQ no. and open part version** | **ASMF/DMF/CEP/CPQ holder name and address** | **Manufacturer name and address (include specific  unit / block)** | **GMP** | | |
| **Date of last inspection** | **Authority** | **cGMP status** |
| {API1} |  | {Supplier1} |  | {YYYY.MM.DD} |  |  |
| {API1} |  | {Supplier2} |  | {YYYY.MM.DD} |  |  |
| {API2} |  | {Supplier1} |  | {YYYY.MM.DD} |  |  |

[Repeat rows if necessary, for multiple APIs or API manufacturers/manufacturing sites.]

Table 1.7-2: FPP manufacturer / packer / FPRC

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site (name and full address including units/blocks/plots)** | **Functions performed  at site** | **GMP** | | |
| **Date of last inspection** | **Authority** | **cGMP status** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

# MODULE 3: QUALITY

[Please repeat Section 2.1 (3.2.S Drug substance) for each additional API **and** API source]

## 3.2.S Active Pharmaceutical Ingredient *(name, manufacturer)*

[Indicate which option applies for the submission of API information; please check one only]

Table 3.2.S-1: API information

|  |  |  |
| --- | --- | --- |
| **Name of API:** | |  |
| **Name of API manufacturer:** | |  |
|  | 1. Confirmation of API WHO prequalification document | |
|  | 2. Certificate of suitability to the European Pharmacopoeia (CEP) | |
|  | 3. Active pharmaceutical ingredient master file (APIMF[[4]](#footnote-4)) procedure:  APIMF number assigned by SAHPRA (if known): \_\_\_\_\_\_\_; version number(s) including amendments (and/or date(s)) of the open part: \_\_\_\_\_\_\_; version number(s) including amendments (and/or date(s)) of the restricted part: \_\_\_\_\_\_\_. | |
|  | 4. Full details in the PD (open part of the APIMF)  Document version number/identifier of current Module 3.2.S (when applicable): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |

Table 3.2.S-2: Compliance with monograph/pharmacopoeia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference monograph/pharmacopoeia** |  | | | | | |
| **Comply with monograph/pharmacopoeia** | **Yes** |  | **Yes, with deviations[[5]](#footnote-5)** |  | **No** |  |
| **List deviations if relevant** |  | | | | | |

### 3.2.S.1 General Information (*name, manufacturer*)

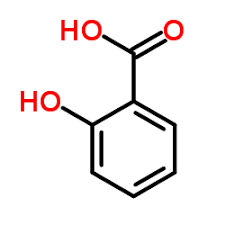
#### 3.2.S.1.1 Nomenclature (name, manufacturer)

Table 3.2.S.1.1-1: General information

|  |  |
| --- | --- |
| **International non-proprietary name (INN or INNM):** |  |
| **Chemical names:** |  |
| **Other name:** |  |
| **Chemical Abstracts Service (CAS) registry number:** |  |
| **Laboratory code:** |  |
| **Molecular formula:** |  |
| **Relative molecular mass:** |  |

#### 3.2.S.1.2 Structural formula (*name, manufacturer*)

**[Example**

Molecular formula: CxHxOx]

#### 3.2.S.1.3 General properties (*name, manufacturer*)

Table 3.2.S.1.3-1: Summary of properties

|  |  |
| --- | --- |
| **Property** |  |
| **Physical characteristics:** |  |
| **pKa-value(s):** |  |
| **Partition coefficient:** |  |
| **Hygroscopicity:** |  |
| **Stereochemistry:** |  |
| **Polymorphism** |  |
| **Particle size distribution (PSD)** |  |
| **Refractive index (liquids):** |  |

Table 3.2.S.1.3-2: Solubility in aqueous medium at 37 °C (required for all APIs)

|  |  |  |
| --- | --- | --- |
| **pH (buffered)** | **Solubility (mg/ml)** | **Dose/solubility volume** |
| 1,2 |  |  |
| 4,5 |  |  |
| 6,8 |  |  |
| Other (provide pH) |  |  |

For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

\* corresponding to the lowest solubility determined over the physiological pH range (pH 1,2 to 6,8) and temperature (37 ± 0,5 °C).

e.g. highest dose = 500 mg, solubility (at 37 °C and pH 4,5) = 31,2 mg/ml

16,03 ml < 250 ml, therefore the substance is highly soluble at pH 4,5

### 3.2.S.2 Manufacture(s) (name, manufacturer)

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

Table 3.2.S.2-1: Manufacturer information

|  |  |  |  |
| --- | --- | --- | --- |
| **Name and address (including block(s)/plot number/unit(s))** | **Responsibility** | **API-PQ number /APIMF/CEP number** | **Letter of access provided?[[6]](#footnote-6) (Applicable to CEP & CPQ)** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

#### 3.2.S.2.2 Description of manufacturing process and process controls (*name, manufacturer*)

1. Flow diagram of the synthesis process(es):
2. Brief narrative description of the manufacturing process(es):
3. Alternate processes and explanation of their use:
4. Reprocessing steps and justification:

[Where a CEP, CPQ or APIMF procedure is followed, this section may not be applicable – simply stipulate CEP, CPQ or APIMF procedure, as relevant.]

#### 3.2.S.2.3 Control of materials (*name, manufacturer*) – for API option 4 only (full details of the API, please see *Table 3.2.S-1*)

1. Name of starting material(s) and/or intermediates:
2. Name and manufacturing site address of starting material and intermediate manufacturer(s):

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

#### 3.2.S.3.1 Elucidation of structure and other Characteristics (name, manufacturer)

1. List of studies performed (e.g. IR, UV, NMR, MS, elemental analysis, X-ray) and conclusion from the studies (e.g. whether results support the proposed structure):
2. Summary of studies performed to identify potential polymorphic forms (including solvates): <including identification of and data on the API lot used in bioavailability studies> (if applicable)
3. Summary of studies performed to identify the particle size distribution of the API (if PSD is critical): <including identification of and data on the API lot used in bioavailability studies> for all APIs
4. Other characteristics:

[Where a CEP, CPQ or APIMF procedure is followed, this section may not be applicable – simply stipulate CEP, CPQ or APIMF procedure, as relevant.]

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

Table 3.2.S.3.2-1: Impurities (potential and actual) and residual solvents

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of impurity (API-synthesis related and/or degradation products)** | **Structure** | **Origin** | **Acceptance Criteria** |
|  |  |  |  |
|  |  |  |  |
| **Name of solvent** |  |  |  |
|  |  |  |  |
|  |  |  |  |

[Please indicate as per CEP submitted.]

### 3.2.S.4 Control of the API (name, manufacturer)

#### 3.2.S.4.1 Specifications (name, manufacturer)

1. API specifications of the FPP manufacturer:

Table 3.2.S.4.1-1: Summary of specifications

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

[List any additional tests by the FPP manufacturer in the table above.]

1. API specifications of the API manufacturer:

Table 3.2.S.4.1-2: Summary of specifications

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

[List any additional tests by the API manufacturer in the table above.]

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

Table 3.2.S.4.3-1: Validation of analytical procedures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Validation Parameter** | **Analytical Procedure** | | | |
| **Assay** | **Impurities** | **Residual Solvents** | **Other** |
| Method Type: | [HPLC] | [HPLC] | [GC] |  |
| Method Number: | [*No. X*] | [*No. Y*] | [*No. Z*] |  |
| Accuracy |  |  |  |  |
| Precision: |  |  |  |  |
| Repeatability |  |  |  |  |
| Intermediate precision |  |  |  |  |
| Specificity |  |  |  |  |
| Detection limit (specify) |  |  |  |  |
| Quantitation limit (specify) |  |  |  |  |
| Linearity |  |  |  |  |
| Range (specify) |  |  |  |  |
| Robustness |  |  |  |  |
| Solution stability |  |  |  |  |
| + indicates that the parameter is acceptably tested and validated  - indicates that the parameter is not tested  ? indicates that questions remain before the parameter is judged to be acceptable | | | | |

[Add any additional columns as needed for other validated API analytical procedures in the table above.]

#### 3.2.S.4.4 Batch analyses (*name, manufacturer*)

Table 3.2.S.4.4-1: Batch analyses information

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Specification** | **Results** | |
| **Batch no:** | **Batch No:** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

[Add any additional columns as needed for batch analyses data if more than two API batches are available in the table above.]

### 3.2.S.5 Reference standard (*name, manufacturer*)

1. If a pharmacopoeial monograph is claimed, the pharmacopoeial standard should be used. Include the lot number of the reference standard used.
2. State if a certificate of analysis and overlaid IR spectra have been submitted.
3. State if a secondary reference standard (e.g. working standard) is standardized against the compendial reference standard or primary reference standard.
4. The source(s) of the reference standards or materials (e.g., in-house, Ph. Eur., USP) used in the testing of the drug substance (e.g., for the identification, purity, potency tests). If a Ph. Eur. reference standard is used for quantitative analysis, the reference standard should be for content (not for identity only).

### 3.2.S.6 Container closure system (*name, manufacturer*)

Table 3.2.S.6-1: Description of the container closure system(s) for the storage and shipment of the API:

|  |  |
| --- | --- |
| **Packaging component** | **Specifications**  **(e.g. identification (IR))** |
|  |  |
|  |  |

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

#### 3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

1. Proposed storage conditions and re-test period (or shelf-life, as appropriate):

Table 3.2.S.7.1-1: Storage information

|  |  |  |
| --- | --- | --- |
| **Container closure system** | **Storage statement** | **Re-test period[[7]](#footnote-7)** |
|  |  |  |
|  |  |  |

## 3.2.P Finished Pharmaceutical Product (FPP) (name, dosage form)

Table 3.2.P-1: Compliance with monograph/pharmacopoeia (if applicable)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference monograph/pharmacopoeia** |  | | | | | |
| **Comply with monograph/pharmacopoeia** | **Yes** |  | **Yes, with deviations[[8]](#footnote-8)** |  | **No** |  |

### 3.2.P.1 Description and Composition of the pharmaceutical product (*name, dosage form*)

A brief description of the final product

1. Description of the FPP (in signed specifications):
2. 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):

Table 3.2.P.1-1: Composition of the FPP

|  |  |  |  |
| --- | --- | --- | --- |
| **Ingredient and grade** | **Reference** | **Function** | **Quantity per dosage unit** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

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

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

### 3.2.P.2 Pharmaceutical Development (name, dosage form)

#### 3.2.P.2.2 Final pharmaceutical product (name, dosage form)

#### 3.2.P.2.2.1 Formulation Development (name, dosage form)

1. Information on primary (submission, registration, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:

Summary of batch numbers

Table 3.2.P.2.2.1-1: Summary of batch numbers

|  |  |  |  |
| --- | --- | --- | --- |
| **Batch number(s) of the FPPs used in** | | | |
| **Bioequivalence or biowaiver** | <e.g. bioequivalence batch A12345> <e.g. biowaiver batch X12345> | | |
| **For proportional strength biowaiver: the bioequivalence batch of the reference strength** |  | | |
| **Dissolution profile studies** | | | |
|  |  |  |  |
| **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)** | | | |
| ‹ 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)** |  |  |  |

(ii) Summary of formulations and discussion of any differences

Table 3.2.P.2.2.1-2: Summary of formulations

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Relevant batches** | | | | | |
| **Comparative bioavailability or biowaiver** | | **Stability** | | **Process validation** | |
| **Batch No. & Size** |  | |  | |  | |
| **Component and quality standard (e.g., NF, BP, Ph. Eur, in-house)** | **Theor. quantity per batch(**e.g. kg/batch) | **Theor. quantity per unit strength** | **Theor. quantity per batch** | **Theor. quantity per unit strength** | **Theor. quantity per batch** | **Theor. quantity per unit strength** |
| [complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection] | | | | | | |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Subtotal 1 |  |  |  |  |  |  |
| [complete with appropriate title e.g. Film-coating] | | | | | | |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Subtotal 2 |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |

#### 3.2.P.2.3 Manufacturing Process Development (*name, dosage form*)

1. Explain the selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular critical aspects. Where relevant, the method of sterilisation should be explained and justified, and compatibility with production equipment e.g. filter media established.
2. If the manufacturing process of the product influences important physicochemical properties of the API (e.g. polymorphic form in case of a BCS low soluble API), demonstrate that the property of the API is not changed during manufacture.
3. Discuss differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product.
4. Discuss the discriminatory nature of the QC medium.

**Example:**

The proposed manufacturing process is a standard process utilised in tablet manufacture and consists of several steps including sifting, blending, and direct compression. The process has been sufficiently characterized. In-process testing was done for the common blend (description, water content, assay and blend uniformity), during compression (appearance, diameter, average weight, hardness, thickness, friability and, as applicable, content uniformity or uniformity of weight) and at packaging (leak test). Critical steps and intermediates are adequate, and these include preparation of the powder blend, compression of tablets. A flow diagram and detailed description of the manufacturing process have been provided.

The manufacturing process was verified to be consistent with that established under Pharmaceutical Development Data and this was verified with the BMR for the biobatch (batch No.) for the {XXX} mg strength and for the biowaiver batch for the {XXX} mg strength (batch No.). Process validation data were provided for three commercial scale batches (batch size 150 000 tablets for {XXX} mg strength and 100 000 tablets for the {XXX} mg strength). The results show consistency in the manufacturing of the three batches.]

### 3.2.P.3 Manufacture (name, dosage form) (refer to table 1.7-2)

#### 3.2.P.3.2 Batch formula (name, dosage form)

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

Table 3.2.P.3.2-1: FPP components

|  |  |
| --- | --- |
| **Strength (label claim)** |  |
| **Master/blank production document reference number and/or version[[9]](#footnote-9)** |  |
| **Proposed/intended 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)** |
| [Complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection] | |
|  |  |
|  |  |
| Subtotal 1 |  |
| [Complete with appropriate title e.g. Film-coating] | |
|  |  |
|  |  |
| Subtotal 2 |  |
| Total |  |

[Please add additional columns for additional strengths and additional batch sizes for each strength.]

#### 3.2.P.3.3 Description of manufacturing process and process controls *(name, dosage form)*

1. Flow diagram of the manufacturing process:
2. Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

#### 3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)

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

Table 3.2.P.3.4-1: Summary of manufacturing process controls

|  |  |
| --- | --- |
| **Step (e.g. granulation, compression, coating)** | **Controls (parameters/limits/frequency of testing)** |
|  |  |
|  |  |
|  |  |
|  |  |

*Proposed/validated holding periods for intermediates (including bulk product):*

#### 3.2.P.3.5 Process validation and/or evaluation *(name, dosage form)*

1. A process validation protocol (VP) or report (VR) Number:
2. The validation of the maximum holding time of the final product before packaging and the holding time of FPP intermediates before further processing:
3. Conditions during storage and/or shipping:

### 3.2.P.5 Control of pharmaceutical product *(name, dosage form)*

#### 3.2.P.5.1 Specification(s) *(name, dosage form)*

1. Specification(s) for the FPP:

Table 3.2.P.5.1-1: FPP specifications

|  |  |  |  |
| --- | --- | --- | --- |
| **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 |  |  |  |
| Identification |  |  |  |
| Impurities |  |  |  |
| Assay |  |  |  |
| Bacterial endotoxin |  |  |  |
| Dissolution |  |  |  |

[List any additional tests by the FPP manufacturer in the table above.]

#### 3.2.P.5.3 Validation of analytical procedures (name, dosage form)

Table 3.2.P.5.3-1: Validation parameters

| **Validation Parameter** | **Analytical Procedure** | | | |
| --- | --- | --- | --- | --- |
| **Assay** | **Related substances** | **Dissolution** | **Other** |
| Method Type: | [IR] | [HPLC] | [HPLC] |  |
| Method Number: | [*No. X*] | [*No. Y*] | [*No. Z*] |  |
| Accuracy |  |  |  |  |
| Precision: |  |  |  |  |
| * Repeatability |  |  |  |  |
| * Intermediate precision |  |  |  |  |
| Specificity |  |  |  |  |
| Detection limit (specify) |  |  |  |  |
| Quantitation limit (specify) |  |  |  |  |
| Linearity |  |  |  |  |
| Range (specify) |  |  |  |  |
| Robustness |  |  |  |  |
| Solution stability |  |  |  |  |
| + indicates that the parameter is acceptably tested and validated   * indicates that the parameter is not tested   ? indicates that questions remain before the parameter is judged to be acceptable | | | | |

[Add any additional columns as needed for other validated pharmaceutical product analytical procedures in the table above.]

#### 3.2.P.5.4 Batch analysis *(name, dosage form)*

Table 3.2.P.5.4-1: Batch analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Specification** | **Results** | |
| **Batch no:** | **Batch No:** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

### 3.2.P.6 Reference standards or materials *(name, dosage form)*

1. Purification method if applicable:
2. Establishment of purity (potency):
3. CoA, with a potency statement:

### 3.2.P.7 Container closure system *(name, dosage form)*

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

Table 3.2.P.7-1: Description of container closure systems

|  |  |  |  |
| --- | --- | --- | --- |
| **Description (including materials of construction)** | **Strength** | **Unit count or fill size (e.g., 60s, 100s)** | **Container size (e.g. 5 ml, 100 ml)** |
|  |  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |  |
|  |  |  |
|  |  |  |

### 3.2.P.8 Stability (name, dosage form)

#### 3.2.P.8.1 Stability summary and conclusion *(name, dosage form)*

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

Table 3.2.P.8.1-1: Storage information

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

#### 3.2.P.8.2 Post-approval stability protocol and stability commitment *(name, dosage form)*

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)):

Table 3.2.P.8.2-1: Stability protocol summary

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | | **Primary** | **Commitment** | **Ongoing** |
| **Storage condition(s) (◦C, % RH)** | |  |  |  |
| **Batch number(s)/batch size(s)** | |  |  |  |
| **Tests and acceptance criteria** | **Tests** | **Acceptance Criteria** | **Acceptance Criteria** | **Acceptance Criteria** |
| Description |  |  |  |
| Moisture |  |  |  |
| Impurities |  |  |  |
| Assay |  |  |  |
| **Testing frequency** | |  |  |  |
| **Container closure system(s)** | |  |  |  |
|  | |  |  |  |

[Add any additional rows as needed for other tests and acceptance criteria in the table above.]

1. Bracketing and matrix design for commitment and/or continuing (i.e. ongoing) batches, if applicable:

[*If applicable, include information here*]

#### 3.2.P.8.3 Stability data *(name, dosage form)*

Table 3.2.P.8.3-1: Stability data

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

# 3.2.R.1 PHARMACEUTICAL AND BIOLOGICAL AVAILABILITY AND MODULE 5

## Biostudies for generics

Table 3.1-1: Bioequivalence information

|  |  |
| --- | --- |
| Study title |  |
| CRO |  |
| GCP status |  |
| Study Protocol Number(s) |  |
| Report number(s) |  |
| Test Batch size, batch number |  |
| Date of manufacture of the test batch |  |
| Reference product & HCR |  |
| Batch Number & Exp date |  |
| Country of procurement |  |
| Study period |  |
| Principal investigator |  |
| Sponsor |  |
| No. of subjects enrolled in the study |  |
| No. of subjects that completed the study |  |
| RSA Reference Product / Applicant |  |
| Batch Number & Exp date |  |

## Bioequivalence for the X mg tablets

Table 3.1-2: Bioequivalence data

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter (n)** | **Test mean/ SD/CV** | **Reference mean/ SD/CV** | **Point estimate** | **90 % Confidence limits** | | **Intra-sub CV %** |
| **AUC0-t [ng\*h/ml]** |  |  |  |  |  |  |
| **Cmax [ng/ml]** |  |  |  |  |  |  |
| **AUC0-∞ [ng\*h/ml]** |  |  |  |  |  |  |
| **tmax [h]** |  |  |  |  |  |  |
| **t1/2 [h]** |  |  |  |  |  |  |
| **Kel [h-1]** |  |  |  |  |  |  |

## Biowaiver for the Y mg tablets:

Table 3.2-1: Biowaiver information: Additional strength

|  |  |
| --- | --- |
| Study title |  |
| Study date |  |
| Laboratory |  |
| GLP status |  |
| Is the pharmacokinetics linear across the dosage range? |  |
| Test Batch strength(s), size(s), batch number(s) |  |
| Date of manufacture of the test batch(es) |  |
| Reference product strength (Biostudy strength) |  |
| Batch Number & Expiry date |  |
| Dissolution conditions |  |
| Study Protocol Number(s) |  |
| Report number(s) |  |

Table 3.2-2: Biowaiver information: BCS

|  |  |
| --- | --- |
| Study title |  |
| Study date |  |
| Laboratory |  |
| GLP status |  |
| Have Solubility studies been conducted? |  |
| Study Protocol Number(s) |  |
| Report number(s) |  |
| Have Permeability studies been conducted? |  |
| Study Protocol Number(s) |  |
| Report number(s) |  |
| BCS Classification |  |
| Test Batch strength(s), size(s), batch number(s) |  |
| Date of manufacture of the test batch(es) |  |
| Reference product |  |
| Batch Number & Expiry date |  |
| Dissolution conditions |  |
| Study Protocol Number(s) |  |
| Report number(s) |  |

|  |  |  |
| --- | --- | --- |
| Signed Attestation | | |
| I, the undersigned, certify that the information and material included in this attestation is accurate and complete | | |
| Name of Responsible Pharmacist / Pharmacist Authorised to Communicate with the Health Authority | Signature: | Date: |
| Title, Company: | Email Address: | Telephone Number: |

# UPDATE HISTORY

|  |  |  |
| --- | --- | --- |
| **Date** | **Reason for update** | **Version and publication** |
| July 2019 | First publication: Summary of Critical Regulatory Elements document released for implementation and comment | Version 1, July 2019 |
| December 2019 | Deadline for comment | December 2019 |
| January 2020 | Response to queries raised from the comment period on the general information, move of administrative table to the front of the document, amendment of requirements from Module 1, move of table 1.11.1 to the bioequivalence section 3, update to the requirements in section 3.2.S.1 and the example, example tables to be in grey in section 3.2.S.1.3, amendment to the wording on table 3.2.S.4.1-2, removal of commercial batches on table 3.2.P.2.2.1-2, removal of columns of quantity per batch on table 3.2.P.3.2-1, addition of columns on commitment batches and ongoing stability batches to table 3.2.P.8.2-1 and removal of tables on commitment batches and ongoing stability | Version 2, January 2020 |
| March 2020 | Second publication: Streamlined and aligned to SAHPRA requirements and new letterhead.  Amendment of information on variations in the general section  Removal of Module 1.3  Removal of examples and guide text from the document  Amendments to the requirements in section 3.2.S.2.3, addition of section 3.2.S.3.1 and tables on the Biowaiver information for additional strength and BCS  Released for comment | Version 2, January 2020 |
| June 2020 | Comments from ITG working group | Version 2, January 2020 |
| July 2020 | Amendments to the general instructions and wording in sections on the update history, removal of irrelevant abbreviations, addition of redacted reports and the RRAs procedures to table on foreign registration, expansion on the requirements in section 3.2.S.2.2, 3.2.S.2.3, 3.2.S.3.1, 3.2.S.5, 3.2.P.2.3, removal of section 3.2.P.3.1 to avoid duplication of data, removal of wording on largest intended commercial batch size and other intended commercial batch size in 3.2.P.3.2, to comply with SAHPRA’s requirements.  Released for comments | Version 2, January 2020 |
| October 2020 | Comments from industry | Version 2, January 2020 |
| November 2020 | Third publication: Rearrangement to the sequence of sections to allow for logical flow of information. Reformatting of margins of the document to remove unused space at the start of each page and change in the page numbering. Amendments to the section names and numbering to be in line with ZA-CTD. Use of new terminology from dosage form to pharmaceutical form. Amendment to include (s) on the manufacturer details required to accommodate for cases where more than one manufacturer is applied for. Removal and addition of some wording from the SCoRE and amendments to tables for ease of flow of information. Inclusion of indication that the updates on the SCoRE can be marked in track changes, however, the document sent to SAHPRA must be highlighted in yellow. Update to the table on foreign registration/collaborative procedure to include not applicable as an option for applications that will not use the reliance/collaborative procedure. Amendments in 3.2.S.1.3 to the wording on the formula for dose solubility volume, inclusion of an example and amendments to comply with metrication. Amendments in 3.2.S.4.1 to include the API specifications of the API manufacturer. Amendments in 3.2.S.5 (b) to include overlaid IR spectra for the reference standards. Amendment to table 3.2.P.2.2.1-2 to include the theroretical quantity per unit strength for batch information. | Version 3, November 2020 |

1. . Also referred to as the DMF (Drug Master File), DSMF (Drug Substance Master File) and ASMF (Active Substance Master File) [↑](#footnote-ref-1)
2. . Recognised regulatory authorities (RRAs) include EMA (Centralised Procedures), EU (Decentralised Procedures and Mutual Recognition Procedures (MRPs)), US FDA, Japan MHLW, Swissmedic, Health Canada, Australia’s TGA, UK MHRA, Zazibona, and WHO Prequalification (PQ) [↑](#footnote-ref-2)
3. . Please note that a letter of access should only be provided if the applicant does not have access to full / unredacted assessment reports and cannot obtain these reports. [↑](#footnote-ref-3)
4. . Also referred to as the DMF (Drug Master File), DSMF (Drug Substance Master File) and ASMF (Active Substance Master File) [↑](#footnote-ref-4)
5. . List deviations from monograph. Deviations include additions and deletions, not an update to the monograph. [↑](#footnote-ref-5)
6. . CEP letter of access from API manufacturer; CPQ letter of access from WHO [↑](#footnote-ref-6)
7. Indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs) [↑](#footnote-ref-7)
8. List deviations from monograph. Deviations include additions and deletions, not an update to the monograph. [↑](#footnote-ref-8)
9. SAHPRA requires an updated master / blank production document reference number and/or version if major changes to the process are made (i.e. not editorial or administrative), as the SCoRE must reflect the current information in the dossier. Please refer to the 2.02 Quality and Bioequivalence Guideline for more information about requirements for master / blank production documents. [↑](#footnote-ref-9)