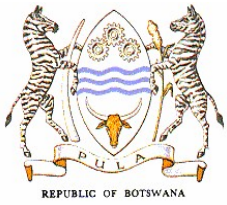
GUIDELINE ON DOSSIER REQUIREMENTS FOR VARIATIONS

Third Edition

August 2018



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ABBREVIATIONS

DRU	Drug Regulatory Unit
API	Active Pharmaceutical Ingredient
FPP	Finished Pharmaceutical Product
INN	International Proprietary Name
NDRA	National Drug Regulatory Authority
DRA	Drug Regulatory Authority
WHO	World Health Organization
ICH	International Conference on Harmonization
PICs	Pharmaceutical Inspection Co-operation Scheme
GMP	Good Manufacturing Practice
QC	Quality Control
TSE	Transmitting Animal Spongiform Encephalopathy
BSE	Bacillus Animal Spongiform Encephalopathy
BP	British Pharmacopoeia
USP	United States Pharmacopoeia
Ph.Eur.	European Pharmacopoeia
Ph. Intl.	International Pharmacopoeia
JP	Japan Pharmacopoeia
SmPC	Summary of Product Characteristics

Introduction:

The medicinal products for human use are granted a marketing authorization for a period of 5 years, renewable upon application three months before expiry. Throughout the life of a medicinal product, the marketing authorization holder is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. Marketing authorization holders may, in addition, wish to alter/improve the medicinal product or to introduce an additional safeguard during the period of five years. Such changes or variations may involve administrative and/or more substantial changes.

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 marketing authorisation. This guide was prepared in order to clarify what documentation should be submitted with each type of Variation. These guidelines have been drawn from the WHO pre-qualification document 2007 & European Commission 2006 and adapted to suite our won requirements in Botswana.
In principle, all parts of the dossier that are affected by a variation are to be resubmitted. Applicants should present a summary of the intended change in tabulated format in which the current state/situation and the situation after the intended change are compared in order to outline the scope of the change in a transparent manner. A justification should always follow why the change needs to be introduced.

The DRU application form "Application for Variation to a Marketing Authorization" should always be used. The application form is self explanatory. The Applicant is responsible for ensuring that the notification complies fully with the correct number of copies of the completed application form, check list and the supporting data, along with correct fee should be submitted to DRU

Classification of Variation:

The Variations may be classified as:
A minor variation is a change, which is unavoidable and can be found listed in Annex I of the present document.

A major variation is a change to the documentation which can be a change for which the submission of a new dossier would be necessary (Annex II).

Procedure for Minor variations

The applicant should ensure that the specific conditions for the minor variation are met, and that the application form is accompanied by:

- A copy of the relevant page(s) of the "Guideline on dossier requirements for minor variations".
- All required documentation as specified in the Guideline.
- Where relevant, the revised product information.

Minor variation notifications should be addressed and sent to the attention of the Drug Regulatory Unit (DRU) at the following address:

THE CHIEF PHARMACIST
Drug Regulatory Unit
3rd Floor, D Block
Ministry of Health
Gaborone, Botswana

Procedure for Major variation

The applicant should ensure that the specific conditions for the major variation are met and that the application form is accompanied by:

- Supporting data relating to the variation applied for;
- Update/Addendum to quality summaries, non-clinical overviews and/or clinical overviews. When non-clinical/clinical study reports are submitted, their relevant Summaries should be included.
- All required documentation as specified in the Guideline.
- Where relevant, the revised product information.

Major variation notifications should be addressed and sent to the attention of the Drug Regulatory Unit (DRU) at the following address:

THE CHIEF PHARMACIST
Drug Regulatory Unit
3rd Floor, D Block
Ministry of Health
Gaborone, Botswana

GENERAL INSTRUCTIONS:

The following Instructions are to be followed:

- The application form for all types of minor/major variation dully filled, signed and stamped should be submitted.

- Application for minor/major Variation shall not be accepted if the product registration has expired.

- The required documents must be submitted in the letter head of the company.

- All declarations should also be on letterhead of the company but can be signed by Responsible Pharmacist.

- All the documents must be submitted in proper file with Index. Incomplete applications and loose documents will not be accepted.

- All applications for approval of minor/major variations must be accompanied covering letter from the manufacturer explaining the proposed variations in the product with justification.

- Photocopies of the certificates of registration/ re-registration and renewal thereof, and minor/major variation(s) approved earlier must be attached with the application.

- Manufacturer shall fill the application form for variation and submit along with necessary documents and samples.

- Samples, whenever submitted to the Drug Regulatory Unit must be identical to the sale pack to be registered and accompanied by the certificate of analysis.

Annex I

MINOR VARIATIONS

Sl. No.	Variation	Conditions	Documentation Required
V1	Change in the name and/or address of the applicant (Marketing Authorization Holder)	1	1

Conditions

1. The applicant of the approved product shall remain the same legal entity.
2. No confusion with the names of existing medicinal products or with INN name of the product.

Documentation:

1. A formal document from the manufacturer/ a relevant official body in which the new name or new address is mentioned.
2. A formal document from the applicant in which the new name of the product is mentioned.
3. Amended immediate label, outer label & package insert for the product with new name.

Sl. No.	Variation	Conditions	Documentation Required
V2	Transfer of applicancy (Marketing Authorization Holder)	1	1, 2, 3, 4

Conditions

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation:

1. Notification letter from current applicant and acceptance letter from new applicant
2. Submission of a revised Application Form.
3. A formal formal document from the manufacturer / a relevant official body in which the new name is mentioned.
4. Amended immediate label, outer label & package insert for the product with new applicant name if applicable.

Sl. No.	Variation	Conditions	Documentation Required
V3	Change in the name and/or address of a manufacturer of the active pharmaceutical ingredient (API)	1	1, 2

Conditions

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation:

5. Replacement of relevant page(s) of the dossier.
6. Replacement of relevant page(s) of the dossier.

Sl. No.	Variation	Conditions	Documentation Required
V4	Change in the name of the finished pharmaceutical product (FPP)	1, 2	1, 2

Conditions

1. No change in the location of the manufacturing site and in the manufacturing operations.
2. No confusion with the International Nonproprietary Name (INN).

Documentation:

1. A formal document from the National Drug Regulatory Authority (NDRA) in which the new name is approved.
2. Replacement of relevant page(s) of the dossier.

Sl. No.	Variation	Conditions	Documentation Required
V5	Change in the name and/or address of the FPP	1	1, 2, 3

Conditions

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation:

1. A formal document from the National Drug Regulatory Authority (NDRA) in which the new name is approved.
2. A formal document from the manufacturer in which the new name or new address is mentioned.
3. Replacement of relevant page(s) of the dossier

Sl. No.	Variation	Conditions	Documentation Required
V6	Change to quality control (QC) testing of the finished product (replacement or addition of a site where batch control/testing takes place)	1, 2	1, 2, 3

Conditions

1. The site is appropriately authorized for GMP compliance by the NDRA.
2. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Documentation

1. The corresponding letter should clearly outline the “approved” and “proposed” quality control sites.
2. Documented evidence that the site is appropriately authorized by the NDRA.
3. Documented evidence that the Method transfer from the old to the new site or new test laboratory has been successfully completed.

Sl. No.	Variation	Conditions	Documentation Required
V7	Deletion of any manufacturing site (including for an API, intermediate or finished product, package site, manufacturer responsible for batch release)	None	1

Conditions

None

Documentation

1. The corresponding letter should clearly name the manufacturer to be deleted.

Sl. No.	Variation	Conditions	Documentation Required
V8	Minor change in the manufacturing process of the API	1, 2	1, 2, 3

Conditions

1. No change in qualitative and quantitative impurity profile or in physicochemical properties.
2. The route of synthesis remains the same, i.e. intermediates remain the same.

Documentation

1. Replacement of relevant page(s) of the dossier.
2. Certificate of analysis of at least two batches manufactured according to the approved and the proposed process.
3. Copy of approved specifications of the API.

Sl. No.	Variation	Conditions	Documentation Required
V9	Change in the batch size of the API or intermediate		
	a) Up to 10-fold increase in original batch size	1, 2, 3	1, 4
	b) Downscaling to 10-fold in original batch size	1, 2, 3, 4	1, 4
	c) More than 10-fold increase in original batch size	1, 2, 3	1, 2, 3, 4, 5, 6

Conditions

1. Any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The change does not affect the reproducibility of the process.
4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation:

1. Replacement of relevant pages of the dossier.
2. The batch numbers of the tested batches having the proposed batch size.
3. Certificate of analysis on a minimum of one production batch manufactured with proposed batch size.
4. Copy of approved specifications of the API.

Sl. No.	Variation	Conditions	Documentation Required
V10	Change in the specification of an API, a starting chemical material/intermediate/reagent used in the manufacturing process of the API		
	a) Tightening of specification limits	1, 2, 3	1, 2
	b) Addition of a new test parameter to the specification of - API - a starting chemical material/intermediate/reagent	 2, 4 2, 4	 1, 2, 3, 4, 5 1, 2, 3, 4

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to approval or a major change procedure after approval).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Copy of approved and proposed specifications.
3. Details of any new analytical method & validation data[(ii)].
4. Certificate of analysis of minimum of two production batches.
5. Justification of not submitted a new bioequivalence study according to the current *DRU guidelines*[(iv)].

Sl. No.	Variation	Conditions	Documentation Required
V11	Change (replacement/addition/other changes) in test procedure for API or starting chemical material/intermediate/reagent used in the manufacturing process of the API	1, 2, 3, 4	1, 2

Conditions

1. The method of analysis should remain the same & no new impurities are detected.
2. Appropriate (re)-validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Comparative validation results showing that the approved test and the proposed one are equivalent.

Sl. No.	Variation	Condition	Documentation Required
V12	Change in		
	a) The re-test period of the API	1, 2	1, 2, 3
	b) The storage conditions for the API	1, 2	1, 2, 3

Conditions

1. Stability studies have been done to the approved protocol .The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation:

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)].

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Sl. No.	Variation	Condition	Documentation Required
V13	Change or replacement of an excipient with a comparable excipient	1, 2, 3, 4	1, 2, 3, 4, 5, 6, 7, 8, 9

Conditions

1. Same functional characteristics of the excipient.
2. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one
3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months (accelerated and real time) satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data will be provided immediately to DRU if outside specifications or potentially outside specification at the end of the approved shelf-life (with proposed action).

Documentation:

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 *DRU guidelines*[iv].
6. Data to demonstrate that the new excipient does not interfere with the finished product specification test method.
7. Stability studies conducted in accordance with DRU guidelines[i]
8. European Certificate of Suitability, if applicable.
9. TSE European Certificate of Suitability , if applicable.

Sl. No.	Variation	Condition	Documentation Required
V14	Change in the specification of an excipient		
	a) Tightening of specification limits	1, 2, 3	1, 2
	b) Addition of a new test parameter to the specification	2, 4	1, 2, 3, 4, 5, 6, 7, 8

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to approval of the product or a major change procedure after approval).

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*
(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*
(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*
(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

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 *DRU 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 *DRU guidelines*[iii].
6. Justification of not submitted a new bioequivalence study according to the current *DRU guidelines* on bioequivalence[iv].
7. Comparative validation results showing that the current test and the proposed one are equivalent.
8. Stability studies conducted in accordance with *DRU guidelines*[i].

Sl. No.	Variation	Condition	Documentation Required
V15	Change in test procedure for an excipient		

	a) Minor changes to an approved test procedure	1, 2, 3	1
	b) Other changes including replacement of an approved test procedure	2, 3, 4	1, 2

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier
2. Comparative validation results showing that the current test and the proposed one are equivalent.

Sl. No.	Variation	Condition	Documentation Required
V16	Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material	1	1, 2, 3, 4

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Condition:

1. Excipient and finished product release and end-of-self life specifications remain the same.

Documentation:

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.
4. TSE European Certificate of Suitability, if applicable.

Sl. No.	Variation	Condition	Documentation Required
V17	Change to comply with a major international pharmacopoeia (BP. Ph.Eur, USP, JP, Ph.Int)		
	a) API	1, 2	1, 2, 3, 4, 5
	b) Excipient	1, 2	1, 2, 3, 4, 5

Conditions

1. The change is made exclusively to comply with a major international pharmacopoeia.
2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.

Documentation:

1. Replacement of relevant page(s) of the dossier.
2. Copy of approved and proposed specifications.
3. Certificate of analysis on two production batches of the relevant substance for all tests in the new specification.
4. Analysis of the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities.
5. Where appropriate, Certificate of analysis of two production batches containing the substance complying with approved and proposed specification.

Sl. No.	Variation	Condition	Documentation Required
V18	Change in the specifications of the immediate packaging of the finished product		
	a) Tightening of specification limits	1, 2, 3	1, 2
	b) Addition of a new test parameter	2, 4	1, 2, 3, 4

Conditions:

1. The change is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the assessment procedure prior to approval of the product or a major change procedure after approval).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

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.

Sl. No.	Variation	Condition	Documentation Required
V19	Change to a test procedure of the immediate packaging of the finished product (Minor change to already existing test procedure or inclusion/replacement/addition of a test procedure	1, 2, 3, 4	1, 2

Conditions:

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.

3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Comparative validation results showing that the previous test and the proposed one are at least equivalent.

Sl. No.	Variation	Condition	Documentation Required
V20	Change to any part of (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of type of plastic used, etc)	1	1

Condition:

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

Documentation:

1. Replacement of relevant pages of the dossier.

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*
(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*
(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*
(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Sl. No.	Variation	Condition	Documentation Required
V21	Change in the qualitative and/or quantitative composition of the immediate packaging material		
	a) Semi-solid and liquid pharmaceutical	1, 2, 3, 4	1, 2, 3, 4, 5
	b) All other pharmaceutical forms	1, 2, 3, 4	1, 4, 5

Conditions:

1. The product concerned is not a sterile product.
2. The packaging type and material remain the same (e.g. blister to blister).
3. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
4. Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation:

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 approved and proposed specifications.
5. The stability studies conducted in accordance with *DRU guidelines*[(i)].

Sl. No.	Variation	Condition	Documentation Required
V22	Change (replacement/addition) in supplier of packaging components or devices	1, 2, 3, 4	1, 2, 3, 4
	- Deletion of a supplier	1	1

Condition:

1. No deletion of packaging component or device.
2. The qualitative and quantitative composition of the packaging components/device remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilization method and conditions remain the same, if applicable.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this extent.
3. Copy of approved and proposed specifications.
4. Evidence of compatibility of the device or packaging component with the finished product.

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Sl. No.	Variation	Condition	Documentation Required
V23	Change to in-process tests or limits applied during the manufacture of the finished product		
	a) Tightening of in-process limits	1, 2, 3	1, 2
	b) Addition of a new test and limits	2, 4	1, 2, 3, 4, 5

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to approval of the product or a major change procedure after approval).
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any change should be within the range of approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Copy of approved end-of-shelf life 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.

Sl. No.	Variation	Condition	Documentation Required
V24	Change in the batch size of the finished product		
	a) Up to 10-fold increase in original batch size	1, 2, 3, 4	1, 4
	b) Downscaling by upto 10-fold in original batch size	1, 2, 3, 4, 5	1, 4
	c) More than 10-fold increase in original	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6

Conditions

1. The change does not affect reproducibility and/or consistency of the product.
2. The change relates only to standard immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different sized equipment.
4. Validation protocol is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the DRU guideline on validation of manufacturing[(ii)].

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*
(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*
(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*
(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation:

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 minimum of one representative production batch[(iii)].
6. Stability studies conducted in accordance with *DRU guidelines*[(i)].

Sl. No.	Variation	Condition	Documentation Required

V25	Change in the colouring/flavouring system currently used in the finished product		
	a) Reduction or deletion	1, 2, 3, 4	1, 2, 6
	b) Increase, addition or replacement	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6

Conditions

1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.
3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test.
4. Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data shall be provided immediately to DRU if outside.
5. Specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photostability testing should be performed.
6. Documentary proof that the specific source of the excipient is TSE/BSE risk free.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Sample of the new product.

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

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. Stability studies conducted in accordance with *DRU guidelines*[(i)].

Sl. No.	Variation	Condition	Documentation Required
V26	Minor change in the manufacture of the finished product	1, 2, 3, 4	1, 2, 3, 4, 5, 6, 7, 8

Conditions

1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. In case of a change in the sterilization process, the change is to a standard pharmacopoeial cycle only.
4. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three

months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Replacement of the relevant page(s) of the dossier.
2. For semisolid and liquid products in which the API is present in non-dissolved form appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.
3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the approved product if outside specifications (with proposed action).
4. Justification of not submitted a new bioequivalence study according to the current *DRU guideline*[(iv)].
5. In case of a change to the sterilization process, validation data should be provided.
6. Copy of approved release and end-of-shelf-life specifications.
7. Certificate of analysis on a minimum of one batch manufactured to both the approved and the proposed process.
8. Stability studies conducted in accordance with *DRU guidelines*[(i)].

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*
(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*
(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*
(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Sl. No.	Variation	Condition	Documentation Required
V27	Change in shape or dimension of the container or closure		
	a) Sterile pharmaceutical forms	1, 2, 3	1, 2, 3
	b) Other Pharmaceutical forms	1, 2, 3	1, 2, 3

Conditions

1. No change in the qualitative or quantitative composition of the container and/or closure.
2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf-life (with proposed action).

Documentation

1. Replacement of the relevant page(s) of the dossier (including description, detailed drawing and composition of the container or closure material).
2. The batch numbers of the batches used in the stability studies should be indicated, where applicable.
3. Samples of the new container/closure.

Sl. No.	Variation	Condition	Documentation Required
V28	Change in the specification of the finished product		
	a) Tightening of specification limits	1, 2, 3	1, 2
	b) Addition of a new parameter	2, 4	1, 2, 3, 4, 5

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to approval of the product or a major change procedure after approval).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Copy of approved and proposed specifications.
3. Details of any new analytical method and validation data[ii].

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

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.

Sl. No.	Variation	Condition	Documentation Required
V29	Change (replacement/addition) in the test procedure of the finished product	1, 2, 3, 4	1, 2

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation:

1. Replacement of relevant pages of the dossier
2. Comparative validation results showing that the previous test and the proposed one are at least equivalent.

Sl. No.	Variation	Condition	Documentation Required
V30	Change or addition of imprints, bossing or other markings (except scoring/breakline) on tablets or printing on capsules	1, 2	1, 2

Conditions

1. Finished product release and end-of-shelf-life specifications have not been changed (except for appearance).
2. Any ink must comply with the relevant standards.

Documentation:

1. Replacement of relevant pages of the dossier.
2. A sample of the product.

Sl. No.	Variation	Condition	Documentation Required
V31	Change or Inclusion of Score/Break Line of Tablet	1	1, 2, 3, 4, 5, 6

Conditions:

1. Finished product release and end-of-shelf-life specifications have not been changed (except for appearance).

Documentation:

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.
6. Sample of the product.

Sl. No.	Variation	Condition	Documentation Required
V32	Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass		
	a) Gastroresistant, modified or prolong release pharmaceutical forms & scored tablets	1, 2	1, 2, 3, 4, 5
	b) All other tablets, capsules, suppositories & pessaries	1, 2	1, 4

Conditions

1. The dissolution profile of the reformulated product is comparable to the old one.
2. Release and end-of-shelf-life specifications of the product have not been changed (except for dimensions).

Documentation:

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 *DRU guidelines* on Bioequivalence[iv].
4. Samples of the finished product.

Sl. No.	Variation	Condition	Documentation Required
V33	Change in coating weight of tablets or weight of capsule shell		
	a) Immediate release oral dosage forms	1, 3, 4	1, 4
	b) Modified or prolonged release dosage forms	1, 2, 3, 4	1, 2, 3, 4

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one.
2. The coating is not a critical factor for the release mechanism.
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation:

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 *DRU guidelines* on Bioequivalence[iv].
4. Stability studies conducted in accordance with *DRU guidelines*[i].

Sl. No.	Variation	Condition	Documentation Required
V34	Change (number of units in a pack/fill weight/fill volume) in pack size of the finished product	1, 2	1, 2, 3

Conditions

1. New pack size should be consistent with the posology and treatment duration as approved in the SmPC.
2. The primary packaging material remains the same.

Documentation:

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 in SmPC.
3. Written commitment that the stability studies will be conducted in accordance with *DRU Guidelines*(i).

Sl. No.	Variation	Condition	Documentation Required
V35	Change in shelf-life of the finished product (as packaged for sale/after first opening/after dilution)	1, 2, 3	1, 2, 3

Conditions

1. Stability studies have been done to the approved protocol. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf-life does not exceed five years.

Documentation:

1. Replacement of relevant pages of the dossier.
2. Copy of end-of-shelf life specification of finished product, where applicable.
3. Stability studies conducted in accordance with *DRU guidelines*(i).

Note: **(i) Stability Studies:** In all cases of variations and changes the manufacturer should conduct stability studies whether or not the intended change will have an impact on the quality characteristics of APIs and or finishes products. The stability studies should be conducted in accordance with *DRU guidelines.*

(ii) Validation Studies: Should be done in accordance with *DRU guidelines.*

(iii) Comparative Dissolution Studies: Should be conducted in accordance with *DRU guidelines.*

(iv) Bioequivalence Data: Justification for not submitting Bioequivalence study should be in accordance with *DRU Guidelines.*

Sl. No.	Variation	Condition	Documentation Required
V36	Addition or replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded)	1, 2	1, 2, 3

Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.
2. The new device is compatible with the FPP and the FPP can still be accurately delivered.

Documentation

1. Replacement of the relevant page(s) of the dossier (including description, detailed drawing and composition of the device material and supplier where appropriate).
2. Reference to international standards marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
3. Samples of the new device.

Sl. No.	Variation	Condition	Documentation Required
V37	Change of Product Labeling Due to Safety Update	None	1, 2, 3

Conditions:

None

Documentation:

1. Replacement of relevant page(s) of the dossier.
2. Justification and clinical documents to support proposed changes.
3. Copy of a draft label.

Sl. No.	Variation	Condition	Documentation Required
V38	Change in package insert, addition/modification of - indication - new dosage regimen with no change to indication - deletion of contraindications, warnings, side effects, precautions, drug interactions, etc	None	1, 2, 3, 4, 5

Condition:

None

Documentation:

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.

ANNEX II

MAJOR VARIATIONS

Major changes exceed the scope of minor changes as listed in Annex I, e.g. they exceed/do not comply with the conditions to be fulfilled along with the change, but still do not cover the changes listed in Annex III.

They most likely consist of a:

i) **Change or addition of the manufacturing site of FPP (Manufacturer remains the same)**
ii) **Replacement or addition of a new manufacturing site or manufacturer of an API**
iii) **Change in the manufacturing process of the API**
iv) **Change in the composition of the finished product**
v) **Change of immediate packaging of the product**

It remains the applicant's responsibility to provide the relevant documentation (relevant parts of the dossier) expected to prove that the intended major change will not have an impact on the quality of the product.

Sl. No.	Variation	Condition	Documentation Required
V39	Addition of a packaging site of the FPP	1	1, 2, 3, 4, 5

Condition:

1. The change pertains only to non-sterile products.

Documentation:

1. GMP certificate from the local NMRA.
2. Amended artwork of the immediate label & outer label.
3. Specifications and Standard test procedures for the bulk container.
4. Transport Validation Protocol.
5. Hold Time Studies Data in the bulk container prior to shipping or Hold Time Studies Protocol for post shipping.

Sl. No.	Variation	Conditions	Documentation Required
V40	Change or addition or replacement of the manufacturing site of FPP (Manufacturer remains the same) involving:		
	a) Secondary packaging for all types of FPPs	2, 3	1, 2, 10

	b) Primary packaging site:		
	- Solid dosage forms, e.g. tablets & capsules	2, 3, 4	1, 2, 4, 10
	- Semi-solid, e.g. creams & Ointments, etc. or Liquid dosage forms, e.g. suspensions, emulsions, etc.	2, 3, 4, 5	1, 2, 4, 10
	c) All other manufacturing operations	1, 2, 3, 5	1, 2, 3, 4, 5, 6, 7, 8, 9, 10

Conditions

1. No change in the batch formula, description of manufacturing process and process intermediates or FPP specifications.
2. Satisfactory inspection in the last three years either by WHO or a drug regulatory authority (DRA) in the International Conference on Harmonization (ICH) or The Pharmaceutical Inspection Co-operation Scheme (PICs) region and associated countries.
3. Site appropriately authorized for GMP compliance by a NDRA (to manufacture the pharmaceutical form and the product concerned).
4. Product concerned is not a sterile product.
5. Validation protocol is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

Documentation:

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. Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.
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. Stability studies conducted in accordance with *DRU guidelines*[(i)].
9. For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.
10. The variation application should clearly outline the approved & proposed finished product manufacturers.

Sl. No.	Variation	Conditions	Documentation Required
V41	Replacement or addition of a new manufacturing site or manufacturer of an API	None	1- 9.

Documentation:

1. Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorization or a certificate of GMP compliance, if applicable.
2. A side-by-side comparison of the manufacturing flow charts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences.
3. Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
4. Replacement of relevant page(s) of the dossier.
5. If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, stability studies should have been started with at least two pilot scale or production scale batches and at least six months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to DRU if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6. A copy of the FPP manufacturer's API specifications.
7. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
8. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) and there is a significant difference in particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.
9. An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.

ANNEX III

CHANGES THAT MAKE A NEW APPLICATION NECESSARY

Changes that make a new application necessary consist of:

1. **Changes to the API**
   - Change of the API to a different API.
   - Inclusion of an additional API to a multicomponent product.
   - Removal of one API from a multicomponent product.

2. **Changes to the pharmaceutical form/dosage form**
   - Change from an immediate-release product to a slow- or delayed-release dosage form and vice versa.
   - Change from a liquid to a powder for reconstitution, or vice versa.
   - Change in the dose of one or more APIs

3. **Changes in the route of administration**

4. **Change or addition of the manufacturing site of FPP (Manufacturer changes)**