South African Health Products
Regulatory Authority
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General Guideline for the Submission of PEM Post-Registration Amendments

This guideline represents the current thinking of SAHPRA on this topic. It does not establish any rights for any person and is not binding on SAHPRA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact PEM Post Registration Team on postregqualityvariations@sahpra.org.za

Document History

Final Version	Reason for Amendment	Effective Date [dd Month yyyy]
1	New	
2		

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Contents

Glossary/List of Abbreviations

Abbreviation/ Term	Meaning
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
COA	Certificate of Analysis
CTD	Common Technical Document
DVP	Digital Variations Portal
EMA	European Medicines Agency
EMA variations classification guideline	Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures
FTP	File Transfer Protocol
FPP	Final Pharmaceutical Product
PEM	Pharmaceutical Evaluation Management
PI/PIL	Professional Information/Patient Information Leaflet
QIS	Quality Information Summary
QOS	Quality Overall Summary
QP	Qualified Person
RRA	Recognised Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority

1. INTRODUCTION

1.1 Purpose

The purpose of this document is to provide general information to applicants to assist in the processing of post-registration quality variation submissions, to identify common quality related deficiencies in recently assessed post-registration applications, and to provide additional guidance to help industry address these deficiencies in future submissions made to the unit. This will facilitate timeous processing and approval of post-registration quality variation applications by decreasing the number of deficiencies observed.

1.2 Scope

This guideline is relevant only to submissions made to for variations affecting the quality of orthodox human medicines. It does not include veterinary, biological, and complementary medicines.

1.3 General Information

1.3.1. Communication with the unit:

- All queries, including Z-code and extension requests, must be directed to postregqualityvariations@sahpra.org.za.
- For application follow ups, please consult industry facing tracker. If the application in question does not appear on the industry facing tracker one month after date of submission, please follow up with the unit. When following up with the unit, a copy of the proof of submission and the application letter must be attached to your email.
- Applicants are requested to refrain from sending unnecessary status update queries. An applicant may follow up on the status of a Type II submission if they have not received feedback from the unit 120 working days after date of submission.

1.3.2. Submission of multiple variations in a single application

- Applicants may include multiple variations of a single variation type/classification (e.g. an application may contain multiple Type IA **OR** multiple Type IB **OR** multiple Type II variations) in a single application.

- Applicants may **not** group variations of different types/classifications (e.g. Type IA variations should not be submitted with Type IB or Type II variations) unless changes are consequential **i.e. meaningful to be reviewed together.** A consequential variation is regarded as a change, which is an unavoidable and direct result of another change (i.e. the 'main change') and not simply a change which occurs at the same time.

  Cases where the submission of changes of different variation types/classifications in a single application are considered acceptable:

  - One or more of the variations in the submission is a major variation of type II; all other variations (Type IA or Type IB) in the submission are variations which are consequential to this major variation of type II.

  - One or more of the variations in the group is a minor variation of type IB; all other variations (Type IA) in the submission are minor variations which are consequential to this minor variation of type IB.

1.3.3 Z-code requests

The process for Z-code request is defined below:

1. Prior to submitting a Z- Code request to SAHPRA, the applicant must first confirm that a relevant code for such a variation does not exist in the EMA Variations Classification guideline and SAHPRA variation addendum.

2. If code does not exist in the guideline, the applicant should refer to CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/200 (https://www.hma.eu/human-medicines/cmdh/procedural-guidance/variation/art-5-recommendations.html) for common Z- code classifications. If the variation has received a Z-code classification from EMA, the applicant may use the same classification when submitting to SAHPRA.

3. If the unforeseen variation is not included in the documents referenced above, the applicant must send a Z-code request to the unit for confirmation of variation code and classification of the variation. A Z-code request form must accompany the Z-code request. Please see Z-code request form template in annexure 1.

1.3.4 Type II submissions

To facilitate timeous evaluation and approval of Type II variations, SAHPRA has included Type II variations guide in this communication (refer to annexure 3). This document provides guidance on the technical data requirements to support common Type II variations. Please note: This guidance lists only the minimum technical data requirements for Type II variations. Applicants are advised to include additional data in support of the Type II variation if available. SAHPRA reserves the right to request further data if deemed necessary.

1.3.5 Inspectorate/Quality Combined:

The following variations are evaluated by both quality and inspectorate unit:

- B.II.b.1.b
- B.II.b.1.c (for pharmaceutical forms manufactured by complex manufacturing processes)
- B.II.b.1.d
- B.II.b.1e
- B.II.b.1.f

Applicants are requested to pay the relevant fees and provide supporting documents applicable to both units. In addition to the documents listed in EMA Variations Classification Guideline, applicants are requested to provide batch manufacturing records (3.2.R.7) from proposed site for product (s) in question. Recommendation letters issued by the unit reflect outcome/regulatory decision taken by PEM Post Registration unit only. A separate communication will be issued by inspectorate. Please note that this change is not implementable unless approval is received from both the quality and inspectorate units.

1.3.6 Introduction of a new manufacturing site for the finished product:

The following complex related changes could be considered for submission under a single type II scope B.II.b.1 - Addition of a new finished product (FP) manufacturing site:

- Minor changes to the manufacturing process;
- Changes in batch size; and
- in-process controls to adapt to the new manufacturing site settings.

Complex related changes submitted under a single type II should always be clearly identified in the amendment schedule. A clear description of all the related changes should be provided in the precise scope. All the related changes should be listed in the present/proposed table of the amendment schedule.

Changes affecting the FP not directly related to the introduction of the new manufacturing site such as changes in excipients, specification parameters /limits for the FP, container closure system including suppliers, should be submitted as additional variations.

1.3.7 Quality requirements for baseline submissions

Checklist for quality requirements for baseline submissions has been included in Annexure II. Applicants are requested to appended completed checklist to the cover letter (module 1.0) of the baseline submission. In instances where a document specified on the list has been has not been included in the submission, a justification for the omission must be provided.

Common Deficiencies:

Module 1:

1.0 Application Letter

- For product registered through reliance, kindly indicate this in the cover letter.
- When the same variation is applied for, for different products (duplicates, clones, or same molecules only) in separate submissions, kindly indicate this in the cover letter. This will (i) allow for simultaneous evaluation of both submissions and (ii) will allow SAHPRA to internally rely on recommendation made for past applications.
- For API source change variations supported by an ASMF, the applicant must provide confirmation that restricted part has been submitted to SAHPRA.

1.2.2.1 Proof of Payment

- Provide proof of payment breakdowns when bulk payments are made.

1.2.2.6 API change control

- For variations that require QP Declaration (e.g., addition/replacement of API or FPP manufacturer), include declaration in this section. Please refer to EMA guidance and template for QP declaration '' Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template" https://www.ema.europa.eu/en/template-qualified-persons-qp-declaration-concerning-good-manufacturing-practice-compliance-active.

1.5.2.1 Amendment Schedule

- Ensure the amendment schedule is organized in a clear and logical manner.
- Ensure all variations (including code and classification) listed in 1.0 are included the amendment schedule. Variations found in amendment schedule but not listed in the cover letter will not be evaluated.

- A justification/reason must be included for every variation applied for. Failure to provide adequate justification will result in queries which will further delay the approval process.
- Poorly populated/formatted amendment schedules will result in a rejection of the submission.

1.5.5. PI/PIL Amendments/Updates

- For quality variations affecting the PI/PIL (e.g., change in appearance of FPP, change in container, storage conditions etc.), include a revised PI/PIL in your submission (1.5.5).

- Once variations affecting the PI/PIL are approved, applicants must submit the amended PI/PIL as well as PEM approval letter or variation summary report (for applications submitted on the DVP) to the clinical unit. Refer to variation's addendum for clinical codes.

1.8 Validation Template

- Applicants are advised include a completed validation template in their submission. A PDF version of this document should be included in 1.8 and Word version in working documents folder of your submission.

- The PEM section (section C) of the VALIDATION TEMPLATE FOR Ectd VARIATION APPLICATIONS (OF-HPA-03A) is applicable to both eCTD and eSubmission applications and should therefore be included in submissions made on the DVP and FTP. It is noted that hyperlinking of the validation template may not be feasible for eSubmissions so a concession is made by SAHPRA in this regard.

- For z-code applications: all conditions and all documentation requirements are applicable; as far as is relevant. Alternatively, the applicant may populate Z-code information in Type II section of the validation template (Section C)

Module 3:

Module 3.2.S

3.2.S.2.1 : Applicants are reminded to provide supporting data listed in the CEP/CPQ section of 2.02 Quality and Bioequivalence Guideline and WHO TRS 970 when adding/replacing API manufacturer supported by CEP/CPQ, in addition to documents required by EMA. Applicants are also reminded to include information relating to the GMP status of API and intermediate manufacturing site.

3.2.S.4.1 Ensure API and FPP manufacturer API specifications are signed, dated and version controlled

3.2.S.4.2 For changes to analytical method (B.I.b.2 variations), please ensure document 2 (Comparative validation results, or if justified comparative analysis results ….) listed in EMA Variations Classification Guide is provided.

3.2.S.4.4. Batch analysis

- In addition to tabulated batch analysis, include corresponding COAs.
- EMA requirements (number of batches, batch size etc). for batch analysis change depending on the type of variation applied for. Please ensure batch analysis provided is in line with EMA requirement. Applicants may include more batches than stipulated in EMA guideline but not less.

3.2.S.4.5

- Addition of non-pharmacopeial specifications and/or specification limits must be justified. Provide supporting data when necessary.
  Justification of removal of non-significant and/or obsolete specifications must be provided. This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.

Module 3.2.P

3.2.P.1

- For variations where the appearance of the final product is changed, include photographs of the final product in this section.

- For Quantitative changes to Inactive Pharmaceutical Ingredients (IPI) e.g., B.II.a.3.a1: deletion or partial deletion of an ingredient to affect the colour or flavour of the finished product. These percentages are based on the assumption that the drug substance in the product is formulated to 100 % of the label claim. The total additive effect of all excipient changes should not be more than 5 %.

EXCIPEIENT	**PERCENT EXCIPIENT (w/w) OUT OF TOTAL DOSAGE FORM WEIGHT**
FILLER	±5
DISINTEGRANT	
STARCH	±3
OTHER	±1
BINDER	±0.5
LUBRICANT	
CALCIUM (Ca) OR MAGNESIUM (Mg) STEARATE	±0.25
OTHER	±1
GLIDANT	
TALC	±1
OTHER	±0.1
FILM COAT	±1

- For changes to the technical grade of an IPI and changes in excipients greater than those listed above but less than or equal to the following percent ranges e.g., B.II.a.3.b.2 qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the finished product.

EXCIPEIENT	PERCENT EXCIPIENT (w/w) OUT OF TOTAL DOSAGE FORM WEIGHT
FILLER	±10
DISINTEGRANT	
STARCH	±6
OTHER	±2
BINDER	±1
LUBRICANT	
CALCIUM (Ca) OR MAGNESIUM (Mg) STEARATE	±0.5
OTHER	±2
GLIDANT	
TALC	±2
OTHER	±0.2
FILM COAT	±2

3.2.P.3.1 Please refer to note 1.3.2 of this document for information relating to addition/replacement of final product manufacturers.

3.2.P.3.5 Batches used for process validation studies must be consecutive. If batches are manufactured consecutively but batch numbering is not consecutive, kindly include batch numbering SOP in your submission.

3.2.P.5.1 Ensure in process and FPP specifications are signed, dated and version controlled.

3.2.P.5.2 : For changes to analytical method (B.II.d.2 variations), please ensure document 2 (Comparative validation results, or if justified comparative analysis results ….) listed in EMA Variations Classification Guide is provided.

3.2.P.5.4 Batch analysis

- In addition to tabulated batch analysis, include corresponding COAs.
- EMA requirements (number of batches, batch size etc.) for batch analysis change depending on the type of variation applied for. Please ensure batch analysis provided are in line with EMA requirement for that particular variation. Applicants may include more batches than stipulated in EMA guideline but not less unless justified.

3.2.P.5.6 Justification of Specifications

- Addition of non-pharmacopeial specification and/or specification limits must be justified. Provide supporting data when necessary.
- Justification of removal of non-significant and/or obsolete specifications must be provided. Provide supporting data when necessary. This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.

3.2.P.7 Container Closure System

For variations wherein the container closure system is changed, include photographs of new/modified container in this section.

3.2.P.8 Stability

- For amendments that may potentially affect the stability of the FPP, a reminder to include stability data and relevant declarations as required by EMA.
- Stability data provided in support of variations should not be older than 5 years (i.e., batches should not be older than 5 years).

Module 3.2.R

3.2.R.7 Batch Records

For variations that affecting the production process of the final product e.g. new FPP manufacturer, change in manufacturing process, batch size , in-process controls and/or ingredients , updated signed master and executed batch records in English will be required by SAHPRA.

3.2.R.8 Quality Overall Summary and Quality Information Summary

- A completed Quality Information Summary must accompany all quality variation submissions made to SAHPRA.
- Quality Overall Summaries are only required for API source change variations (B.1.a.1.b & B.1.a.1.g) or when extensive changes to the DMF are applied for. A partial QOS wherein only sections pertaining to proposed source are populated will be sufficient. SAHPRA reserves the right to request full QOS where deemed necessary.
- A PDF version of this document should be included in 3.2.R.8 and a Word version should be included in the working documents folder.

2. REFERENCES

The following related documents are referenced:

- SAHPRA Quality and Bioequivalence Guideline (SAHPGL-PEM-02)
- SAHPRA BAU Variations Communication (SAHPGL-HPA-05)
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)

3. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision It will be reviewed on this timeframe or as required.

Annexure I - Z- Code request template. *(Populate this information on a document that includes your company letter head)*

Z-Code Request

Application Number (s)	
Proprietary Name(s)	
Active Pharmaceutical Ingredient	
Dosage Form	

(Box below to be duplicated if multiple variations)

Code Proposed By Applicant	
Current Information	**Proposed Information**
Description of Variation:	
Background of Change/Justification of Change:	

Signature:

Date:

Annexure II – CTD checklist

Checklist below is to be included in submissions of that include CTD conversion variation. This checklist should also be included as an annex to the cover letter for the baseline sequence when converting from Esubmission to ECTD.

Variation classification/ code: Type IA, B.II.CTD

3.2.S. Active Pharmaceutical Ingredient / Drug Substance (*To be duplicated when there is more one API or more than one API manufacturer)*

API: **API Manufacturer**

DMF/SAHPRA APIMF no:

Description or critical issue	**Included in the application (Yes / No) If Not Applicable, state N/A**	
	Yes	**No**
3.2.S.1. General Information		
3.2.S.1.1. Nomenclature		
3.2.S.1.2. Structure		
3.2.S.1.3 general properties		
3.2.S.2 Manufacture		
3.2.S.2.1 Manufacturer (Name, Physical address - country, state, city, road, plot number, unit, block/workshop)		
3.2.S.2.2. Description of the manufacturing process and process controls		
a) Reaction scheme showing chemical reactions and reagents		
• manufacturing flow chart showing reaction conditions and in-process controls		
b) A detailed narrative of the synthetic process or where to locate it in the dossier (AP or RP)		
c) Materials reprocessing and reworking		
• Solvent recovery and reuse.		
3.2.S.2.3 Control of Materials		
a) List of the starting materials		
• Key starting material:		
b) Source of the starting material		
c) Specifications of the starting material		
d) CoAs from API SM manufacturer and API manufacturer		
3.2.S.2.4 Critical steps, parameters and controls. (only sterile APIs)		
3.2.S.2.5 Process validation and / or evaluation (only sterile APIs)		
3.2.S.2.6 Manufacturing process development (only sterile APIs)		
3.2.S.3 Characterization		

3.2.S.3.1 Elucidation of Structure and other Characteristics		
• Control of polymorphism, if applicable.		
• Particle size distribution, if applicable		
3.2.S.3.2 Impurities		
• *Nitrosamine risk assessment*		
3.2.S.4 Control of the API		
3.2.S.4.1. Specifications of the API ***(API & FPP Manufacturers)***		
• Reference number and/or version number or date		
• Compendial or in-house.		
• Summary of specifications.		
• Variations - requested by assessors or company initiated.		
3.2.S.4.2 Analytical procedures		
• Standard Testing Procedures (STPs) reference numbers		
• Compendial or in-house.		
• Summary of key parameters		
*3.2.S.4.3 Validation data of analytical procedures (**all in-house methods)***		
• Protocol and report reference numbers or version numbers/dates		
• Batch numbers, types and sizes used.		
• Summary of data		
3.2.S.4.4 Batch analyses		
• *Batch analysis data and CoAs*		
3.2.S.5 Reference Standards or Materials		
• Primary and secondary reference standard information		
• Overlaid IR spectrum		
3.2.S.6 Container Closure System		
• **Specification including identification test**		
3.2.S.7 Stability		
3.2.S.7.1 Stability Summary and Conclusions		
• Batch numbers, type and sizes used.		
• Study conditions.		
• Shelf life and labelling instructions for storage.		
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment		
• Any stability commitments.		
3.2.S.7.3 Stability data		
• Summary of data tables		
Motivation of omission of documents, if applicable:		

3.2.P. FINAL PHARMACEUTICAL PRODUCT (FPP)

Description or critical issue	Included in the submission (Yes / No) If Not Applicable, state N/A	
	Yes	**No**
3.2.P.1 Description and Composition of the FPP		
a) Description of the FPP		
b) Composition of the FPP		
3.2.P.2 Pharmaceutical Development		
• Identification of the bio batch and bio batch size		
• Key quality attributes		
• Complete comparative in vitro dissolution study report (Or see module 3.2.R.1.4.1)		
• Pharmaceutical development report including data on the discriminatory nature of the dissolution method		
3.2.P.3 Manufacture		
3.2.P.3.1 Manufacturer(s)		
• Name and address of the site of the manufacturer (Physical address - country, state, city, road, plot number, unit, block/workshop)		
3.2.P.3.2 Batch Formula		
Batch formula for each strength (bracketing approach may be used for different batch size)		
3.2.P.3.3 Description of Manufacturing Process and Process Controls		
• Reference of master manufacturing formula/method or product master file (See 3.2.R.7)		
• Approved sources of API(s):		
(1) Name(s) of API(s)		
(2) Approved sources: name and address [see details in an (ii) above]		
(3) Material codes by FPP manufacturer.		
(4) Specifications used by FPP manufacturer		
• Identification of the commercial batch size		
• Outline of key manufacturing steps.		
• Key processing equipment		
3.2.P.3.4 Controls of Critical Steps and Intermediates		
• Identified critical parameters and in process controls		
3.2.P.3.5 Process Validation and/or Evaluation		
• Protocol and report reference numbers or version numbers/dates		
• Batch numbers, types and sizes used.		
• Summary of data		
• Hold times data		
• Media fill study and validation of the sterile manufacturing process		
3.2.P.4 Control of Excipients		

• Specifications of all excipients		
• Analytical methods for in-house methods		
3.2.P.5 Control of the FPP		
3.2.P.5.1 Specifications		
• Signed, dated and version-controlled specifications		
• Compendial or in-house.		
• Summary of specifications		
• Variations - requested by assessors or company initiated.		
3.2.P.5.2 Analytical methods:		
• Standard Testing Procedures (STPs) reference numbers		
• Compendial or in-house.		
• Summary of key parameters		
3.2.P.5.3 Validation of analytical procedures		
• Protocol and report reference numbers or version numbers/dates		
• Batch numbers, types and sizes used.		
• Summary of data		
3.2.P.5.4 Batch analyses		
• *Batch analysis data and CoAs*		
3.2.P.5.5 Characterisation of impurities		
3.2.P.5.6 Justification of specifications		
3.2.P.6 Reference standards or materials		
3.2.P.7 Container Closure System		
• Signed, specifications for all primary packaging materials		
• Pack size and description of packaging - highlight any packages withdrawn and reasons.		
• Product code, if any		
3.2.P.8 Stability data:		
3.2.P.8.1 Stability Summary and Conclusions		
• Batch numbers, type and sizes used.		
• Study conditions.		
• Shelf life and labelling instructions for storage.		
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment		
• Any stability commitments.		
3.2.P.8.3 Stability data		
• Summary of data		
• In-use stability data		
Variations and change control		
• Major changes made or proposed.		
• Requirement or commitment for revalidation or stability testing.		
• Frequency of changes and implications to change control - to and from changes following assessment.		
Motivation of omission of documents, if applicable:		

3.2.R. Regional Information

Description or critical issue	Included in the application (Yes / No) If Not Applicable, state N/A	
	Yes	**No**
3.2.R.1 Pharmaceutical and Biological Availability		
3.2.R.1.1 Overview		
3.2.R.1.2. Reference Products		
3.2.R.1.3 Certificates of Analysis		
3.2.R.1.4 Pharmaceutical availability studies		
3.2.R.2 Parent API Manufacturer with various Sites		
• Declaration		
3.2.S.R.3 Certificate(s) of suitability with respect the Ph.Eur. (CEPs) Confirmation of WHO API Prequalification (CPQ)		
3.2.R.4 Multiple API manufacturers		
3.2.R.4.1 Comparison of APIs		
3.2.R.4.2. Batch Analysis Data		
3.2.R.4.3. Confirmation of compliance with guidelines		
3.2.R.4.3. Certificates of Analysis		
3.2.R.6 Materials of animal/human origin		
3.2.R.7 Production Documentation		
3.2.R.7.1 Executed Production Documentation		
3.2.R.7.2 Blank/Master Production Documentation		
3.2.R.8 Other		
3.2.R.8.1 QIS document		
Motivation of omission of documents, if applicable:		

Bioequivalence (status quo (exemption) remains unchanged for all old medicines

Description or critical issue	**Included in the report (Yes / No)**
1. **Summary (Module 3.2.R.1)**	
1.1 Summary of bioequivalence studies performed	
1.2 Tabulation of the composition of the formulation(s) proposed for marketing and those used for bioequivalence studies	
2. Clinical Study Report (Module 5.3.1.2)	
3. Analytical Validation Report and Bioanalytical Study Report (Module 5.3.1.4)	
4. Case report forms and chromatograms	
Motivation of omission of documents, if applicable:	

BCS based Biowaiver

Description or critical issue	**Included in the report (Yes / No) If Not Applicable, state N/A**
1. Justification for a BCS Biowaiver (Module 3.2.R.1)	
2. Solubility (Solubility studies)	
3. Absorption / Permeability studies	
4. Comparison of test and comparator formulations	
5. Comparative in vitro dissolution study report	
Motivation of omission of documents, if applicable:	

Biowaiver for additional strengths

Description or critical issue	**Included in the report (Yes / No) If Not Applicable, state N/A**
1 Test product	
2 Reference strength	
3 Comparison of Test and Reference strengths	
4 Comparative in vitro dissolution: Studies comparing different strengths of the test product	
5 Comparative in vitro dissolution: Studies comparing each strength of the test product to equivalent strength of comparator product; only to be submitted in the case in vitro dissolution data between different strengths of Test product (see Section 4) are not similar	
Motivation of omission of documents, if applicable:	

Annexure III: Minimum Requirements for common Type II variations

B. QUALITY CHANGES (3.2.S)

B.I ACTIVE SUBSTANCE

B.I.a) Manufacture (3.2.S.2)

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.I.a.1 Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier			
1(b)	Introduction of a manufacturer of the active substance supported by an ASMF/DMF	None	1 - 10	Type II
1(c)	The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability	None	1 - 10	Type II
1 (g)	Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier	None	1 - 10	Type II

Documentation required

1. Relevant documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-chemistry-active-substances_en.pdf

2. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) where 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.
3. (3.2.S.4.1 and 3.2.S.4.2) A copy of the signed, dated and version controlled FPP manufacturer's API specifications.
4. (3.2.S.4.3) A validation data of the in-house analytical methods used by the FPP manufacturer.
5. (3.2.S.4.4) Batch analysis of the API tested by the FPP manufacturer.
6. Reference standards (Primary and Secondary/working reference standard) used by the FPP to routinely test the API. Overlaid IR must be included.
7. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to SAHPRA.
8. (3.2.R.4.1) A side-by-side comparison of the manufacturing flowcharts 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.
9. (3.2.R.4.4) 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.

10. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
2	B.I.a.2 Changes in the manufacturing process of the active substance			
1(b)	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product	None	1 - 18	Type II

Documentation required

1. (3.2.S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).

2. (3.2.S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.

3. (3.2.S.2.4) Information on controls of critical steps and intermediates, where applicable.

4. (3.2.S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.

5. (3.2.S.3.1) Evidence for elucidation of structure, where applicable.

6. (3.2.S.3.2) Information on impurities.

7. (3.2.S.4.1 and 3.2.S.4.2) A copy of signed, dated and version-controlled specifications and analytical procedures of API (and starting material and intermediate, if applicable).

8. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.

9. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
10. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar 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.
11. (3.2.S.4.1 and 3.2.S.4.2) A copy of the signed, dated and version controlled FPP manufacturer's API specifications.

12. (3.2.S.4.3) A validation data of the in-house analytical methods used by the FPP manufacturer.

13. (3.2.S.4.4) Batch analysis of the API tested by the FPP manufacturer.

14. Reference standards (Primary and Secondary/working reference standard) used by the FPP to routinely test the API. Overlaid IR must be included.

15.(3.2.P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to SAHPRA.

16.(3.2.R.4.1) A side-by-side comparison of the current process and the new process.

17. (3.2.R.4.4) 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 manufactured using approved and proposed manufacturing process.

18. A discussion of the impact of the change in manufacturing process of the API on the safety, efficacy and quality of the FPP.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Procedure type**
3	B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance			
3(d)	More than 10-fold increase compared to the originally approved batch size	None	1 - 3	Type II

Documentation required

1. (3.2.S.2.2) A brief narrative description of the manufacturing process.

2. (3.2.S.4.1) A copy of the currently accepted signed dated and version-controlled specifications of the API (and of the intermediate, if applicable).

3. (3.2.S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
4	B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance			
4(d)	Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	None	1 - 4	Type II
4(e)	Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	None	1 - 4	Type II

Documentation required

1. (3.2.S.4.1) Copy of the current and proposed API specifications dated and signed, dated and version controlled by the API manufacturer.

2. (3.2.S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (3.2.S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.

4. (3.2.S.4.4) Batch analysis data (in tabular format) issued by the API manufacturer for a minimum of two batches.

5. Justification as to why the change does not affect the final product specifications.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance			
1(e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product	None	1 - 8	Type II
1(f)	Change outside the approved specifications limits range for the active substance	None	1 - 8	Type II
1(g)	Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	None	1 - 8	Type II

Documentation required

1. (3.2.S.4.1) A copy of the proposed API specifications (of the API manufacture or FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.

2. (3.2.S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (3.2.S.4.3) Copies or summaries of validation or verification reports issued by the API manufacturer or FPP manufacturer, if new analytical procedures are used.

4. (3.2.S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.

5. (3.2.S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.

6. (3.2.S.4.5) Justification of the proposed API specifications (e.g., test parameters, acceptance criteria, or analytical procedures).

7. (3.2.P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study.

8. Justification as to why the change does not affect the final product specifications.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Procedure type**
1	B.I.d.1 Change in the retest period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier			
1.a.2	Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines	None	1 - 3	Type II

Documentation required

1. (3.2.S.7.1) A commitment to provide ongoing stability data of at least 2 product batches of the API packed in study in the proposed primary packaging type.

2. (3.2.S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.

3. (3.2.S.7.3) 06 months accelerated stability data of the API.

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-e-evaluation-stability-data-step-5_en.pdf

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:			
1(a)	a) One unit operation in the manufacturing process of the active substance including the resulting in- process controls and/or test procedures	None	1 - 3	Type II

Documentation required

1. The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g., interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.
2. Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.I.e.2 Introduction of a post approval change management protocol related to the active substance (Type II)			

Documentation required

1. Detailed description for the proposed change.

2. Change management protocol related to the active substance.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.I.e.4 Changes to an approved change management protocol			
1(a)	Major changes to an approved change management protocol	None	1	Type II

Documentation required (as per EMA variation guideline)

1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.II. FINISHED PRODUCT

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
3	B.II.a.3.b Changes in the composition (excipients) of the finished product			
3b.2	Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product	None	(2 – 5 & 7 - 11)	Type II
3.b.4	Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk	None	(2 – 11)	Type II
3.b.5	Change that is supported by a bioequivalence study	None	(1 – 11)	Type II

Documentation required

1. (Module 5) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on bioequivalence.

2. (3.2.P.1) Description and composition of the FPP.

3. (3.2.P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product).

4. (3.2.P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.

5. (3.2.P.4) Control of excipients, if new excipients are proposed.

6. (3.2.P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information

should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.

7. (3.2.P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.

8. (3.2.P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

9. (3.2.P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

10. (3.2.R.1.4.1) The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.

11. (3.2.R.7) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Procedure type**
4	B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells			
(b)	Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism	None	(1 - 6)	Type II

Documentation required

1. (Module 5) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on bioequivalence.

2. (3.2.P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.

3. (3.2.P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.

4. (3.2.P.8.1) Results of stability testing generated on at least one pilot- or production-scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

5. (3.2.R.1.4.1) The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.

6. (3.2.R.7) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Procedure type**
4	B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells			
(b)	Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism	None	(1 - 6)	Type II

Documentation required

1. (Module 5) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on bioequivalence.

2. (3.2.P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.

3. (3.2.P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.

4. (3.2.P.8.1) Results of stability testing generated on at least one pilot- or production-scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

5. (3.2.R.1.4.1) The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.

6. (3.2.R.7) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
3	B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product			
(b)	Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	None	(1 - 7)	Type II
(d)	Introduction of a non-standard terminal sterilisation method	None	(5 – 7, 9)	Type II
(e)	Introduction or increase in the overage that is used for the active substance	None	(1 – 8)	Type II

Documentation required

1. (Module 5) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on bioequivalence.
2. (P.2) Discussion on the development of the manufacturing process; where applicable:

- comparative in vitro testing, e.g., multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);

- comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be submitted or be available on request);

- microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.

3. (3.2.P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation. For sterile FPPs, process validation and/or evaluation studies.

4. (3.2.P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.

5. (3.2.P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

6. (3.2.P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.

7. (3.2.R.7) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

8. Justification for introduction or increasing of an overage

9. (3.2.P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
4	B.II.b.4 Change in the batch size (including batch size ranges) of the finished product			
(d)	The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes.	None	(1 - 6)	Type II
(e)	More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms	None	(1 - 6)	Type II (Sahpra variation addendum)

Documentation required

1. (3.2.P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g., lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
2. (3.2.P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3. (3.2.P.5.1) Copies of release and shelf-life specifications.
4. (3.2.P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action).
5. (3.2.P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-

term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

6. (3.2.R.7) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Procedure type**
5	B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product			
(d)	Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	None	(1 - 6)	Type II
(e)	Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	None	(1 - 6)	Type II

Documentation required

1. (3.2.P.3.4/3.2.P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.

2. (3.2.P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

3. (3.2.P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.

4. (3.2.P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.

5. (3.2.P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.

6. (3.2.P.5.6) Justification and supporting data for the addition or deletion of the tests and widening of the approved IPC limits.

B.II.c) Control of excipients

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.II.c.1 Change in the specification parameters and/or limits of an excipient			
(d)	Change outside the approved specifications limits range	None	(1 - 2)	Type II
(e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	None	(1 - 2)	Type II

Documentation required

1. (3.2.P.4.1) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).

2. (3.2.P.4.4) Justification and supporting data for the widening or deletion of the specifications of the excipients

B.II.d) Control of finished product

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.II.d.1 Change in the specification parameters and/or limits of the finished product			
(e)	Change outside the approved specifications limits range	None	(1 -6)	Type II
(f)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	None	(1 – 6)	Type II

Documentation required

1. (3.2.P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (3.2.P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (3.2.P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (3.2.P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (3.2.P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.
6. (3.2.P.5.6) Justification and supporting data for the widening or deletion of the specifications of the final product.

B.II.e) Container closure system

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.II.d.1 Change in the specification parameters and/or limits of the finished product			
1.a.4	The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	None	(1 - 5)	Type II

Documentation required

1. (3.2.P.2) Data on the suitability of the container-closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
2. (3.2.P.3.5) For sterile FPPs, process validation and/or evaluation studies.
3. (3.2.P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).
4. (3.2.P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.
5. (3.2.P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
4	B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)			
(b)	The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	None	Non-sterile FPP's (1 - 2) Sterile FPP's (1 - 3)	Type II

Documentation required

1. (3.2.P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).

2. (3.2.P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies.

3. (3.2.P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
7	B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)			
(c)	Any change to suppliers of spacer devices for metered dose inhalers	None	(1 - 2)	Type II

Documentation required

1. (3.2.P.2) Data to demonstrate accuracy, precision and compatibility of the device.

2. Justification for the change of the device.

B.II.f) Stability

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.II.f.1 Change in the shelf-life or storage conditions of the finished product			
1.b.4	Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines	None	(1 - 3)	Type II

Documentation required

1. (3.2.P.8.1) A commitment to provide ongoing stability data of at least 2 product batches of the API packed in study in the proposed primary packaging type.

2. (3.2.P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.

3. (3.2.P.8.3) 06 months accelerated stability data of the API.

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-e-evaluation-stability-data-step-5_en.pdf

B.II.g) Design Space and post approval change management protocol

Description of change		Conditions to be fulfilled	Documentation required	Procedure type
1	B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning (as per EMA variation guideline)			
(a)	One or more-unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures	None	(1 - 3)	Type II
(b)	Test procedures for excipients / intermediates and/or the finished product	None	(1 – 3)	Type II

Documentation required

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

Description of change	Conditions to be fulfilled	Documentation required	Procedure type
2	B.II.g.2 Introduction of a post approval change management protocol related to the finished product (as per EMA variation guideline)		

Documentation required

1. Detailed description for the proposed change.

2. Change management protocol related to the finished product.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).