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| --- |
| **SUMMARY OF CRITICAL REGULATORY ELEMENTS (SCoRE) DOCUMENT** |

|  |  |
| --- | --- |
| Version 1 – Draft publication for comment | 12 April 2019 |
| Due date for comment | 10 May 2019 |

General:

* Please note that the Summary of Critical Regulatory Elements (SCoRE), does not replace the Quality Overall Summary (QOS), nor does it replace the requirements outlined in the relevant guideline documents
* The SCoRE is designed to facilitate applicants in the construction of data required by the authority to facilitate rapid evaluation of applications in the backlog
* The PDF version of the document should be included in Module 2.2 of the eCTD (TBC) submission (Note: the PDF version may be appended to the introduction, creating a single document to avoid validation errors)
* An additional MS word version of SCoRE should be included in the working documents folder
* It is recommended that the font used in the main text be Arial, size 11
* The SCoRE document should be revised and submitted with the change history (see table below these instructions) each time additional data is provided during the assessment process. If no revision is necessary due to no change in the information, a statement should be made to this effect in the covering letter
* For variations, the SCoRE document should be completed in its entirety (regardless of the proposed change), it should include information on all strengths, with any changes highlighted in yellow and it should be provided at the time of filing
* As per revised SAHPRA APIMF[[1]](#footnote-1) procedure (note: currently under development), if information is in the closed part of the DMF, reference to the closed part should be made (where applicable)
* Please delete all blue text (guides and examples) when submitting the SCoRE document
* Do not change or delete the titles and the numbering style (add “Not applicable” if necessary)

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**Update history**

The SCoRE document version should start with V001 for the first submission. Each resubmission of the SCoRE document should incrementally increase the version by 1 (i.e. V002 for the second version, or first resubmission of an amended SCoRE document). This version number should be included in the header 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 blue text and italicised below – please delete this text before submitting the SCoRE document 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 IA* | *V003* |
|  |  |  |  |
|  |  |  |  |

**List of abbreviations**

|  |  |
| --- | --- |
| API | Active Pharmaceutical Ingredient |
| BCS | Biopharmaceuticals Classification System |
| BTIF | Bioequivalence Trial Information Form |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CMC | Chemistry, Manufacture and Control |
| CoA | Certificate of Analysis |
| CPQ | Confirmation of WHO API Prequalification |
| CTD | Common Technical Document |
| EMA | European Medicines Agency |
| FPP | Finished Pharmaceutical Product |
| GMP | Good Manufacturing Practice |
| ICH | International Council for Harmonisation |
| IPRP | International Pharmaceutical Regulators Programme |
| LOD | Limit of Detection |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| PD | Product Dossier |
| Ph. Eur | European Pharmacopoeia |
| PQ | Pre-qualification |
| PPL | Periplakin (protein coding gene) |
| QIS | Quality Information Summary |
| QOS | Quality Overall Summary |
| RSA | Republic of South Africa  |
| SADC | Southern African Development Community |
| SAHPRA | South African Health Products Regulatory Authority |
| SCoRE | Summary of Critical Regulatory Elements |
| SmPC | Summary of Medicinal Product Characteristics |
| SOP | Standard Operating Procedures |
| SRA | Stringent Regulatory Authority |
| TGA | Therapeutic Goods Administration |
| US FDA | United States of America Food and Drug Administration |

**Summary of Critical Regulatory Elements (SCoRE)**

|  |  |
| --- | --- |
| Applicant name |  |
| Applicant email address |  |
| Application number | Master | Duplicate |
|  |  |
| Product (proprietary) name | Master | Duplicate |
|  |  |
| Approved name (INN or INNM) |  |
| Dosage form |  |
| Strength |  |
| Date of initial application |  |
| Date of receipt of initial application by SAHPRA |  |
| Date of current submission (SCoRE amendment) |  |
| FPP manufacturer used for development batches |  |
| FPP manufacturer applied for |  |
| API manufacturer used for development batches |  |
| API manufacturer applied for |  |

**Foreign registration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| <<Name of reference country 1>>  | Date of registration |  | Full assessment reports?  | Y/N |
| <<Name of reference country 2>>  | Date of registration |  | Full assessment reports? | Y/N |
| <<Name of reference country 3>>  | Date of registration |  | Full assessment reports? | Y/N |
| Add additional rows as required |  |  |  |  |

1. Module 1
	1. Module 1.3 South African labelling and packaging

For NCEs and generics with clinical data only:

1. Provide a brief synopsis of the new chemical entity (NCE) application here using the Summary Basis of Registration (SBRA) format. Refer to the Clinical Guidelines for the SBRA format and an example.
2. Indicate if the NCE has been approved by any of the regulatory authorities with which SAHPRA aligns itself: FDA, EMA, MHLW (Japan), Health Canada, Swiss Medic, TGA (Australia), MHRA (UK), and Zazibona (products registered prior 2016, post 2016 – mutual recognition).

For all NCEs and generics:

1. Comment if the most recent PSUR/PBRER and, if relevant, a Benefit/Risk analysis and applicable Risk Management Plan is included in your application, if the medicine applied for registration, is already registered by one or more Regulator (s) with which SAHPRA aligns itself.
2. Reflect here that [product name, dosage form and strength] is manufactured by [name of the FPP manufacturer] [laboratory name] is/are generic product(s) to the innovator product [product name, dosage form and strength] from [name of the innovator manufacturer], where relevant.
3. Provide a motivation when generic product has been used as a reference product.
4. Provide a brief commentary on indications, target population, posology (with regard to the ability of the FPP to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device) here.
5. Include ATC classification as well a mechanism of action.
6. Comment on the application content aligned with the most recent Regulations, policies, directives, monographs, position statements and guidelines of SAHPRA relevant to your application. Name and list the relevant documents that were used in the alignment process of your application.

The professional information (PI) and patient information leaflet (PIL) must be drafted in line with the current regulations and respective guidelines.

The applicant should refer to the following guidelines with regard to the requirements of the submission:

* General Information Guidelines
* Professional Information for Human Medicine Guidelines
* Patient Information Leaflet guidelines
* Clinical Guidelines
* Clinical Variation Guidelines

Example:

<Proposed Proprietary Name> <Product Strength(s)> <Product Dosage Form>manufactured by <Name of FPP manufacturer> are/is a generic product(s) to the innovator product <Innovator Product Name> <Product Strength(s)> <Product Dosage Form> from < Name of Innovator product manufacturer > are/is indicated for the treatment of XXX as add-on therapy in patients with mild to moderate persistent XXX, who are inadequately controlled on XYX as an alternative treatment option to XYX in patients with mild persistent XXX who do not have a recent history of serious XXX that required XYY and who have demonstrated that they are not capable of using XYX; and for the prophylaxis of XXX for patients in which the predominant component is XYZ.

Product XYZ tablet/injection/capsule is a cysteinyl leukotriene (CysLT) D4 receptor antagonist that binds with high affinity and selectivity to the CysLT1 receptor. This results in inhibition of bronchoconstriction, and decreased peripheral blood eosinophils.

* 1. Module 1.7 Good manufacturing practice

Table 1.7-1

|  |  |
| --- | --- |
| **Name of API** |  |
| **ASMF/DMF no. and open part version** |  |
| **ASMF/DMF holder name and address** |  |
| **Manufacturer name and address (include specific unit)** |  |
| **Manufacturer GMP status and date of last inspection/agency** |  |

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

**Final product manufacturer/packer/FPRC**

Table 1.7-2

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

* 1. Module 1.11 Bioequivalence (where applicable)

Table 1.11-1

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

1. Module 3: Quality aspects
	1. 3.2.S Drug substance (Or Active pharmaceutical ingredient (API)) (Name, Manufacturer)

*Indicate which option applies for the submission of API information: <check one only>*

Table 3.2.S-1

|  |  |
| --- | --- |
| **Name of API:** |  |
| **Name of API manufacturer:** |  |
|  | Confirmation of API prequalification document |
|  | Certificate of suitability to the European Pharmacopoeia (CEP) |
|  | Active pharmaceutical ingredient master file (APIMF[[2]](#footnote-2)) 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: \_\_\_\_\_\_\_. |
|  | Full details in the PD (open part of the DMF)Document version number/identifier of current Module 3.2.S: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

Compliance with monograph/pharmacopoeia

Table 3.2.S-2

|  |  |
| --- | --- |
| **Reference monograph/pharmacopoeia** |  |
| **Comply with monograph/pharmacopoeia** | **Yes** |  | **Yes with deviations[[3]](#footnote-3)** |  | **No** |  |
|  |  |

Guide:

Provide the description and general properties of the API><Include the chemical structure, empirical formula and the relative molecular mass of the API> Comment on any property that may impact on the quality and performance of the finished pharmaceutical product that may require additional user requirements (e.g. aqueous solubility over the physiological pH range and particle size distribution and polymorphism).

Example:

The active substance is chemically designated as sodium salt of [Chemical name]. (Chemical name) It is described in the current USP- and/or the European Pharmacopeia (Ph. Eur). [Name of the API] is a white to pale yellow coloured, amorphous hygroscopic powder. [Name of the API] is poorly soluble in buffered media in the physiological pH range 1.2 to 7.5.

The API is known to exhibit <confirm absence/presence of polymorphism> and <API manufacturer(s) name> produces the <State the polymorphic form>. <API name> is <confirm absence/presence of chiral centers> e.g. chiral molecule containing single asymmetric carbon atom; <API manufacturer(s) name><confirm absence/occurrence of isomers, and provide a brief discussion> e.g. produces the R-isomer. The other isomer <Isomer Name> is further monitored by the specification of not more than <specification limit> of the isomer by <Analytical method> e.g. chiral HPLC. <API name> consist of carbon-carbon double bond that gives rise to the scope for geometrical isomerism. Cis-isomer <Isomer Name> of drug substance is controlled in the final specification for the API. The isomer produced by <API manufacturer(s) name> is a trans-isomer.

* + 1. 3.2.S.1 General Information (name, manufacturer)
			1. 3.2.S.1.1 Nomenclature

General information

Table 3.2.S.1.1-1

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

* + - 1. 3.2.S.1.2 Structural formula

Example

Molecular formula: CxHxOx

* + - 1. 3.2.S.1.3 General properties expanded

Guide:

Specify the properties relevant to the performance of the product and give values, e.g., pKa, solubility in aqueous medium, polymorphism, isomers, particle size distribution etc. where relevant.

General properties expanded

Table 3.2.S.1.3-1

|  |  |
| --- | --- |
| **Property** |  |
| **Physical characteristics:** |  |
| **pKa-value(s):** |  |
| **Partition coefficient:** |  |
| **Hygroscopicity:** |  |
| **Stereochemistry:** |  |
| **Polymorphism** |  |
| **Particle size distribution (PSD)[[4]](#footnote-4)** |  |
| **Refractive index (liquids):** |  |

Solubility in aqueous medium at 37 °C

Table 3.2.S.1.3-2

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

* + 1. 3.2.S.2 Manufacture (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 and address (including block(s)/unit(s)) | Responsibility | API-PQ number /APIMF/CEP number (if applicable) | Letter of access provided? (Applicable to CEP & CPQ) |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Guide:

* The name, address (including unit/plot/block), and responsibility of each manufacturer, including contractors and manufacturer(s) of the intermediates (if sourced from a third party), and each proposed production site or facility involved in manufacturing and testing should be provided.
* This includes the facilities involved in the manufacture and testing of the API or key intermediates. If certain companies are responsible only for specific steps of the process (e.g. milling, micronization sterilisation, packaging, labelling, testing and storage facilities of the drug substance or key intermediates), then this should be indicated.
* The list of manufacturers should specify the actual addresses for the location, including the unit, plot or block (if any), where the relevant manufacturing or testing operation will be performed, rather than the administrative offices.
* The API manufacturer is [Name of the API Manufacturer, address (including unit/plot/block)] and was deemed to be cGMP compliant based on inspection by [Name of the Authority].
	+ - 1. 3.2.S.2.2 Description of manufacturing process and process controls

Guide:

* Provide a brief description of the manufacturing process. Provide a brief discussion on the starting material, for complex starting materials provide justification.
* A sequential procedural narrative of the manufacturing process. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). If information is in the closed part of the DMF, reference to the closed part should be made.
* Please request the API manufacturer to send the closed part of the DMF directly to SAHPRA where applicable
* The flow diagram of the synthesis process should include the chemical structures of starting materials, intermediates, reagents and the API reflecting stereochemistry. The flow diagram should identify reagents, catalysts and solvents used in each step.
* Where intermediates are used that resemble the API closely, CoAs of these should be included.
* If more than one manufacturing site is responsible for the last few stages of production, purification and/or micronisation (if applicable) of the drug substance, alternative processes undertaken at the different site(s) should be described and any significant differences should be assessed.
* If the drug substance is prepared as sterile and used as sterile by the FPP manufacturer, a complete description should be provided for the method used in the sterilisation. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided.
* The information on the manufacturing process should start from well-characterized starting materials (or CoA).
* Where CEP, CPQ and DMF procedure is followed, this section may not be applicable – simply stipulate N/A in this instance

Example:

The manufacturing process involves condensation of starting material to produce the tertiary butyl amine salt, purification and lastly formation of the sodium salt of xxxx. The starting material, although complex and only one step to the final API, was justified in line with ICH Q7, Q11 guidelines. The starting material is sourced from two manufacturers, and the controls for the starting material i.e. Specifications and test methods were provided and found to be sufficient. Potential impurities (including the Impurity A, Impurity B) have been well discussed in relation to their origin and potential carry-over into the final API. Manufacturing consistency was demonstrated with three API batches.

* + - 1. 3.2.S.2.3 Control of materials (name, manufacturer) – for API option 4 only (full details of the API)
1. Name of starting material:
2. Name and manufacturing site address of starting material manufacturer(s):
	* 1. 3.2.S.3 Characterisation (name manufacturer)
			1. 3.2.S.3.2 Impurities

Guide:

* A description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities should be provided. Are all the actual impurities included in the pharmacopeial monograph?
* State the maximum observed levels (actual numerical results) from batch analysis (S4.4), at least three batches.
* If residual solvents have been identified, then the solvent(s) used, their classification as per ICH Q3C, the synthesis step(s) in which they are used, the observed levels from batch analysis data and, if applicable, the LOQ and proposed limits must be indicated.
* Discussion of the potential genotoxic impurities should be provided.
* Please indicate N/A if a CEP is submitted

Impurities (potential and actual)

Table 3.2.S.3.2-1

|  |  |  |  |
| --- | --- | --- | --- |
| Name and structure of impurity (API-synthesis related and/or degradation products) | Acceptance Criteria | LOQ | Results from batch analysis (include batch number and use) |
|  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

Residual solvents

Table 3.2.S.3.2-2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Residual solvents | Classification (ICH Q3C) | Step used | Limits | Results (batch analysis – include batch numbers) |
|  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

* + 1. 3.2.S.4 Control of the API (name, manufacturer)
			1. 3.2.S.4.1 Specification (name, manufacturer)
1. **API specifications of the FPP manufacturer:**

Table 3.2.S.4.1-1

|  |  |
| --- | --- |
| 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 |  |  |
| etc. |  |  |
|  |  |  |
|  |  |  |

Guide:

* Tabulated summary of the proposed specification (including test parameters and acceptance criteria)
* The standard claimed by the APIMF/DMF Holder or applicant (e.g., Ph. Eur./BP/USP/In-house).
* Indicate if there is reduced testing proposed for certain parameters.
* A discussion/justification on the acceptability of the proposed specification and claimed standard.
* Specifications should cover all of the relevant quality parameters such as identity, organoleptic, physical, chemical and stereochemical properties, potency and microbiological quality. Organoleptic properties may include appearance, colour and clarity of solution, but never taste or smell. Physical properties may include crystalline/polymorphic form, particle size distribution, specific optical rotation, solubility, melting point, molecular weight. For APIs with low BCS solubility (dos-soluble volume > 250 ml), PSD and polymorphic form are generally regarded critical and should be derived from the FPP biobatch.
* Note: API specification controlled by the FPP manufacturer should be reflected here and it should be clearly separated from the specification controlled by the API manufacturer.

Example:

The API specification from the FPP manufacturer was noted to comply with the Ph. Eur pharmacopeia monograph for xxxx sodium includes tests for appearance, solubility, identification (IR, enantiomeric purity, test for sodium), heavy metals, water content, Impurity A (enantiomer), related substances (HPLC- Impurity B, C, D, E, F, G), assay (HPLC), and residual solvents (GC). Particle size distribution (psd) limits at three levels based on characterization of the API lot used in the biobatch were included in the specs with limits d10 (less than 10 μm), d50 as a range (20 - 75 μm) and d90 (less than 250 μm). Sufficient data were provided from the five batches justifying the consistency in producing the desired polymorph for xxxx, therefore, exclusion of the polymorphic identity test in the specifications was considered justified.

The analytical methods were described and comply with the Ph. Eur monograph for xxxx sodium. Nonetheless, the manufacturer performed full validation for the analytical methods. The specifications includes GC test for residual solvents, thus the GC method for residual solvents is considered acceptable and validated. Data on three consecutive batches of xxxx sodium manufactured according to the proposed manufacturing process in the proposed manufacturing site was provided. All batches represented full-scale production and complied with the requirements in the API specification.

| Validation Parameter | Analytical Procedure |
| --- | --- |
| Assay | Impurities | Residual Solvents |  |
| 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 |

* + - 1. 3.2.S.4.4 Batch analyses

Table 3.2.S.4.4-1

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

* + 1. 3.2.S.5 Reference standard
* If a pharmacopoeial monograph is claimed, the pharmacopoeial standard should be used.
* State if a certificate of analysis has been submitted.
* State if a secondary reference standard (e.g. working standard) is standardized against the compendial reference standard or primary reference standard.
* 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).
	+ 1. 3.2.S.6 Container closure system (name, manufacturer)
1. **Description of the container closure system(s) for the storage and shipment of the API:**
	* 1. 3.2.S.7 Stability
			1. 3.2.S.7.1 Stability summary and conclusions (name, manufacturer)
2. Proposed storage conditions and re-test period (or shelf-life, as appropriate):

Table 3.2.S.7.1-1

|  |  |  |
| --- | --- | --- |
| Container closure system | Storage statement | Re-test period[[5]](#footnote-5) |
|  |  |  |
|  |  |  |

Guide:

* Summarise the studies undertaken to support the proposed re-test period/shelf-life. Information to state include: batch numbers and size, manufacturing site, manufacturing date, container closure system(s), storage conditions (long-term, intermediate (if applicable), accelerated) and completed testing intervals. A table is recommended.
* Summarise the conditions and results of stress testing studies of the drug substance.
* The storage requirements for the API as derived from the stability data generated by the API manufacturer and specified by the manufacturer of the API
* A description of the API container closure system(s) must be included.
* State the proposed re-test period/shelf-life and storage condition derived from the stability data
* Please stipulate N/A if a CEP is submitted

Example:

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). Data for three batches were given with 60 months real time and 6 months accelerated data packed in triple low-density polyethylene (LDPE) bags placed in HDPE containers. In addition, forced degradation studies have been performed and demonstrated the stability indicating nature of the analytical method for assay. Xxxx sodium is sensitive to light as per Ph. Eur.

The stability studies confirmed the proposed re-test period of 48 months. The applicant provided commitment to perform stability studies at 30°C /75% RH to suit climatic conditions in the SADC region. In addition, the stability protocols were revised to include monitoring of the enantiomeric purity in stability studies as per revised specifications.

Xxxx Sodium is packed in a triple laminated LDPE bag along with silica gel bag and kept inside HDPE container. The product should be stored at controlled room temperature in a tightly closed container under nitrogen atmosphere, protect from light and moisture.

* 1. 3.2.P Drug product (or Finished pharmaceutical product (FPP))

Compliance with monograph/pharmacopoeia (if applicable)

Table 3.2.P-1

|  |  |
| --- | --- |
| Reference monograph/pharmacopoeia |  |
| Comply with monograph/pharmacopoeia | Yes |  | Yes with deviations[[6]](#footnote-6) |  | No |  |
|  |  |

* + 1. 3.2.P.1 Description and composition of the FPP

A brief description of the final product

Example:

[product name, dosage form and strength] is white to off white, orange flavoured, sweet round shaped biconvex chewable tablets Excipients used in the preparation of [product name, dosage form and strength] are well known excipients used in chewable tablets preparations such as e.g. Magnesium stearate, microcrystalline cellulose, e.t.c. The tablets are packed in 10’s Aluminium/Aluminium blister packs. Such three blisters are packed in a carton. The GMP status of the API manufacturer [Name of the API Manufacturer, address (including unit/plot/block)] was based on inspection by the [Name of the Authority]. The cGMP compliance of the FPP manufacturer [Name of the FPP Manufacturer, address (including unit/plot/block)] was confirmed based on inspection by [Name of the Authority].

Guide:

The formulation should show the INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant) and approved names of inactive pharmaceutical ingredients (IPIs), including those that do not remain in the final product after manufacturing e.g. granulating agents and gases used for flushing. IPIs not present in the final product should be indicated.

The name and the quantity of the API and the name and quantity stated under “Composition” in the professional information and PIL should correspond. The name and quantity of the API per dosage unit should also correspond to the final product specifications.

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

|  |  |  |
| --- | --- | --- |
| 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. 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 |  |  |  |  |  |  |  |

(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:
	* 1. 3.2.P.2 Pharmaceutical Development (name, dosage form)
			1. 3.2.P.2.2 Drug Product (name, dosage form)
				1. 3.2.P.2.2.1 Formulation Development
2. Information on primary (submission, registration, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:

(i) Summary of batch numbers:

Table 3.2.P.2.2.1-1

|  |
| --- |
| **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

|  |  |
| --- | --- |
| Component and quality standard (e.g. NF, BP, Ph. Eur, in-house) | Relevant batches |
| Comparative bioavailability or biowaiver | Stability | Process validation | Commercial (3.2.P.3.2) |
| <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 | % |
| <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 |  |  |  |  |  |  |  |  |

Guide:

* Present the Quality Target Product Profile of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy.
* Is the formulation development supported by clinical development?
* Discussion of bioequivalence between commercial formulation and clinical trial formulations, if different, should be provided
* Discuss if applicable differences in finished product quality attributes (e.g. impurity and dissolution profile) in case of different strengths or a line extension.
* Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties.
* Early development formulations for pre-clinical and clinical studies should be highlighted where relevant, and comments made relating to the findings of these studies.
* Additional details should be given if the development encompasses a paediatric formulation including information for which age group this is intended, if appropriate

Example:

Xxxx Sodium Tablets x mg are marketed across USA and elsewhere under the trade name of CC® tablets x mg (Company ABCD USA) containing Xxxx sodium. The aim of the pharmaceutical development was to develop stable, essentially similar formulation, bioequivalent to the innovator product, CC tablets x mg (Company ABCD USA). The tablets have been developed as immediate release solid dosage forms for oral administration. The qualitative formulation was developed and each of the excipient was selected for its intended use based on optimization studies.

The manufacturing process employs direct compression technique in the manufacturing of finished pharmaceutical product. Adequate justification was provided for selection of the direct compression procedure for manufacture of the FPP. Based on the process optimization at various stages it was demonstrated that the proposed formula and process is adequate to consistently get the required quality.

A bioequivalence study was conducted for the 5mg strength, under fasting conditions, in order to prove in-vivo bioequivalence between xxxx test and an acceptable reference product. Comparative in-vitro dissolution for the additional strength (x mg strength – batch number 041201149) was performed against the higher strength (x mg strength – batch number 041008033) in pH 0.5% SLS (official dissolution media), pH 6.8 Phosphate buffer, pH 4.5 Acetate buffer and 0.1N HCl. The formulation of Xxxx Sodium Tablets x mg is dose proportional to Xxxx Sodium Tablets 5mg manufactured by NSM Laboratories Limited, India.

The release medium is 0.5% sodium lauryl sulfate (similar to the method for xxxx tablets stated by Office of Generic Drugs, US FDA). The acceptance criterion has been derived from the dissolution profile in this medium …

* + - 1. 3.2.P.2.3 Manufacturing Process Development (name, dosage form)

Guide:

* 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.
* 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.
* 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 should be discussed.

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 x mg strength and for the biowaiver batch for the x mg strength (batch No.). Process validation data (tool) were provided for three commercial scale batches (batch size 150,000 tablets for 4mg strength and 100,000 tablets for the 5mg strength). The results show consistence in the manufacturing for the three batches.

* + 1. 3.2.P.3 Manufacture
			1. 3.2.P.3.1 Manufacturer(s) (name, dosage form)
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:

Table 3.2.P.3.1-1

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

* + - 1. 3.2.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 SCoRE>

1. List of all components of the FPP to be used in the manufacturing process and their amounts 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

|  |  |  |  |
| --- | --- | --- | --- |
| **Strength (label claim)** |  |  |  |
| **Master production document (BMR) 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 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 |  |  |  |

* + - 1. 3.2.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:
	* + 1. 3.2.P.3.4 Controls of critical steps and intermediates
3. Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Table 3.2.P.3.4-1

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

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

* + - 1. 3.2.P.3.5 Process validation and/or evaluation
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:
	* 1. 3.2.P.5 Control of drug product
			1. 3.2.P.5.1 Final product specifications
4. Specification(s) for the FPP:

Table 3.2.P.5.1-1

|  |
| --- |
| 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 |  |  |  |
| etc. |  |  |  |

Guide:

* Specifications (titles and limits) should be listed in tabulated form for in-process controls, FPP intermediate controls, final product controls (batch release), stability controls, and in-use (if applicable). If the in-process controls are submitted in 3.2.P.3.3 a cross reference will suffice.
* In-process controls should be clearly identified as such including those performed on bulk e.g. liquids and semi-solids prior to packaging.
* If a product is included in a recognised pharmacopoeia any deviation from the relevant monograph should be justified.
* The description of the final product and the description given under “Identification” in the professional information and patient information leaflet should correspond. The description should be such that visual identification of counterfeit medicines is facilitated where possible.
* See the ICH Guidelines: Q3B, Q6A and Q6B and Appendix 2 of the Stability guideline for the specifications required for each dosage form. If any specification is not appropriate for a particular product, a motivation should be included. Other parameters not appropriate for stability testing should also be included as release specifications, e.g. a specification for residual organic solvents used during the coating procedure, or sterility.

Example:

The product specification is a standard one for tablets. The specifications contain tests with suitable limits for appearance, identification (HPLC and UV), uniformity of dosage units by content uniformity, friability of cores, water content (by Karl-Fisher), thickness of cores, hardness, disintegration, average weight, assay (HPLC), related substances (HPLC), dissolution, microbial limits. Full details of all analytical methods have been provided. All non-pharmacopoeial methods have been satisfactory validated.

Batch analysis data was provided on three commercial scale batches of the finished product. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. It has been shown that tablets can be manufactured reproducibly according to the finished product specifications.

* + - 1. 3.2.P.5.4 Batch analysis

Table 3.2.P.5.4-1

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

* + 1. 3.2.P.6 Reference standards
1. Purification method if applicable:
2. Establishment of purity (potency):
3. CoA, with a potency statement:
	* 1. 3.2.P.7 Container closure system
4. Description of the container closure systems, including unit count or fill size, container size or volume:

Table 3.2.P.7-1

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

* + 1. 3.2.P.8 Stability
			1. 3.2.P.8.1 Stability summary and conclusion
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

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

Guide:

* A tabulated summary of the data, clearly indicating the batch number and pack types/sizes (production, pilot or experimental) of batches, packaging material, storage conditions and storage period, and manufacturer of the API with API batch numbers, should be included for each final product manufacturer.
* Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies. Bracketing & Matrix designs – acceptable?
* Are the methods used the same as or different to those described in P.5? Are they well validated and shown to be stability indicating?
* Confirm that the containers used in the stability studies are the same as those proposed for marketing of the product as described in the professional information and patient information leaflet.
* Are the number of batches, and their sizes, used in the stability studies in accordance with the requirements of the stability guideline? Clarify.
* Note that the qualification of impurities carried out on the API may not necessarily address degradants induced by the product matrix, product manufacturing process or product ageing. In addition, other product characteristics may change on storage and these need to be justified with reference to the preclinical and clinical results.
* Confirm if the proposed shelf life and storage conditions are adequate.

In–Use stability:

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

Example:

Stability studies under the following conditions of 30°C/75%RH (long term, 36 months) and 40°C/75%RH (accelerated, 6 months) were carried out on three commercial scale batches. Containers used in the stability studies were the same as those proposed for commercialization.

Tests conducted during stability studies were description, identification by HPLC, average weight, hardness, water content by KF, dissolution, related substances, assay, and microbial limit tests. No significant differences in xxxx assay and degradation products content were observed. In conclusion, stability results showed no increase of the impurities (known and unknown). The results are well within the specification limits.

In summary the stability data provided support the proposed shelf-life of 24 months (product demonstrated to be stable up to 36 months) and storage conditions of “store at or below 30°C, protect from light and moisture” when packed in Alu-Alu blister packs. Pack sizes 10 tablets in a blister, such three blisters packed in a carton, and cartons packed in a shipper.

* + - 1. 3.2.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)):

Table 3.2.P.8.2-1

|  |  |
| --- | --- |
| Parameter | Details |
| **Storage condition(s) (◦C, % RH)** |  |
| **Batch number(s)/batch size(s)** | *<primary batches>* |
| **Tests and acceptance criteria** | Description |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| 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)):

Table 3.2.P.8.2-2

|  |  |
| --- | --- |
| 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 |  |
| Moisture |  |
| Impurities |  |
| Assay |  |
| 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)):

Table 3.2.P.8.2-3

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

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

*If applicable, include information here*

* + - 1. 3.2.P.8.3 Stability data

Table 3.2.P.8.3-1

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

1. Biostudies for generics
	1. Bioequivalence for the x mg tablets

Guide:

The study should be designed in such a way that the formulation effect can be distinguished from other effects However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as parallel designs for very long half-life substances, and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics could be considered. In general, single dose studies will suffice, but there are situations in which steady-state studies may be required in which case the steady-state study design should be motivated.

Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients. Use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be accepted in exceptional cases as due to the recent development in the bio-analytical methodology, it is unusual that parent moiety cannot be measured accurately and precisely. e.g.,; A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study (………….) of ………. (B. No.) manufactured by XY Laboratories Limited, India comparing BJ Tablets? mg (Lot No.: xxx), manufactured by Co., USA, in healthy, adult, male, human subjects was performed under fasting condition.

Additional information:

Multi-source (generic) drug products need to conform to the same standards of quality, efficacy and safety required of the originator's (innovator/brand) products. A reasonable assurance must be provided that they are, as intended, clinically interchangeable with innovator product or acceptable comparator products. Pharmaceutically equivalent multi-source pharmaceutical products must be shown to be therapeutically equivalent to one another in order to be considered interchangeable:

Example:

The study was conducted at BXX Clinical Research, Steve Biko Hospital, Pretoria – 0001, SA in 2018. MCC, SA and MHRA from UK recently inspected the CRO in 2017. Proof of acceptable GCP inspection in 2017 from South Africa Medicines Control Council for a study conducted in 2010 was provided. Therefore, this was found sufficient to demonstrate that the CRO conducts studies to acceptable levels of compliance with international GCP requirements. The study was conducted in 72 health subjects aged between 19 and 40 years.

xxxx sodium in plasma was analysed using a sufficiently validated UPLC-MS/MS method. Bioequivalence was demonstrated with the 90% confidence interval of the ratio of the geometric means for the test and reference product within acceptance limits of 80 – 125% for Cmax and AUC.

Provide a snapshot of tabulated “mean Pharmacokinetic and Statistical results of the Test and reference products” see template of table below:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 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]**  |  |  |  |  |  |  |

* 1. Biowaiver for the Xmg tablets

Example

xxxx Sodium Tablets X mg (lower strength) proposed for commercial supplies is dose proportional to Xxxx Sodium Tablets Y mg (higher strength) used for performing bioequivalence study. Xxxx shows linear pharmacokinetics from 1 to 10 mg. The manufacturing process for the Xmg strength and Ymg strength were confirmed to the similar. The comparative dissolution in release media and buffered media at pH 1.2, pH 4.5 and pH 6.8 of the batch used in the bioequivalence study and the proposed commercial batch of Xxxx Sodium Tablets X mg demonstrated similarity in the dissolution profiles.

|  |
| --- |
| **Signed Attestation** |
| I, the undersigned, certify that the information and material included in this attestation is accurate and complete |
| Name of Authorised Signing Official: | Signature: | Date: |
| Title, Company: | Email Address: | Telephone Number: |

1. Also referred to as DSMF (drug substance master file) and ASMF (active substance master file) [↑](#footnote-ref-1)
2. Also referred to as DSMF (drug substance master file) and ASMF (active substance master file) [↑](#footnote-ref-2)
3. List deviations from monograph [↑](#footnote-ref-3)
4. If dose soluble volume is > 250 ml (see below), PSD is derived from the API lot used in the FPP biobatch. [↑](#footnote-ref-4)
5. Indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs) [↑](#footnote-ref-5)
6. List deviations from monograph [↑](#footnote-ref-6)