The broad policy of the Ministry of Health aims at ensuring that all drugs manufactured, imported or exported, distributed or sold in Botswana are of acceptable quality, safety and efficacy. The process of drug registration forms an important basis for evaluating and assuring drug safety, efficacy and quality.

This addendum supports the registration guideline of June 2009. It is designed to assist applicants in preparation of dossiers and improve efficiency at the Drugs Regulatory Unit (DRU).

**SUBMISSION OF DOSSIERS**

1. **Number of copies of applications**

ONE (1) hard copy and CD with soft copy (in PDF format) of the registration application (dossiers) shall be submitted.

A summary of each dossier (see Appendix I) in Microsoft Word (compatible with Windows 2003) shall be included in the CD of the dossier.

A covering letter must be attached to each MH 2048 document submitted. To expedite unpacking of documents the covering letter should itemise the contents of the submission.

2. **Incomplete submissions**

Incomplete and/or dossiers not presented according to MH 2048 forms or Common Technical Document (CTD) will be rejected and the application fee is not refundable.

3. **Fee structure**

The Fee structure in Appendix II shall be applied.
ANNEX I

SUMMARY OF DOSSIER - DRUG REGULATORY UNIT

GENERAL INSTRUCTIONS:
Please review all the instructions thoroughly and carefully prior to completing the Summary of Dossier.
Provide as much detailed, accurate and final information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for DRU Use Only!
Please state the exact location (Annex number) of any appended documents in the relevant sections of the Summary of Dossier.
Before submitting the completed Summary of Dossier, kindly check that you have provided all requested information.
Should you have any questions regarding this Form, please contact the Drugs Regulatory Unit (DRU).

A properly filled out and signed original copy of the SUMMARY OF DOSSIER with all its annexes (including a copy in Word on CD-ROM) must be submitted to the DRU together with the dossier. The entire dossier should be submitted both as hard-copy and on CD-ROM. As always, the dossier with the Summary of Dossier should be sent to the following address:

The Chief Pharmacist
Drugs Regulatory Unit
Department of Clinical Services
Ministry of Health
Office 3D4, Floor 3 Block D
Ministry of Health Headquarters
Government Enclave
Gaborone
Botswana
1.0 Drug and Applicant details

<table>
<thead>
<tr>
<th>Name, Address, Telephone and FAX numbers, and email address of Applicant:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name of drug:</td>
</tr>
<tr>
<td>DRU Application Reference Number:</td>
</tr>
<tr>
<td>International Non-Proprietary Name of the drug:</td>
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<tr>
<td>Strength and dosage form:</td>
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<tr>
<td>Pack size(s):</td>
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<tr>
<td>Pharmacological classification (ATC):</td>
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<tr>
<td>Indications:</td>
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<tr>
<td>Name and physical address of Manufacturer(s):</td>
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<tr>
<td>Date of submission:</td>
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<tr>
<td>DRU Category:</td>
</tr>
<tr>
<td>List ICH or PIC/S Country Registrations, WHO Prequalification and/or Other Foreign registrations with appended certificates:</td>
</tr>
<tr>
<td>GMP certificate issued by competent authority in country of manufacture in terms of WHO Certification Scheme</td>
</tr>
</tbody>
</table>
### 1. 2.0 Formulation - Schedule of ingredients

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>Specifications**</th>
<th>Unit (mg/unit)</th>
<th>Quantities for Production Batch</th>
<th>Quantities for Stability Batch</th>
<th>Reason or Purpose for inclusion</th>
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- For solid dosage forms include capsule and coating information, e.g., film or EC coating
- **If compendia specifications are used specify compendium: Ph Eur, JP, Int Ph, USP, IP...

**Comments:**

(a) **3.0 Package insert**

**Comments:**

4.0 **Container Specification and control**

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

(b) Materials of construction of each primary packaging component:

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

**Comments:**
5.1 Active Pharmaceutical Ingredient (API)

5.1.1 Properties of API
5.1.1.1 API not described in BP, PhInt, PhEur, or USP

(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and summary of the interpretation of evidence of structure:

(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):

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

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

(e) Potentially critical, additional characteristics:
   - Physical description (e.g., appearance, colour, physical state):
   - Physical form (e.g., polymorphic form, solvate, hydrate):
   - Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):
   - Drug solubility in 250 ml water
   - Partition coefficient
   - Hygroscopicity

Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):

5.1.1.1 API described in BP, PhInt, PhEur, or USP

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

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

(c) Potentially critical, additional characteristics:
   - Physical description (e.g., appearance, colour, physical state):
   - Physical form (e.g., polymorphic form, solvate, hydrate):
   - Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):
   - Drug solubility in 250 ml water
   - Partition coefficient
   - Hygroscopicity

Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):

Comments:

5. 1. 2 Site of Manufacture

List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access), if applicable):
5.1.3 API route of synthesis

5.1.3.1 API not described in BP, PhInt, PhEur, or USP

(ii) Controls of Critical Steps and Intermediates

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

(i) Process Validation and/or Evaluation

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

Manufacturing Process Development

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

(b) Impurities

(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:

List of impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and origin:

<table>
<thead>
<tr>
<th>API-related Impurity (chemical name or descriptor)</th>
<th>Structure</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Potential impurity of the starting material(s)</td>
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<td></td>
<td>Unreacted starting material(s)</td>
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<tr>
<td></td>
<td></td>
<td>Unreacted intermediate(s)</td>
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<td></td>
<td></td>
<td>By-product(s)</td>
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<td></td>
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<td>Reagent(s)</td>
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<td></td>
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<td>Catalyst(s)</td>
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<td></td>
<td></td>
<td>Residual solvent(s)</td>
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<tr>
<td></td>
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<td>Potential degradant(s)</td>
</tr>
</tbody>
</table>

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

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

- Justification of proposed acceptance criteria for impurities:

Comments:

5.1.3.1 API described in BP, PhInt, PhEur, or USP
List process-related impurities not included in the monograph(s) (e.g., key intermediates, residual solvents), which can be identified from the simplified flow diagram and text-book level narrative of the synthetic process:

### 5.1.4 API Specifications

<table>
<thead>
<tr>
<th>Test*</th>
<th>Analytical Procedure</th>
<th>Acceptance Criteria</th>
<th>Results from one of the batches (from CoA)</th>
</tr>
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<tbody>
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</table>

* For Compendial Procedures Specify Compendia. Non-compendial products specifications should conform to ICH Q6 (includes stability studies).

CoA = certificate of analysis

(i) **Justification of Specification**

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

(c) **Reference Standards or Materials**

(a) Source of reference standards or reference materials (e.g., House, USP, BP, PhEur, PhInt):

Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard):

**Comments:**

### II. 5.2 Finished Product

### 5.2.1 Pharmaceutical development

5.2.1.1 Company research and development

Discussion of the:

- key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP:
- for FDC products, compatibility of APIs with each other:
Discussion of the:

- choice of excipients (e.g., their concentrations, their characteristics that can influence the FPP performance):
- compatibility of the API(s) with excipients:

**Formulation Development**

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

(b) Discussion of the differences in the formulations for the batches used in the \textit{in vivo} studies (e.g., pivotal clinical, comparative bioequivalence) and the formulation described in 3.3:

(c) Description of batches used in the comparative \textit{in vitro} studies (e.g., dissolution) and in the \textit{in vivo} studies (e.g., pivotal clinical, comparative bioequivalence), including strength, batch number, and type of study:

(d) Summary of results for comparative \textit{in vitro} studies (e.g., dissolution) and comparative \textit{in vivo} studies (e.g., bioequivalence):

(e) Summary of any information on \textit{in vitro-in vivo} correlation (IVIVC) studies:

(f) For scored tablets, provide rationale/justification for scoring:

**Overages**

Justification of overages in the formulation(s) described in 3.3:

**Physicochemical and Biological Properties**

Discussion of the parameters relevant to the performance of the FPP (e.g., pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

**Manufacturing Process Development**

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

(b) Discussion of the differences in the manufacturing process(es) for the batches used in the \textit{in vivo} studies (pivotal clinical, comparative bioequivalence) and the process described in 3.5:

**Container Closure System**

Discussion of the suitability of the container closure system (described in 3.10) used for the storage, transportation (shipping), and use of the FPP (e.g., choice of materials, protection from moisture and light, compatibility of the materials with the dosage form):
Microbiological Attributes
Discussion of microbiological attributes of the dosage form (e.g., preservative effectiveness studies):

Compatibility
If applicable, discussion of the compatibility of the FPP, e.g., with reconstitution diluent(s) or dosage devices, co-administered drugs, etc.:

5.2.1.1 Information from literature

Comments:

5.2.1 Summary of Manufacturing Procedure Flow-Chart
Summary of the manufacturing process, include the types of equipment used and their capacities.

Comments

5.2.1.1 Process Validation and Evaluation
Summary of the process validation and/or evaluation studies conducted (e.g., batch numbers, batch sizes, testing parameters, acceptance criteria) or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g., protocol number, parameters, results):

Comments:

5.2.2 Comments on Specifications for Excipients
For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation with supporting documentation should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter may be found in:

Comments:
(a) **5.2.3 In-process controls specifications and tests, if applicable.**

State all parameters controlled during the production as well as the frequencies of testing. Clearly state the critical parameters.

Comments:

---

**5.2.4 Specifications for finished product**

<table>
<thead>
<tr>
<th>Test</th>
<th>Analytical Procedure (Type/Source/Version)</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Batch release</td>
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</table>
Justification of the specifications (e.g., evolution of tests, analytical procedures, and acceptance criteria, exclusion of certain tests, differences from compendial standard):

Information on the characterization of impurities, not previously provided under API section 2.4 (e.g., summary of actual and potential degradation products, basis for setting the acceptance criteria):

Comments:

(a) 5.3 Stability Testing Data – Finished product

Description of stability study details:

<table>
<thead>
<tr>
<th>Storage Conditions (*°C, % RH)</th>
<th>Parameters monitored*</th>
<th>Batch Number</th>
<th>Batch Size</th>
<th>Container Closure System</th>
<th>Completed (and Proposed) Test Intervals (in months)</th>
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</table>

* Physical appearance, assay, degradation products, dissolution, microbial limits, etc.

Summary and discussion of stability study results:

Extrapolation of data (if applicable)
Include justification with any mathematical models if used.

Proposed storage conditions and shelf life:

Comments on data and shelf life claimed:

5.4 Executed or Original Batch Manufacturing Records/Data

Comments:

(ii) 6.0 PHARMACOLOGICAL AND CLINICAL DOCUMENTATION
Results:
From the log transformed data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test product (mean* ± SD) (n = )</th>
<th>Reference product (mean* ± SD)(n = )</th>
<th>T/R (%)</th>
<th>Confidence interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}</td>
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<tr>
<td>AUC_{0,T}</td>
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<tr>
<td>AUC_{0,∞}</td>
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</table>
**Mean**: please state the type of mean used e.g. geometric mean

**Biowaver**: Justification of biowaver, evidence of proportionality of formulations, Summary of comparative dissolution studies, description of dissolution methods, calculation of F2 values.

**Discussion of results:**

**Conclusion:**

**Comments:**

**6.1 Safety studies**

Summary of safety studies in not more than 1 (one) A4 page.

**6.2 Efficacy studies**

Summary of efficacy studies in not more than 1 (one) A4 page.

**Comments:**

**7.0 References**

*Martindale, Goodman and Gilman, USP-DI, etc.*

**7.1 Label**

**POINTS TO BE COMMUNICATED TO THE MANUFACTURER**

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

**A.** General remark, if applicable

**B.** Observations, information

**ACTIVE PHARMACEUTICAL INGREDIENT(s) (INN)**

**FINISHED PHARMACEUTICAL PRODUCT (INN .mg PHARMACEUTICAL FORM)**

**C.** Overall conclusion
Please fill in the relevant conclusion, based on the review of the data on quality, in the first part of the document.

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

**D. Outstanding commitments**

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

**RECOMMENDATIONS FOR INSPECTION**

<table>
<thead>
<tr>
<th>2. Evaluator</th>
<th>3. Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Reviewer</td>
<td>5. Date</td>
</tr>
</tbody>
</table>
ANNEX II

SADC GUIDELINES FOR REGISTRATION

5. Same/Separate Applications

5.1 Tablets / Capsules / Suppositories / Lozenges
(i) Different pack-sizes of the same strength and formulation will require one application.
(ii) Different strengths and/or formulations will require separate applications.

5.2 Syrups/Liquids/Solutions (non parenterals)/Creams/ointments
(i) Different container sizes of the same strength and formulation will require one application.
(ii) Same container size of different strengths and/or formulations will require separate applications.

5.3 Ampoules, Vials and Large Volume Parenterals
(i) Ampoules containing identical solutions of the same strength but of different volumes will require separate applications;
(ii) Ampoules containing solutions of different strengths will require separate applications;
(iii) Ampoules and/or single dose vials containing dry powder, crystals etc, of different mass will require separate applications;
(iv) Ampoules and single dose vials containing the same respective masses of dry powder, crystals etc, will require separate applications;
(v) Ampoules, single dose vials, as well as disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid will require one application.
(vi) Dental cartridges containing fluids of different volumes will require one application;
(vii) Ampoules containing "water for injection", but of different volume will require one application.
(viii) Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection, will require one application.
(ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, will require separate applications.;
(x) Multi-dose vials of the same strength and formulation in different volumes will require separate applications.
(xi) Multi-dose vials and a single dose ampoule of the same formulation will require separate applications.
(xii) Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted will require one application;
(xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) will require one application provided that the diluent is also fully described in the dossier together with the product;
(xiv) An ampoule of diluent to be used with any biological preparation will require one application;
(xv) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers of exactly the same type of material, will require separate applications;
(xvi) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers made of different types of materials, will require separate applications;

(xvii) A preparation, packed in plastic containers and intended also to be marketed in glass containers containing the same volume and the same formulation, it will require one application provided the following data are submitted:
(a) characteristics of the rubber stopper;
(b) specifications for the glass;
(c) a comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;
(d) data on particulate matter (contamination);
(e) stability data with reference to the effect of the pH of the solution.

(xviii) Products with the same strength and formulation but with different colours and/or flavours will require separate applications;

(xix) Applications containing the same active ingredient(s), and where additional indications are sought, where such new indications render the product in a different scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

5.4 Different applicants/proprietary names for the same formula

(i) Same formula applied under different proprietary names will require separate applications.

(ii) Same formula from different applicants will require separate applications