CHECKLIST FOR VARIATIONS APPLICATIONS FOR MEDICINES

INTRODUCTION:

This document describes the requirements of a Variation application submitted for an existing application for registration of medicine or already registered medicine in Botswana which requires regulatory approval.

The following documents must be submitted with each Variation, as given below:

- **Application form**
- **Table of Contents**
- **Specific Supporting documents**
- **Payment fee**

DOSSIER REQUIREMENTS FOR MINOR VARIATION

V1	**Change in the name and/or address of the applicant (Marketing Authorization Holder)**		
	Supporting Documents		
	1)	A formal document from the manufacturer/ a relevant official body in which the new name or new address is mentioned.	☐

V2	**Change or inclusion in the name and/or address of a manufacturer of the active substance**		
	Supporting Documents		
	1)	Replacement of relevant page(s) of the dossier.	☐
	2)	Declaration from the supplier of the finished product that the route of synthesis, quality control procedures & specifications of the API are the same as the previous one.	☐
	3)	Certificate of analysis (in a comparative tabular format) for at least two batches (minimum pilot scale) of the drug substance from the current and proposed manufacturers/sites.	☐
	4)	A letter of commitment to conduct the appropriate stability study for the drug product manufactured with the drug substance from the proposed manufacturer	☐

V3	**Change or addition of the name and/or address of manufacturer of the finished product or Change or addition of the name and/or address of manufacturer of the finished product**		
	Supporting Documents		
	1)	A formal document from the manufacturer in which the new name or new address is mentioned.	☐
	2)	Replacement of relevant page(s) of the dossier.	☐

	3)	Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned: a GMP certificate.	☐
	4)	The batch numbers of batches (≥ 3) used in the validation study should be indicated and validation protocol should be submitted[ii].	☐
	5)	Copy of release and end of shelf-life specifications.	☐
	6)	Certificate of Analysis of one batch of finished product from the new manufacturing site.	☐
	7)	Amended immediate label, outer label & package insert for the product from new site.	☐
	8)	The batch numbers used in stability studies[i].	☐
	9)	For sterile or parentarals products, validation data of the manufacturing process and sterilization process at the proposed site for products should be provided.	☐

V4	**Change in the specification of an API, a starting chemical material/intermediate/reagent used in the manufacturing process of the API**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of proposed specifications.	☐
	3)	Details of any new analytical method & validation data[iii].	☐
	4)	Certificate of analysis of minimum of two production batches.	☐
	5)	Justification of not submitted a new bioequivalence study according to the current WHO guideline[iv].	☐

V5	**Change in re-test period and storage condition of the API**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of approved specifications of the API.	☐
	3)	Results of appropriate real time stability studies conducted in accordance with the relevant stability guidelines on at least two pilot or production scale batches of the API in the intended packaging material and covering the duration of the requested re-test period or requested storage conditions[i].	☐

V6	**Change or replacement of an excipient with a comparable excipient**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Justification of change/choice of excipient with appropriate development pharmaceutics.	☐
	3)	Documentary proof that the specific source of the excipient is TSE/BSE risk free.	☐
	4)	For solid dosage forms, comparative dissolution profile of at least two pilot scale batches of the finished product in the new and old composition[iii].	☐
	5)	Justification of not submitted a new bioequivalence study according to the current WHO guideline[iv].	☐
	6)	Data to demonstrate that the new excipient does not interfere with the finished product specification test method.	☐
	7)	Stability studies in accordance with relevant guidelines[i]	☐
V7	**Change in the specification of an excipient**		

	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of proposed specifications.	☐
	3)	Details of any new analytical method & validation data in accordance with relevant guidelines[ii].	☐
	4)	Certificate of analysis of minimum of two production batches.	☐
	5)	Comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient in accordance with relevant guidelines[iii].	☐
	6)	Justification of not submitted a new bioequivalence study according to the current WHO guideline[iv].	☐
	7)	Comparative validation results showing that the current test and the proposed one are equivalent.	☐
	8)	The batch numbers used in the stability studies[i].	☐

V8	**Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material**		
	Supporting Documents		
	1)	Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.	☐
	2)	Documentary proof that the specific source of the excipient is TSE/BSE risk free.	☐
	3)	Study of equivalence of the material and the impact on production of the pharmaceutical product.	☐

V9	**Change in the specifications of the immediate packaging of the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of proposed specifications.	☐
	3)	Details of any new analytical method & validation data[ii].	☐
	4)	Certificate of analysis of minimum of two batches in the new specifications.	☐

V10	**Change to a test procedure of the immediate packaging of the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Comparative validation results showing that the previous test and the proposed one are atleast equivalent.	☐

V11	**Change in the qualitative and/or quantitative composition of the immediate packaging material**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Appropriate data/information on new packaging material.	☐
	3)	Proof must be provided that no interaction between the content and the packaging material occurs.	☐

	4)	Copy of proposed specifications.	☐
	5)	The batch numbers used in stability studies[(i)].	☐

V12	**Change (replacement, addition or deletion) in supplier of packaging components or devices**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Data to demonstrate accuracy, precision and compatibility of the packaging component remain the same.	☐
	3)	Copy of proposed specifications.	☐

V13	**Change to in-process tests or limits applied during the manufacture of the product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of proposed specifications.	☐
	3)	Details of any new analytical method and validation data[(ii)].	☐
	4)	Certificate of analysis on two production batches of the finished product for all tests in the new specification	☐
	5)	Justification for addition of new tests and limits.	☐

V14	**Change in the batch size of the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Certificate of analysis on a minimum of one production batch manufactured with proposed batch size..	☐
	3)	Copy of release and end-of-shelf life specifications.	☐
	4)	The validation protocol & batch numbers (≥ 3) used in the validation study[(ii)].	☐
	5)	For solid dosage forms: dissolution profile data on a of minimum one representative production batch[(iii)].	☐
	6)	The batch numbers used in stability studies[(i)].	☐

V15	**Change in the colouring/flavouring system currently used in the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Sample of the new product.	☐
	3)	Documentary proof that the specific source of the excipient is TSE/BSE risk free.	☐
	4)	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods.	☐
	5)	For solid dosage forms: dissolution profile data on a minimum of one representative production batch[(iii)].	☐
	6)	The batch numbers used in stability studies[(i)].	☐

V16	**Change in the specifications of the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Copy of proposed specifications.	☐
	3)	Details of any new analytical method and validation data[ii].	☐
	4)	Certificate of analysis on two production batches of the finished product for all tests in the new specification.	☐
	5)	Justification for addition of new tests and limits.	☐

V17	**Change (replacement/addition) in the test procedure of the finished product**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Comparative validation results showing that the previous test and the proposed one are atleast equivalent	☐

V18	**Change or addition of imprints, bossing or other markings (except scoring/breakline) on tablets or printing on capsules**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	A sample of the product.	☐

V19	**Change or Inclusion of Score/Break Line of Tablet**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Detailed drawing or written description of the current and proposed tablet.	☐
	3)	Justification to support the change or inclusion of score/break line.	☐
	4)	Official letter of commitment to inform users of the relevant changes, and that the current product stocks will be exhausted before the new product is marketed.	☐
	5)	Current and proposed release and shelf life specifications.	☐

V20	**Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass**		
	Supporting Documents		
	1)	Replacement of relevant pages of the dossier.	☐
	2)	Comparative dissolution data on at least one pilot scale batch of the current & proposed dimensions[iii].	☐
	3)	Justification of not submitting a new bioequivalence study according to current WHO Guidelines on Bioequivalence[iv].	☐
	4)	Samples of the finished product.	☐

V21	**Change coating weight of tablets or weight of capsule shell**	
	Supporting Documents	
	1) Replacement of relevant pages of the dossier.	☐
	2) Comparative dissolution profile data of at least two pilot batches of the new formulation[iii].	☐
	3) Justification of not submitting a new bioequivalence study according to current WHO Guidelines on Bioequivalence[iv].	☐
	4) The batch numbers used in stability studies[i].	☐

V22	**Change (number of units in a pack/fill weight/fill volume) in pack size of the finished product**	
	Supporting Documents	
	1) Replacement of relevant pages of the dossier.	☐
	2) Justification of new pack-size, showing that the new size is consistent with the dosage regimen & duration of use as prescribed.	☐
	3) Written commitment that the stability studies will be conducted in accordance with WHO Guidelines[i].	☐

V23	**Change in shelf-life of the finished product (as packaged for sale/after first opening/after dilution)**	
	Supporting Documents	
	1) Replacement of relevant pages of the dossier.	☐
	2) Copy of end-of-shelf life finished product specification, where applicable.	☐
	3) The batch numbers used in stability studies[i].	☐

V24	**Change of Product Labeling Due to Safety Update**	
	Supporting Documents	
	1) Replacement of relevant pages of the dossier.	☐
	2) Justification and clinical documents to support proposed changes.	☐

V25	**Change in package insert**	
	Supporting Documents	
	1) Replacement of relevant pages of the dossier.	☐
	2) Justification and clinical documents to support proposed changes.	☐
	3) Legalized approval of the Health Authority of country of origin for the new changes.	☐
	4) Comparison between old and new package insert	☐
	5) Copy of new package insert.	☐