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SCOPE

This annexure contains details on the specific categories and codes for variations specific to the quality of registered medicines. This guideline is relevant only to submissions made for variations affecting the quality of orthodox human medicines. It does not include veterinary, biological, and complementary medicines. It must be noted that the scientific quality requirements remain the same as those specified in the Quality and Bioequivalence guideline (SAHPGL-PEM-02).

GENERAL INFORMATION FOR PEM POST REGISTRATION

Classification of quality variations

The below classifications have been adapted from the EMA variation classification.

The variations classifications for Type I and Type II changes are detailed below.

Type IA_{AN} variations are implemented by the application and notification sent to the South African Health Products Regulatory Authority (SAHPRA) within a year of implementation.

Type IA_{IN} variations are immediately implementable; however, the Authority should be notified within 47 working days.

Type IB variations become implementable after 87 working days, if no communication is received from SAHPRA.

Each deleted parameter must be submitted as separate variations.

If one or more conditions are not met, the applicant must classify the change using a higher code, for e.g., If a condition of type IA is not met, the variation is upgraded to a Type IB.

At a minimum the following must be included on the certificate on analysis (COA) and the stability data:

- Manufacturer
- Batch size
- Date of manufacture
- Test date
- Expiry date
- Specification number
- If applicable, provide justification for observed out of specification result

Type I variations

A – Administrative Changes

A.3 Change in name of the active substance or of an excipient

1**. Type IA$_{IN}$ A.3 Change in name of the active substance or of an excipient**

- Conditions to be fulfilled- 1
- Documentation to be supplied- 1,2,3

Conditions

1. The active substance/excipient must remain the same.

Documentation

1. Proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the SAHPRA recognised Pharmacopeia.
2. Revised product information (Sections of PI/PIL).
3. Amendment of the relevant section(s) of the dossier.

A.4 Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no SAHPRA recognised pharmacopeia or Certificate of Suitability or World Health Organization (WHO) CPQ document is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier).

Commented [MG1]: Spell out and then abbreviate.

- Conditions to be fulfilled- 1
- Documentation to be supplied- 1,2,3

Conditions

1. The manufacturing site and all manufacturing operations must remain the same.

Documentation

1. A formal document from a relevant official body (e.g., Chamber of Commerce) in which the new name and/or address is mentioned.
2. Amendment of the relevant section(s) of the dossier.

3. In case of change in the name of the holder of the Active Substance Master File Holder, updated 'letter of access.

A.7 – Type IA - Deletion of manufacturing sites for an active substance, intermediate, or supplier of a starting material, reagent, or excipient (when mentioned in the dossier) (*).

- Conditions to be fulfilled- 1, 2
- Documentation to be supplied- 1,2

Conditions

1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion.
2. The deletion should not be due to critical deficiencies concerning manufacturing.

Documentation

1. The amendment schedule should clearly define the present' and 'proposed' manufacturers.
2. Amendment of the relevant section(s) of the dossier.

A.8 Type IA -Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance (*) Note: this variation does not apply when the information has been otherwise transmitted to the authorities ('Responsible pharmacist (RP) declaration').

- Conditions to be fulfilled- none
- Documentation to be supplied- 1, 2

Documentation

1. Written confirmation from the manufacturer of the finished product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices.
2. RP declaration. Refer to OF-PEM-POST-XXXX.

B - Quality Changes

B.I - Active Substance

B.I.a – Manufacture of API: Change in the manufacture 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 SAHPRA recognised pharmacopeia or Certificate of Suitability or WHO CPQ document is part of the approved dossier.

1. **Type IA_{IN} B.I.a.1.a. The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer**
   - Condition to be fulfilled – 1, 2, 3
   - Documentation to be supplied: 1,2,3,4,5,6,7
2. **Type IA B.I.a.1.f. Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place**
   - Condition to be fulfilled – 2,4

Documentation to be supplied: 1, 5

3. **Type IB B.I.a.1.h. Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method**
   - Documentation to be supplied: 1, 2, 4, 5, 8

4. **Type IA B.I.a.1.i. Introduction of a new site of micronisation**
   - Condition to be fulfilled – 2,5
   - Documentation to be supplied: 1, 4, 5, 6

5. **Type IB B.I.a.1.k. New storage site of master cell bank and/or working cell bank**
   - Documentation to be supplied: 1, 5

Conditions

1.	For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances, the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
2.	The active substance is not a biological/immunological substance or sterile.
3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.
4.	Method transfer from the old to the new site has been successfully completed.
5.	For poorly soluble API (BCS class II/IV) the particle size specification of the active substance and the corresponding analytical method remain the same.

Documentation:

1.	Amendment of the relevant section(s) of the dossier.
2.	A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route, quality control procedures and specifications of the active substance

	and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.
3.	Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
4.	Batch analysis data (in a comparative tabular format) and certificate of analysis for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5.	The amendment schedule should clearly define the present' and 'proposed' manufacturers.
6.	A declaration by the Responsible Pharmacist (RP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Responsible Pharmacist (RP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances. Refer to OF-PEM-POST-XXXX.
7.	Where relevant, a commitment of the manufacturer of the active substance to inform the applicant or FPP manufacturer of any changes to the manufacturing process, specifications, and test procedures of the active substance.
8.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, A reference to the EudraGMP database will suffice. A GMP certificate issued within the last three (3) years by the relevant competent authority.

B.I.a.2 - Changes in the manufacturing process of the active substance

1. **Type IA B.I.a.2.a. Minor change in the manufacturing process of the active substance**
   - Condition to be fulfilled – 1,2, 3,4,5,6,7
   - Documentation to be supplied: 1,2,3

2. **Type IB B.I.a.2.e. Minor change to the restricted part of an Active Substance Master File**
   - Documentation to be supplied: 1, 2,3, 4

Conditions

1.	No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties
2.	The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal

	products, the geographical source, production of the herbal substance and the manufacturing route remain the same.
3.	The specifications of the active substance or intermediates are unchanged.
4.	The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.
5.	The active substance is not a biological/immunological substance.
6.	The change does not refer to the geographical source, manufacturing route or production of an herbal medicinal product.
7.	The change does not refer to the **restricted part** of an Active substance DMF or APIMF or 3.2.S.

Documentation

1.	Amendment of the relevant section(s) of the dossier.
2.	Batch analysis data (in comparative tabular format) and certificate of analysis of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.
3.	**Signed, dated and version-controlled** copy of approved specifications of the active substance.
4.	A declaration from the marketing authorisation holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.

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

1. **Type IA B.I.a.3.a. Up to 10-fold increase compared to the originally approved (biolot)* batch size**
   - Condition to be fulfilled – 1, 2, 3,4,6,7,8
   - Documentation to be supplied: 1,2,4

2. **Type IA B.I.a.3.b. Downscaling down to 10-fold**
   - Condition to be fulfilled – 1,2,3,4,5
   - Documentation to be supplied: 1, 2,4

3. **Type IB B.I.a.3.d. More than 10-fold increase compared to the originally approved (biolot)* batch size**
   - Documentation to be supplied: 1, 2,3,4

*** The batch size of the API that was used to manufacture the FPP biobatch (applicable to solid oral dosage forms)**

Conditions

1.	Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, 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 product concerned is not a biological/immunological medicinal product.
4.	The change does not adversely affect the reproducibility of the process.
5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6.	The specifications of the active substance/intermediates remain the same.
7.	The active substance is not sterile.
8.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.

Documentation

1.	Amendment of the relevant section(s) of the dossier.
2.	Batch analysis data (in a comparative tabulated format) and certificate of analysis (COA) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
3.	**Signed, dated and version-controlled** copy of approved specifications of the active substance.
4.	A declaration from the applicant or the ASMF holder or FPP manufacturer as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

B.1.a.4 - Change to in-process tests or limits applied during the manufacture of the active substance

1. **Type IA B.I.a.4.a: Tightening of in-process limits**
   - Condition to be fulfilled – 1, 2,3,4
   - Documentation to be supplied: 1,2

2. **Type IA B.I.a.4.b. Addition of a new in-process test and limits**
   - Condition to be fulfilled – 1,2,5,6
   - Documentation to be supplied: 1, 2,3,4,6

3. **Type IA B.I.a.4.c. Deletion of a non-significant in-process test**
   - Condition to be fulfilled – 1,2,7
   - Documentation to be supplied: 1, 2,5

4. **Type IB B.I.a.4.f. Addition or replacement of an in-process test because of a safety or quality issue**
   - Condition to be fulfilled – None

- Documentation to be supplied: 1, 2,3,4,6

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopeial microbiological methods).
7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed in-process tests should be listed on the amendment schedule.
3. Details of any new non-pharmacopeial analytical method and validation data.
4. Batch analysis data and COAs on two production batches of the active substance for all specification parameters.
5. Justification/risk assessment from the applicant or the ASMF Holder or the FPP manufacturer, as appropriate, that the in-process tests are non-significant, or that the in-process tests are obsolete.
6. Justification from the applicant or the ASMF Holder or the FPP manufacturer as appropriate for the new in-process test and limits.

B.I.b - Control of API

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. Type IA_{IN} B.I.b.1.a. Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release

- Condition to be fulfilled – 1, 2,3,4
- Documentation to be supplied: 1,2

2. Type IA B.I.b.1.b Tightening of specification limits

- Condition to be fulfilled – 1,2,3,4
- Documentation to be supplied: 1, 2

3. **Type IA B.I.b.1.c. Addition of a new specification parameter to the specification with its corresponding test method**
   - Condition to be fulfilled – 1,2,5,6,7
   - Documentation to be supplied: 1, 2,3,4,5,7

4. **Type IA B.I.b.1.d. Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)**
   - Condition to be fulfilled – 1,2,8
   - Documentation to be supplied: 1, 2,6

5. **Type IB B.I.b.1.h. Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method because of a safety or quality issue**
   - Condition to be fulfilled – None
   - Documentation to be supplied: 1, 2,3,4,5,7

6. **Type IB B.I.b.1.i[@]. Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country**
   - Documentation to be supplied: 1, 2,3,4,5,7

* When changes to specifications parameters and/ or limits result from adoption of a new monograph or a monograph from a different pharmacopeia, the variations codes in B.I.b.1 would also apply.

@ Newly adopted monographs do not need to be from the European Pharmacopoeia or the national pharmacopoeia of a European Union member state. SAHPRA will be accepting monographs from all Recognised Regulatory Authorities as stipulated in the General Information and Quality and Bioequivalence guidelines.

Conditions

1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7.	For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH/VICH limits, any new impurity control should be in line with the SAHPRA recognised pharmacopeia.
8.	The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

Commented [MG2]: Is there just one recognised pharmocopeia? If not, then "a" is appropriate.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications must be listed on the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COAs on two production batches of the relevant substance for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification.
6. Justification/risk assessment from the applicant or the ASMF Holder or the FPP manufacturer, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
7. Justification from the applicant or the ASMF Holder or the FPP manufacturer as appropriate of the new specification parameter and the limits.

B.I.b.2 - Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance

1. Type IA_{IN} B.I.b.2.a. Minor changes to an approved test procedure

- Condition to be fulfilled – 1, 2,3,4
- Documentation to be supplied: 1,2

2. Type IA B.I.b.2.b. Deletion of a test procedure for the active substance or a starting material/reagent/inter- mediate, if an alternative test procedure is already authorised

- Condition to be fulfilled – 7
- Documentation to be supplied: 1

3. Type IA B.I.b.2.c. Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance.

- Condition to be fulfilled – 1,2,3,5,6
- Documentation to be supplied: 1, 2

4. Type IB A B.I.b.2.e. Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate

- Documentation to be supplied: 1, 2

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. 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).**
4. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopeial microbiological methods).
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
6. The active substance is not biological/immunological.
7. An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c- Container Closure (API)

B.I.c.1 - Change in immediate packaging of the active substance

1. Type IA B.I.c.1.a Qualitative and/or quantitative composition

- Condition to be fulfilled – 1, 2,3
- Documentation to be supplied: 1,2,3,4,6

2. Type IB B.I.c.1.c Liquid active substances (non-sterile)

- Condition to be fulfilled – None
- Documentation to be supplied: 1, 2,3,5,6

Conditions

1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2. Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three (3) months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three (3) months' stability data do not yet have to be available. These studies must be finalised, and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
3. Sterile, liquid, and biological/immunological active substances are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier.

2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O2, CO2 moisture), including a confirmation that the material complies with relevant pharmacopoeia requirements on plastic materials and objects in contact with foodstuffs.
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements on plastic material and objects in contact with foodstuffs.
4. A declaration from the applicant or the ASMF holder or FPP manufacturer as appropriate that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three (3) months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).
6. Comparison of the current and proposed immediate packaging specifications, if applicable should be provided on the amendment schedule.

B.1.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance

1. Type IA B.I.c.2.a Tightening of specification limits

- Condition to be fulfilled – 1,2,3,4
- Documentation to be supplied: 1,2

2. Type IA B.I.c.2.b Addition of a new specification parameter to the specification with its corresponding test method

- Condition to be fulfilled – 1,2,5
- Documentation to be supplied: 1,2,3,4,6

3. Type IA B.I.c.2.c Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)

- Condition to be fulfilled – 1,2
- Documentation to be supplied: 1, 2,5

4. Type IB A B.I.c.2.d Addition or replacement of a specification parameter because of a safety or quality issue

- Documentation to be supplied: 1,2,3,4,6

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.

2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications should be included on the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COAs on two batches of the immediate packaging for all specification parameters.
5. Justification/risk assessment from the applicant or the ASMF Holder or the FPP manufacturer, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
6. Justification from the applicant or the ASMF Holder or the FPP manufacturer as appropriate, of the new specification parameter and the limits.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance

1. **Type IA B.I.c.3.a. Minor changes to an approved test procedure**
   - Condition to be fulfilled – 1,2,3
   - Documentation to be supplied: 1,2

2. Type IA B.I.c.3.b. Other changes to a test procedure (including replacement or addition)

- Condition to be fulfilled – 1,3,4
- Documentation to be supplied: 1,2

3. Type IA B.I.c.3.c. Deletion of a test procedure if an alternative test procedure is already authorised

- Condition to be fulfilled – 5
- Documentation to be supplied: 1

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. 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).
3. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
4. The active substance/finished product is not biological/immunological.
5. There is still a test procedure registered for the specification parameter, and this procedure has not been added through an IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d – Stability (API)

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 and WHO CPQ document covering the retest period is part of the approved dossier

1. Type IA B.I.d.1.a.1 Retest period/storage period reduction

- Condition to be fulfilled – 1
- Documentation to be supplied: 1,2,3

2. Type IB B.I.d.1.a.4 Retest period/storage period - Extension or introduction of a retest period/ storage period supported by real time data

- Documentation to be supplied: 1,2,3

3. Type IA B.I.d.1.b.1 Storage conditions - Change to more restrictive storage conditions of the active substance

- Condition to be fulfilled – 1
- Documentation to be supplied: 1, 2,3

4. Type IB A B.I.d.1.b.3. Storage conditions- Change in storage conditions of the active substance

- Condition to be fulfilled – None
- Documentation to be supplied: 1, 2,3

5. Type IA B.I.d.1.c. Change to an approved stability protocol

- Condition to be fulfilled – 1,2
- Documentation to be supplied: 1, 4

Conditions

1.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2.	The changes do not concern a widening of the acceptance criteria in the parameters tested a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1.	Amendment of the relevant section(s) of the dossier. This must contain 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 active substance in the authorised packaging material and covering the duration of the requested retest period or requested storage conditions.
2.	Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3.	**Signed, dated and version-controlled** copy of approved specifications of the active substance.
4.	Justification for the proposed changes.

B.I.e – Design space and Post-Approval change management protocols (API)

B.1.e.3 - Deletion of an approved change management protocol related to the active substance

1. Type IA in B.I.e.3 Deletion of an approved change management protocol related to the active substance

- Condition to be fulfilled – 1,
- Documentation to be supplied: 1,2

Conditions

1.	The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1.	Justification for the proposed deletion.
2.	Amendment of the relevant section(s) of the dossier.

B.I.e.4 - Changes to an approved change management protocol

1. Type IB B.I.e.4.b Minor changes to an approved change management protocol that do not change the strategy defined in the protocol

- Documentation to be supplied: 1

Documentation

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.I.e.5 Implementation of changes foreseen in an approved change management protocol

1. **Type IA_{IN} B.I.e.5.a. The implementation of the change requires no further supportive data**
   - Condition to be fulfilled – 1
   - Documentation to be supplied: 1,2,4

2. **Type IB B.I.e.5.b. The implementation of the change requires further supportive data**
   - Documentation to be supplied: 1,2,3,4

3. **Type IB B.I.e.5.c. Implementation of a change for a biological/immunological medicinal product**
   - Documentation to be supplied: 1, 2,3,4,5

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier.
5. **Signed, dated and version-controlled** copy of approved specifications of the active substance.

B.II – Finished Product

B.II.a – Description and Composition (FPP)

B.II.a.1[@] Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking

1. **Type IAin B.II.a.1.a. Changes in imprints, bossing or other markings**
   - Condition to be fulfilled – 1, 2,3,4
   - Documentation to be supplied: 1,2

2. **Type IB B.II.a.1.b. Changes in scoring/break lines intended to divide into equal doses**
   - Documentation to be supplied: 1,2,3

[@] In lieu of samples of finished product, provide clear annotated pictures/photographs of the final product described in 3.2.P.1. These snapshots can be included in 1.3.6.

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 pharmaceutical legislation.
3.	The scoring/break lines are not intended to divide into equal doses.
4.	Any product markings used to differentiate strengths should not be completely deleted.

Documentation

1.	Amendment of the relevant section(s) of the dossier and including a detailed drawing or written description of the current and new appearance and including revised product information (PI/PIL) as appropriate.
2.	Provide pictures/ photographs of the final product described in 3.2.P.1. These pictures/photographs must be included in 1.3.6.
3.	Results of the appropriate SAHPRA recognised pharmacopoeia tests demonstrating equivalence in characteristics/correct dosing.

B.II.a.2[@] Change in the shape or dimensions of the pharmaceutical form

1. Type IAin B.II.a.2.a. Immediate release tablets, capsules, suppositories, and pessaries

- Condition to be fulfilled – 1, 2,3,4
- Documentation to be supplied: 1,4

2. Type IB B.II.a.2.b. Gastro-resistant, modified, or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses

- Condition to be fulfilled – None
- Documentation to be supplied: 1,2,3,4,5

[@] In lieu of samples of finished product, provide clear annotated pictures/photographs of the final product described in 3.2.P.1. These snapshots can be included in 1.3.6.

Conditions

1.	If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.
2.	Release and end of shelf-life specifications of the product have not been changed (except for dimensions).
3.	The qualitative or quantitative composition and mean mass remain unchanged.
4.	The change does not relate to a scored tablet that is intended to be divided into equal doses.

Documentation

1.	Amendment of the relevant section(s) of the dossier and including a detailed drawing of the current and proposed situation and including revised product information as appropriate.
2.	Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant human guidance on Bioavailability.

3. Justification for not submitting a new bioequivalence study according to the relevant human guidance on Bioavailability.
4. Provide pictures/ photographs of the final product described in 3.2.P.1. These pictures/photographs must be included in 1.3.6.
5. Results of the appropriate SAHPRA recognised pharmacopoeia tests demonstrating equivalence in characteristics/correct dosing.

B.II.a.3 Changes in the composition (excipients) of the finished product

1. **Type IA_{in} B.II.a.3.a.1 Changes in components of the flavouring or colouring system - Addition, deletion, or replacement**
   - Condition to be fulfilled – 1,2,3,4,5,6,7,9
   - Documentation to be supplied: 1,2,4,5,6
2. **Type IA B.II.A.3.a.2 Changes in components of the flavouring or colouring system - Increase or reduction**
   - Condition to be fulfilled – 1,2,3,4
   - Documentation to be supplied: 1,2,4

3. **Type IA B.II.A.3.b.1 Other excipients - Any minor adjustment of the quantitative composition of the finished product** with respect to excipients
   - Condition to be fulfilled – 1,2,4,8,9
   - Documentation to be supplied: 1,2,7

4. **Type IB B.II.A.3.b.6 - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level**
   - Documentation to be supplied: 1,3,4,5,6,7,8,9

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 of an identification test.
4. Stability studies have been started under ICH/VICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5. Any new proposed components must comply with the relevant EU regulations/USFDA for colours for use in foodstuffs (Any regulatory authority recognised by SAHPRA).

6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current Note for Guidance on Minimising the Risk of Trans- mitting Animal Spongiform Encephalopathy Agents via Human Medicinal Products.
7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.
8. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability, see the relevant human guidance on Bioavailability.
9. The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.
10. The product concerned is not a biological/immunological medicinal product.

Documentation

1. Amendment of the relevant section(s) of the dossier and including identification method for any new colorant, where relevant, and including revised product information as appropriate. The updates should include the COA from the inactive pharmaceutical ingredient supplier, and the FPP manufacturer. Functionality tests must be included on the COA. The IPI grade should be reflected on the COA, if applicable.
2. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
3. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three (3) months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4. Provide pictures/ photographs of the final product described in 3.2.P.1. These pictures/photographs must be included in 3.2.P.1.
5. Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human Medicinal Products. The following information should be included for each such material: Name of manufacturer, species, and tissues from which the material is a derivative, country of origin of the source animals and its use.
6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7. Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition.
9. Justification for not submitting a new bioequivalence study according to the current Note for Guidance on The Investigation of Bioavailability and Bioequivalence.

B.II.a.4. Change in coating weight of oral dosage forms or change in weight of capsule shells

1. Type IA B.II.a.4.a. Solid oral pharmaceutical forms:

- Condition to be fulfilled – 1, 2, 3, 4
- Documentation to be supplied: 1, 2

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product 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.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three (3) months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalised. Data will be provided immediately to SAHPRA if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

B.II.a.6 Deletion of the solvent/diluent container from the pack

1. Type IB B.II.a.6

- Documentation to be supplied: 1, 2

Documentation

1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product.
2. Revised product information (Sections of PI/PIL).
3. Amendment of the relevant section(s) of the dossier

B.II.b Manufacture (FPP)

B.II.b.1 Replacement or addition of a manufacturing site for part or all the manufacturing process of the finished product

1. Type IA_{IN} B.II.b.1.a Secondary packaging site:

- Condition to be fulfilled – 1, 2
- Documentation to be supplied: 1, 3, 8

2. Type IA_{IN} B.II.b.1.b. Primary packaging site:

- Condition to be fulfilled – 1, 2, 3, 4, 5
- Documentation to be supplied: 1, 2, 3, 4, 8, 9

3. Type IB B.II.b.1.e. Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products:

- Condition to be fulfilled – N/A
- Documentation to be supplied: 1, 2, 3, 4, 5, 6, 7, 8, 9

4. Type IB B.II.b.1.f. Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products:

- Documentation to be supplied: 1, 2, 3, 4, 5, 6, 7, 8

Conditions

1. Satisfactory inspection in the last three (3) years by an inspection service of one of the Member States of the of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and SAHPRA. (The GMP aspects to be pronounced by SAHPRA Inspectorate Unit.)
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned). (To be pronounced by SAHPRA Inspectorate Unit.)
3. Product concerned is not a sterile product.
4. Where relevant, for instance for suspensions and emulsions, validation scheme 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.
5. Product concerned is not a biological/immunological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice; For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last three (3) years by the relevant competent authority. For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice. (The GMP aspects to be pronounced by SAHPRA Inspectorate Unit.)
2. **Signed and dated** validation protocol and/or validation report. The validation report should include three consecutive batch numbers and where batches does not look consecutive in term of numbers you

	are required to include the SOP of batch numbering. The batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated.
3.	The amendment schedule should clearly define the present' and 'proposed' manufacturers.
4.	**Signed, dated and version-controlled** copy of approved release and end-of-shelf-life specifications.
5.	Batch analysis data and COAs on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
6.	For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.
7.	If the new manufacturing site uses the active substance as a starting material — A declaration by the Qualified Person (QP) or Responsible pharmacist at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the SAHPRA.
8.	Amendment of the relevant section(s) of the dossier.
9.	If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product

1. Type IA B.II.b.2.a Replacement or addition of a site where batch control/testing takes place:

- Condition to be fulfilled – 2, 3, 4, 5
- Documentation to be supplied: 1, 2, 5

2. Type IA_{IN} B.II.b.2.c.1 Replacement or addition of a manufacturer responsible for importation and/or batch release, <u>not including batch control/testing</u>:

- Condition to be fulfilled – 1, 2, 5
- Documentation to be supplied: 1, 2, 3, 4, 5

3. Type IA_{IN} B.II.b.2.c.2 Replacement or addition of a manufacturer responsible for importation and/or batch release, <u>Including batch control/testing</u>:

- Condition to be fulfilled – 1, 2, 3, 4, 5
- Documentation to be supplied: 1, 2, 3, 4, 5

Conditions

Tick in the yes column if the conditions met	Yes	No
1. The manufacturer responsible for batch release must be located within the EU/EEA. At least one batch release site remains within the EU/EEA that is able to certify the product testing for the purpose of batch release within the EU/EEA.		

2. The site is appropriately authorised.		
3. The product is not a biological/immunological medicinal product.		
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.		
5. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EU/EEA.		

Documentation

Tick in the yes column if the required documents have been included
1. For a site within the EU/EEA: Attach copy of manufacturing authorisation(s) or where no manufacturing authorisation exists a certificate of GMP compliance issued within the last three (3) years by the relevant competent authority. For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate, issued within the last three (3) years by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last three (3) years by an EU/EEA competent authority.
2. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers, importer, batch control/testing and batch release sites as listed in section 2.5 of the application form for marketing authorisation.
3. For centralised procedure only: contact details of new contact person in the EU/EEA for product defects and recalls, if applicable.
4. A declaration by the Qualified Person (QP) or Responsible pharmacist for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.
5. 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), including revised product information as appropriate.

Commented [MG3]: No "yes" column here?

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product

1. **Type IA B.II.b.3.a Minor change in the manufacturing process**
   - Condition to be fulfilled – 1, 2, 3, 4, 5, 6, 7
   - Documentation to be supplied: 1, 2, 3, 4, 5, 6, 7, 8

2. **Type IB B.II.b.3.f Minor change in the manufacturing process of an aqueous oral suspension**
   - Documentation to be supplied: 1, 2,4, 6, 7, 8

Conditions

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).
3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
5. The specifications of the finished product or intermediates are unchanged.
6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three (3) months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised, and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier and including a direct comparison of the present process and the new process. Provide 3.2.P.2, if applicable.
2. For semi-solid and liquid products in which the active substance 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; data on the next two full production batches should be available on request or reported if outside specification (with proposed action).
4. Justification for not submitting a new bioequivalence study according to the relevant human guidance on Bioavailability.
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.
6. **Signed, dated and version-control** copy of approved release and end-of-shelf-life specifications.
7. Batch analysis data (in a comparative tabulated format) and COAs on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
8. Declaration that relevant stability studies have been started under ICH/VICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three (3) months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that

these studies will be finalised, and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product

1. **Type IA B.II.b.4.a. Up to 10-fold compared to the originally approved batch size of the biobatch*:**
   - Condition to be fulfilled – 1, 2, 3, 4, 5, 7
   - Documentation to be supplied: 1, 4

2. **Type IA B.II.b.4.b. Downscaling down to 10-fold:**
   - Condition to be fulfilled – 1, 2, 3, 4, 5, 6
   - Documentation to be supplied: 1, 4

3. **Type IB B.II.b.4.e. More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms of the biobatch*:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4, 5

*The batch size of the test product used in the BE study **(solid oral dosage forms).**

Conditions

1.	The change does not affect reproducibility and/or consistency of the product.
2.	The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical 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 scheme 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 relevant guidelines.
5.	The product concerned is not a biological/immunological medicinal product.
6.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7.	The batch size is within the 10-fold range of the batch size foreseen when the registration was granted (**biobatch**) or following a subsequent change not agreed as a Type IA variation.

Documentation

1.	Amendment of the relevant section(s) of the dossier.
2.	Batch analysis data (in a comparative tabulated format) and COA's on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch

data on the next two full production batches should be made available upon request and reported by the applicant if outside specifications (with proposed action).
3. **Signed, dated and version-controlled** copy of approved release and end-of-shelf-life specifications.
4. **Signed and dated** validation protocol and/or validation report. The validation report should include three consecutive batch numbers and where batches does not look consecutive in term of numbers you are required to include the SOP of batch numbering. The batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated.
5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of three (3) months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunological: a declaration that an assessment of comparability is not required.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product

1. **Type IA B.II.b.5.a Tightening of in-process limits:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2
2. **Type IA B.II.b.5.b Addition of a new test(s) and limits:**
   - Condition to be fulfilled – 1, 2, 5, 6
   - Documentation to be supplied: 1, 2, 3, 4, 5, 7
3. **Type IA B.II.b.5.c Deletion of a non-significant in-process test:**
   - Condition to be fulfilled – 1, 2, 7
   - Documentation to be supplied: 1, 2, 6
4. **Type IB B.II.b.5.f Addition or replacement of an in-process test as a result of a safety or quality issue:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4, 5, 7

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.

6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7. The in-process test does not concern the control of a critical parameter, e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form).

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed in-process tests and limits should be included on the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COAs on two production batches of the finished product for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests.
6. Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.
7. Justification of the new in-process test and limits.

B.II.c– Control of excipients (FPP)

B.II.c.1 - Change in the specification parameters and/or limits of an excipient

1. **Type IA B.II.c.1.a. Tightening of specification limits:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2
2. **Type IA B.II.c.1.b. Addition of a new specification parameter to the specification with its corresponding test method:**
   - Condition to be fulfilled – 1, 2, 5, 6, 7
   - Documentation to be supplied: 1, 2, 3, 4, 6, 8
3. **Type IA B.II.c.1.c. Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter):**
   - Condition to be fulfilled – 1, 2, 8
   - Documentation to be supplied: 1, 2, 7
4. **Type IB B.II.c.1.f. Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4, 5, 6, 8
5. **Type IB B.II.c.1.g.[@]Where there is no SAHPRA recognised pharmacopeial monograph for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country:**
   - Condition to be fulfilled – N/A

- Documentation to be supplied: 1, 2, 3, 4, 5, 6, 8

@Newly adopted monographs do not need to be from the European Pharmacopoeia or the national pharmacopoeia of a European Union member state. SAHPRA will be accepting monographs from all Recognised Regulatory Authorities as stipulated in the General Information and Quality and Bioequivalence guidelines.

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7. The change does not concern a genotoxic impurity.
8. The specification parameter does not concern the control of a critical parameter, e.g.: - impurities (unless a particular solvent is definitely not used in the manufacture of the excipient) - any critical physical characteristics (particle size, bulk, tapped density, etc.) - identity test (unless there is a suitable alternative control already present) - microbiological control (unless not required for the dosage form) - the functionality of the IPI.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications should be included on the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COA's on two production batches of the excipient for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification.
6. Justification for not submitting a new bioequivalence study according to the relevant human guideline on Bioavailability.
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
8. Justification of the new specification parameter and the limits.

B.II.c.2 Change in test procedure for an excipient

1. Type IA B.II.c.2.a Minor changes to an approved test procedure:

- Condition to be fulfilled – 1, 2, 3, 4
- Documentation to be supplied: 1, 2

2. Type IA B.II.c.2.b Deletion of a test procedure if an alternative test procedure is already authorised:

- Condition to be fulfilled – 5
- Documentation to be supplied: 1

3. Type IB B.II.c.2.d other changes to a test procedure (including replacement or addition):

- Documentation to be supplied: 1, 2

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3. 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).**
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
5. An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IA($_{IN}$) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier and including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3 Change in source of an excipient or reagent with TSE risk

1. Type IA B.II.c.3.a.1 For excipients or reagents not used in the man facture of a biological/immunological active substance or in a biological/immunological medicinal product:

- Condition to be fulfilled – 1
- Documentation to be supplied: 1

Conditions

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

Documentation

1. Declaration from the manufacturer or the applicant that it is purely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. dissolution characteristics) of the finished product.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopeial excipient (when described in the dossier) or a novel excipient

1. Type IA B.II.c.4.a Minor change in synthesis or recovery of a non-pharmacopeial excipient or a novel excipient:

- Condition to be fulfilled – 1, 2
- Documentation to be supplied: 1, 2, 3, 4

Conditions

1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH/VICH limits), or in physico-chemical properties.
2. Adjuvants are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Batch analysis data (in a comparative tabulated format) and COAs of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.
3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.
4. **Signed, dated and version-controlled** copy of approved and new (if applicable) specifications of the excipient.

B.II.D– Control of finished product

B.II.d.1 Change in the specification parameters and/or limits of the finished product

1. **Type IA B.II.d.1.a. Tightening of specification limits:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2
2. **Type IA_{IN} B.II.d.1.b. Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2
3. **Type IA B.II.d.1.c. Addition of a new specification parameter to the specification with its corresponding test method:**
   - Condition to be fulfilled – 1, 2, 5, 6, 7
   - Documentation to be supplied: 1, 2, 3, 4, 5, 7

4. **Type IA B.II.d.1.d. *Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material):**
   - Condition to be fulfilled – 1, 2, 9
   - Documentation to be supplied: 1, 2, 6

5. **Type IB B.II.d.1.g. Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method because of a safety or quality issue:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4, 5, 7

6. **Type IA_{IN} B.II.d.1.h. Update of the dossier to comply with the provisions of an updated general monograph of the SAHPRA recognised pharmacopeia for the finished product:**
   - Condition to be fulfilled – 1, 2, 3, 4, 7, 8
   - Documentation to be supplied: 1, 2

7. Type IA B.II.d.1.i. Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass) or Ph. Eur. 2.9.6 (Uniformity of content):

- Condition to be fulfilled – 1, 2, 10
- Documentation to be supplied: 1, 2, 4

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.
7. The change does not concern any impurities (including genotoxic) or dissolution.
8. The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre January 2008 (non-harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form and the proposed controls are in line with the harmonised monograph.

9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: - assay, - impurities (unless a particular solvent is not used in the manufacture of the finished product), - any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.), - a test that is required for the dosage form in accordance with the general notices of the Ph. Eur.; any request for skip testing.
10. The proposed control is fully in line with the Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications should be included on the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COAs on two production batches (three (3) production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
7. Justification of the new specification parameter and the limits.

B.II.d.2 Change in the test procedure for the finished product

1. **Type IA B.II.d.2.a. Minor changes to an approved test procedure:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2
2. **Type IA B.II.d.2.b. Deletion of a test procedure if an alternative method is already authorised:**
   - Condition to be fulfilled – 4
   - Documentation to be supplied: 1
3. **Type IB B.II.d.2.d. Other changes to a test procedure (including replacement or addition):**
   - Documentation to be supplied: 1, 2
4. **Type IA B.II.d.2.e. Update of the test procedure to comply with the updated general monograph for SAHPRA recognised pharmacopeia:**
   - Condition to be fulfilled – 2, 3, 4, 5
   - Documentation to be supplied: 1
5. **Type IA B.II.d.2.f. To reflect compliance with SAHPRA recognised pharmacopeia and remove reference to the outdated internal test method and test method number:**
   - Condition to be fulfilled – 2, 3, 4, 5
   - Documentation to be supplied: 1

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3. The method of analysis should remain the same.
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopeial microbiological methods).
5. The registered test procedure already refers to the general monograph of the SAHPRA recognised pharmacopeia and any changes are minor in nature and require update of the technical dossier.

Documentation:

1. Amendment of the relevant section(s) of the dossier and including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.

B.II.E– Container closure (FPP)

B.II.e.1 Change in immediate packaging of the finished product

1. **Type IA B.II.e.1.a.1 Solid pharmaceutical forms:**
   - Condition to be fulfilled – 1, 2, 3,
   - Documentation to be supplied: 1, 2, 3, 4, 6

2. **Type IB B.II.e.1.a.2 Semi-solid and non-sterile liquid pharmaceutical forms:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 5, 6

3. **Type IB B.II.e.1.b.1 Solid, semi-solid and non-sterile liquid pharmaceutical forms:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 5, 6, 7

4. **Type IA B.II.e.1.b.3 Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form:**
   - Condition to be fulfilled – 4
   - Documentation to be supplied: 1, 8

Note: for B.II.e.1.b), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

Conditions

1. The change only concerns the same packaging/container type (e.g. blister to blister).

2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
3. Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three (3) months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, e.g. thicker blister packaging, the three (3) months' stability data do not yet have to be available. These studies must be finalised, and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier. For 3.2.P.7 the primary packaging specification must include suitable identification test/s in the COA, and the corresponding IR spectra, where applicable. Suitability of primary packaging must be provided in 3.2.P.7, if applicable.
2. Appropriate data on the new packaging (comparative data on permeability, e.g. for O2, CO2 moisture).
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopeial requirements on plastic material and objects in contact with foodstuffs.
4. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three (3) months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6. Comparison of the current and proposed immediate packaging specifications should be included in the amendment schedule.
7. Provide pictures/photographs and schematic diagrams of the proposed container closure system described in 3.2.P.7. These pictures/photographs and schematic diagrams must be included in 3.2.P.7.
8. Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product

1. **Type IA B.II.e.2.a. Tightening of specification limits:**
   - Condition to be fulfilled – 1, 2, 3, 4
   - Documentation to be supplied: 1, 2

2. **Type IA B.II.e.2.b. Addition of a new specification parameter to the specification with its corresponding test method:**
   - Condition to be fulfilled – 1, 2, 5
   - Documentation to be supplied: 1, 2, 3, 4, 6

3. **Type IA B.II.e.2.c. Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter):**
   - Condition to be fulfilled – 1, 2
   - Documentation to be supplied: 1, 2, 5

4. **Type IB B.II.e.2.d Addition or replacement of a specification parameter because of a safety or quality issue:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4, 6

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier. For 3.2.P.7 the primary packaging specification must include suitable identification test/s in the COA, and the corresponding IR spectra, where applicable. Suitability of primary packaging must be provided in 3.2.P.7, if applicable.
2. Comparison of current and proposed specifications should be included in the amendment schedule.
3. Details of any new in-house analytical method and validation data.
4. Batch analysis data and COAs on two batches of the immediate packaging for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
6. Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product

1. **Type IA B.II.e.3.a. Minor changes to an approved test procedure:**
   - Condition to be fulfilled – 1, 2, 3,

- Documentation to be supplied: 1, 2

2. **Type IA B.II.e.3.b. Other changes to a test procedure (including replacement or addition):**
   - Condition to be fulfilled – 1, 3, 4
   - Documentation to be supplied: 1, 2

3. **Type IA B.II.e.3.c. Deletion of a test procedure if an alternative test procedure is already authorised:**
   - Condition to be fulfilled – 5
   - Documentation to be supplied: 1

Conditions

1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.
2.	The method of analysis should remain the same.
3.	Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
4.	The active substance/finished product is not biological/immunological.
5.	An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IA(IN) notification.

Documentation

1.	Amendment of the relevant section(s) of the dossier and including a description of the analytical methodology, a summary of validation data.
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)

1. **Type IA B.II.e.4.a. Non-sterile medicinal products:**
   - Condition to be fulfilled – 1, 2, 3
   - Documentation to be supplied: 1, 2, 4

2. **Type IB B.II.e.4.c. Sterile medicinal products:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3, 4

Conditions

1.	No change in the qualitative or quantitative composition of the container.
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 and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial

scale batches and at least three (3) months (six (6) months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier and including description, detailed drawing and composition of the container or closure material and including revised product information as appropriate.
2. Provide pictures/photographs and schematic diagrams of the proposed container closure system described in 3.2.P.7. These pictures/photographs and schematic diagrams must be included in 3.2.P.7.
3. Revalidation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.
4. In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.e.5 Change in pack size of the finished product

1. **Type IA_{IN} B.II.e.5.a.1 Change within the range of the currently approved pack sizes:**
   - Condition to be fulfilled – 1, 2
   - Documentation to be supplied: 1, 3

2. **Type IB B.II.e.5.a.2. Change outside the range of the currently approved pack sizes:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3

3. **Type IA B.II.e.5.b. Deletion of pack size(s):**
   - Condition to be fulfilled – 3
   - Documentation to be supplied: 1, 2

4. **Type IB B.II.e.5.d Change in the fill weight/fill volume of non- parenteral multi-dose (or single-dose, partial use) products:**
   - Condition to be fulfilled – N/A
   - Documentation to be supplied: 1, 2, 3

Note: for B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.

Conditions

1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.
2. The primary packaging material remains the same.
3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier and including revised product information as appropriate.
2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics.
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).

B.II.e.6 Change in any part of the (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 needle shield (different plastic used))

1. **Type IA_{IN} B.II.e.6.a. Change that affects the product information:**
   - Condition to be fulfilled – 1
   - Documentation to be supplied: 1

2. **Type IA B.II.e.6.b. Change that does not affect the product information:**
   - Condition to be fulfilled – 1
   - Documentation to be supplied: 1

Conditions

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

Documentation:

1. 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), including revised product information as appropriate.

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)

1. **Type IA B.II.e.7.a. Deletion of a supplier:**
   - Condition to be fulfilled – 1
   - Documentation to be supplied: 1

2. Type IA B.II.e.7.b. **Replacement or addition of a supplier:

- Condition to be fulfilled – 1, 2, 3, 4
- Documentation to be supplied: 1, 2, 3

**If you are replacing a supplier of a packaging component, you must apply for deletion of the previously approved supplier/s.

Conditions

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

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. For devices for medicinal products for human use, proof of CE marking.
3. Comparative table of current and proposed specifications, if applicable.

B.II.F– Stability (FPP)

B.II.f.1 Change in the shelf-life or storage conditions of the finished product

B.II.f.1.a Reduction of the shelf life of the finished product

1. Type IA_{IN} B.II.f.1.a.1- Reduction of shelf life of the finished product as packaged for sale

- Condition to be fulfilled- 1
- Documentation to be supplied- 1,2,3

2. Type IA_{IN} B.II.f.1.a.2- Reduction of shelf life of the finished product after first opening

- Condition to be fulfilled- 1
- Documentation to be supplied- 1,2,3,4

3. Type IA_{IN} B.II.f.1.a.3- Reduction of shelf life of the finished product after dilution or reconstitution

- Condition to be fulfilled- 1
- Documentation to be supplied- 1,2,3

B.II.f.1.b Extension of the shelf life of the finished product

1. Type IB B.II.f.b.1 As packaged for sale (Supported by real time data)

- Documentation to be supplied- 1,2,3

2. Type IB B.II.f.b.2 after first opening (Supported by real time data)

- Documentation to be supplied- 1,2,3

3. Type IB B.II.f.b.3 After dilution or reconstitution (Supported by real time data)

- Documentation to be supplied- 1,2,3

4. Type IB B.II.f.1.d Change in storage conditions of the finished product or the diluted/reconstituted product
   - Documentation: 1,2,3

5. Type IA B.II.f.1.e. Change to an approved stability protocol
   - Documentation to be supplied- 1,4

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2. The change does not concern a widening of the acceptance criteria in the parameters tested a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier. This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches (1) of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.
2. Revised product information (section of the PI/PIL).
3. Signed, dated and version-controlled copy of approved end of shelf-life finished product specifications and the specifications after dilution/reconstitution or first opening.
4. Justification for the proposed change(s).

B.II.G – Design space and post-approval change management protocol (FPP)

1. Type IA_{IN} B.II.g.3. Deletion of an approved change management protocol related to the finished product

- Condition to be fulfilled- 1
- Documentation to be supplied- 1,2

Conditions

1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier.

B.II.g.4 Changes to an approved change management protocol

1. Type IB B.II.g.4.b. Minor changes to an approved change management protocol that do not change the strategy defined in the protocol.

- Documentation to be supplied- 1

Documentation

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.g.5 Implementation of changes foreseen in an approved change management protocol

1. Type IA_{IN} B.II.g.5.a The implementation of the change requires no further supportive data

- Condition to be fulfilled- 1
- Documentation to be supplied- 1,2,4

2. Type IB B.II.g.5.b The implementation of the change requires further supportive data

- Documentation to be supplied- 1,2,3,4

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the approved change management protocol.

2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol
4. Amendment of the relevant section(s) of the dossier.
5. **Signed, dated and version-controlled** copy of approved specifications of the finished product.

B.III CEP/TSE/MONOGRAPHS/WHO CPQ document

B.III.1 Submission of a new or updated or deletion of Ph. Eur. certificate of suitability/CPQ document:

- **For an active substance**
- **For a starting material/reagent/intermediate used in the manufacturing process of the active substance.**
- **For an excipient**

a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph or WHO CPQ document

1. Type IA_{IN} B.III.1.a.1 New certificate from an already approved manufacture
- Condition to be fulfilled- 1,2,3,4,5,8,11
- Documentation to be supplied- 1,2,3,4,5

2. Type IA B.III.1.a.2 Updated certificate from an already approved manufacture
- Condition to be fulfilled- 1,2,3,4,8
- Documentation to be supplied- 1,2,3,4,5

3. Type IA_{IN} B.III.1.a.3 ***New certificate from a new manufacture (replacement or addition)
- Condition to be fulfilled- 1,2,3,4,5,8,11
- Documentation to be supplied- 1,2,3,4,5

4. Type IA B.III.1.a.4 Deletion of certificate (in case multiple certificates exist per material)
- Condition to be fulfilled- 10
- Documentation to be supplied- 3

5. Type IB B.III.1.a.5 New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free
- Documentation to be supplied- 1,2,3,4,5,6

b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/ reagent/intermediate/or excipient

1. Type IA_{IN} B.III.1.b.1 New certificate for an active substance from a new or an already approved manufacture
- Conditions to be fulfilled: 3,5,6,11

- Documentation to be supplied: 1,2,3,4,5

2. **Type IA B.III.1.b.2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer**
   - Conditions to be fulfilled: 3,6,9
   - Documentation to be supplied: 1,2,3,4,5

3. **Type IA B.III.1.b.3 Updated certificate from an already approved manufacturer**
   - Conditions to be fulfilled: 7,9
   - Documentation to be supplied: 1,2,3,4,5

4. **Type IA B.III.1.b.4 Deletion of certificates (in case of multiple certificates exist per material)**
   - Conditions to be fulfilled: 10
   - Documentation to be supplied: 3

***You must provide an updated 3.2.S.2.1.

Conditions

1. The finished product release and end of shelf-life specifications remain the same.
2. Unchanged (excluding tightening) additional (to Ph. Eur. or International Pharmacopeia) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5. The active substance/starting material/reagent/intermediate/excipient is not sterile.
6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.
7. For veterinary medicinal products: there has been no change in the source of material.
8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9. If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant country requirements.
10. At least one manufacturer for the same substance remains in the dossier.
11. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product the according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Commented [MG4]: Check number formatting - needs to ne "normal" text.

Documentation

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability or WHO CPQ document.
2. The amendment schedule should clearly define the present' and 'proposed' manufacturers.
3. Amendment of the relevant section(s) of the dossier. Note: For B.III.1.a.1 and B.III.1.a.3 you must comply with section 3.2.R.3 of SAHPGL-PEM-02 (Quality and Bioequivalence guideline).
4. Where applicable, a document providing information of any materials falling within the scope of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
5. Where applicable, for active substance, a declaration by the Qualified Person (QP) or RP of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP or RP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances. The manufacture of intermediates also requires a QP/RP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP/RP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites. RP declaration OF-PEM-POST-xxxxx.
6. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 -Change to comply with SAHPRA recognised pharmacopoeia

a) Change of specification(s) of a former in-house specification limit to fully comply with SAHPRA recognised pharmacopoeia

1. Type IA_{IN} B.III.2.a.1. Active substance
- Conditions to be fulfilled: 1,2,3,4,5
- Documents to be supplied: 1,2,3,4

2. Type IA B.III.2.a.2. Excipients/active substance starting material.
- Conditions to be fulfilled: 1,2,4
- Documents to be supplied:1,2,3,4

3. Type IA B.III.2.b. Change to comply with an updated of the relevant monograph of the SAHPRA recognised pharmacopoeia
- Conditions to be fulfilled:1,2,4,5
- Documents to be supplied: 1,2,3,4

Conditions

1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.
2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or, e.g. bioassays, aggregates).
3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened.
4. Additional validation of a new or changed pharmacopoeial method is not required.
5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparison of the current and proposed specifications should be included on the amendment schedule.
3. Batch analysis data (in a comparative tabulated format) and COAs on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.
4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.

SAHPRA code	B.r.a
SAHPRA classification	Type IA
Code description	Submission of Type IA variation for products registered through reliance only.
Details	Applicable to Type IA/Type IAin variations These Type IA variations submitted to the RRA must be classified as Type IA and may be grouped as a single variation provided the following conditions and documentation requirements are met: **Conditions:** • For Type IA & IAin variations submitted to and implementable in the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering

	letter submitted to the RRA and these must concur with covering letter submitted to SAHPRA. **Documentation:** • Provide proof of submission to RRA and if available an acknowledgement or approval communication from the RRA. Any rejection/query letter issued by the RRA regarding these Type IA variations must be provided. • Provide Sameness Declaration **(GLF-PEM-02L)** stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA regardless of evaluation pathway. If proof of submission and/ or approval communication from RRA are not available, the change will remain a Type IA variation and must be submitted under applicable code as per EMA variations guideline.

SAHPRA code	B.r.b
SAHPRA classification	Type IA
Code description	Submission of Type IB variation for products registered through reliance only.
Details	Applicable to Type IB variations These IB variations may be classified as Type IA and may be grouped as a single variation provided the following conditions and documentation requirements are met: **Conditions:** • Type IB variation(s) has been approved by the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must align with the covering letter submitted to SAHPRA. **Documentation:** • Assessment report and approval letter/communication from RRA.

	Any rejection/query letter issued by the RRA regarding these Type IB variations must be provided. • Provide Sameness Declaration **(GLF-PEM-02L)** stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA regardless of evaluation pathway. If assessment reports and approval communication from RRA are not available, the change will remain a Type IB variation and must be submitted under applicable code as per EMA variations guideline.

SAHPRA code	B.r.II
SAHPRA classification	Type IB
Code description	Submission of Type II variation for products registered through reliance only.
Details	Applicable to Type II variations. Each Type II variation may be classified as a (separate) Type IB variation provided the following condition and documentation requirements are met: **Conditions:** • Type II variations have been approved by the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must concur with the covering letter submitted to SAHPRA. **Documentation:** • Assessment report and approval letter/communication from RRA. Any rejection/query letter issued by the RRA regarding these Type II variations must be provided. • Provide a Sameness Declaration stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA

	regardless of evaluation pathway. If assessment reports and approval communication are not available, the change will remain a Type II variation and may only be implemented once approval letter is issued by SAHPRA.

SAHPRA code	B.I.rc
SAHPRA classification	Type IA
Code description	Registration condition for API
Details	This code is to be used when providing data related to the API to comply with the commitments made at the time of registration OR commitments made upon submission and approval of previous variations (e.g. follow-up stability data, batch analysis data etc.).

SAHPRA code	B.II.rc		
SAHPRA classification	Type IA		
Code description	Registration condition for FPP		
Details	This code is to be used when providing data related to the FPP to comply with the commitments made at the time of product registration OR commitments made upon submission and approval of previous variations (e.g. follow-up stability data, batch analysis data etc.).		

SAHPRA code	B.I.n
SAHPRA classification	Type IA
Code description	Provision of nitrosamine risk assessment report as requested in Nitrosamine Communication.
Details	This code is to be used when providing a nitrosamine risk assessment report as requested in the Nitrosamine Communication issued by SAHPRA. • Addition of specification for nitrosamine impurities to API manufacturer specification should be classified as Type IB,

	B.I.b.1.h. • Addition of specification for nitrosamine impurities to finished product specification should be classified as Type IB, B.II.d.1.g.

SAHPRA code	B.II.PV
SAHPRA classification	Type IB
Code description	Amendment of the product labelling in response to a Pharmacovigilance recommendation.
Details	This code is to be used when updating the label due to a Pharmacovigilance recommendation: • Attach all communications from PV to the cover letter. • Updated label. • Additional information specified in the PV recommendation.

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 or WHO CPQ document is part of the approved dossier			

1(b)	Introduction of a manufacturer of the active substance supported by an ASMF/DMF/3.2.S.	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/ DMF/3.2.S and requires a 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. (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.
3. (3.2.S.4.3) A validation data of the in-house analytical methods used by the FPP manufacturer.
4. (3.2.S.4.4) Batch analysis of the API tested by the FPP manufacturer.
5. Reference standards (Primary and Secondary/working reference standard) used by the FPP to routinely test the API. Overlaid IR must be included.
6. (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.

7. (3.2.R.1) For low solubility APIs where the 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.

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.4.2) 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. (3.2.R.4.3) A discussion of the impact of the new API source 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 sterilisation, 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. (3.2.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. (3.2.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. (3.2.R.1) 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 and analytical procedures (if applicable).

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. (3.2.S.5) 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
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 - 7	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 - 7	Type II

Documentation required:

1. Submission of the closed part is required.
2. (3.2.S.4.1) Copy of the current and proposed API specifications dated and signed, dated and version controlled by the API manufacturer.
3. (3.2.S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
4. (3.2.S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
5. (3.2.S.4.4) Batch analysis data (in tabular format) issued by the API manufacturer for a minimum of two (2) batches.
6. (3.2.S.4.5) Justification of specification.
7. (Annexure to 1.0.2) 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) signed, dated and version-controlled by authorised 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 authorised 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. (Annexure to module 1.0.2) 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 guidelines	None	1 - 3	Type II

Documentation required:

1. (3.2.S.7.1) A commitment to provide ongoing stability data of at least two (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 -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 active substances.
3. Amendment of the relevant section(s) of the dossier

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.

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 - 12)	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:

2. (Module 5) Supporting clinical or comparative bioavailability data or (3.2.R.1) justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on

bioequivalence.

3. (3.2.P.1) Description and composition of the FPP.

4. (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).

5. (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.

6. (3.2.P.4) Control of excipients, if new excipients are proposed.

7. (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 National Medicine Regulatory Authority (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.

8. (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.

9. (3.2.P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.

10. (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).

11. (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.

12. (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 (3.2.R.1) 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 three (3) months of accelerated (and intermediate, as appropriate) and three (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 (3.2.R.1) justification for not submitting a new bioequivalence study according to the current SAHPRA guidelines on bioequivalence.
2. (3.2.P.2) Discussion on the development of the manufacturing process; where applicable.
3. 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).
4. 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).
5. 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 a non-dissolved form.

6. (3.2.P.3) Batch formula (where relevant), 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.

7. (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.

8. (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 three (3) months of accelerated (and intermediate, as appropriate) and three (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 the proposed product into the long-term stability programme.

10. (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.

11. Justification for introduction or increasing of an overage.

12. (3.2.P.3.5) Evidence of revalidation studies in the case of terminally sterilised 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 authorised 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 signed, dated and version-controlled by authorised 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 signed, dated and version-controlled by authorised 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.e.1 Change in immediate packaging of the finished product			
a.3	Qualitative and quantitative composition. Sterile medicinal products and biological/immunological medicinal products	None	(1 - 5)	Type II
a.4	Qualitative and quantitative composition 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

b.2	Change in type of container or addition of a new container	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 three (3) months of accelerated (and intermediate, as appropriate) and three (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 4.

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 three (3) months of accelerated (and intermediate, as appropriate) and three (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 sterilised 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
	B.II.e.1.b.2. Change in immediate packaging of the finished product. b) Change in type of container or addition of a new container. 2. Sterile medicinal products and biological/immunological medicinal products.			
				Type II

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 two (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 FPP. 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, 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.