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TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES ON VARIATIONS ON REGISTERED MEDICINAL PRODUCTS

(Made under the Guidelines on Submission of Documentation for Registration of Human Medicinal Products)

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Abbreviations and Acronyms

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
AN	Annual notification
IN	Immediate notification
CEP	Certificate of Suitability to the monograph of European Pharmacopeia
CTD	Common Technical Document
EAC	East African Community
EAC-MRH	East African Community Medicines Registration Harmonization
EAC-NMRAs	East African Community Partner States' National Medicines Regulatory Authorities
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Council on Harmonization
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristics
TMDA	Tanzania Medicines and Medical Devices Authority
NMRA	National Medicines Regulatory Agency

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These guidelines were developed through the EAC MRH Programme as part of the ongoing efforts on harmonization of regulatory standards within the East African Community. Special thanks go to the EAC Secretariat, Partner States' NMRAs and EAC Expert Working Group on Medicines Evaluation and Registration.

Various stakeholders were consulted during the development and adaptation of these guidelines. The Authority would like to extend its sincere gratitude to all our esteemed stakeholders who provided us with constructive comments and inputs.

Last but not the least, my gratitude also goes to TMDA staff who worked diligently towards perfecting the document.

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Foreword

This is the first edition adopted from EAC Guidelines on Variations for Registered Medicinal Products. The guidelines were developed and formatted based on the common technical document (CTD) requirements.

These guidelines are intended to provide guidance to applicants on the conditions to be fulfilled and the type of documentation to be submitted before a variation can be approved by the Authority. These guidelines supersede the current Application Guidelines for Variation of Registered Human Medicinal, 1st Edition of 2008. Four (4) categories of changes that require application for variations have been provided in the guidelines. These include major changes, minor changes, notifications and changes that make a new application necessary.

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the Authority with adequate time for an assessment of the supporting documentation. Decisions on such changes shall be made by the Authority. Particular circumstances are identified where lower reporting requirements (Annual Notification, Immediate Notification or Minor Variation) are possible. The change categories are organized according to the structure of the Common Technical Document (CTD). Specific CTD sections have been identified for individual data requirements in order to assist in the filing of documentation.

It should be noted that the guidelines are applicable only to APIs and excipients manufactured by chemical synthesis, classical fermentation, or semi-synthetic processes and FPPs containing such APIs and excipients. It is further elaborated that minor changes denoted by a letter '**IN**' are considered as "Immediate Notifications" and '**AN**' as "Annual Notification". Such notifications do not require prior acceptance, but must be notified to Authority immediately after implementation (immediate notification), or within 12 months following implementation of annual notification changes.

Submission of documentation in accordance with the requirements of each type of change will significantly facilitate both assessment and approval process. It is therefore critical that the guidelines are construed, comprehended and followed by all Marketing Authorization Holders who intend to make changes to their registered medicinal products.

Marketing Authorization Holders as well as other stakeholders are encouraged to provide comments for improvement based on their experience on the use of these guidelines.

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Introduction

A registered Market Authorization Holder (MAH) is responsible for the registered FPP throughout its life-cycle irrespective of the regular reviews by the Authority. The MAH is required to take into account technical and scientific progress and therefore changes may be required to the registered FPP over time. Regulation of medicinal products (FPPs) is, therefore, considered dynamic, taking into account that changes to the original dossier that was used for registration of the FPP may become necessary during the lifetime of the product. Any changes to a registered FPP (variations), whether administrative or substantial, are subject to approval by the Authority. Henceforth, guidance for the implementation of the different types of variations is set out in this document to facilitate the task of both MAHs and TMDA to guarantee that variations to the FPP do not give rise to public health concerns.

The Guidelines are administrative instrument and, as such, allows for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with Authority to avoid the possible finding that applicable regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that TMDA reserves the right to request information or material, or define conditions not specifically described in these guidelines, in order to allow for adequate assessment of safety, efficacy or quality of the pharmaceutical product. The Authority is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

Scope

These guidelines apply to applicants intending to make changes to a registered pharmaceutical product and related active pharmaceutical ingredient (API). These guidelines should be read in conjunction with other applicable guidelines including the Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products, 1st Edition, and January, 2015 and its annexes.

This guidance document is applicable only to APIs and excipients manufactured by chemical synthesis, **classical fermentation**, or semi-synthetic processes and FPPs containing such APIs and excipients. APIs from fermentation, biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact TMDA regarding planned variations to such products.

These guidelines do not cover the change of Local Technical Representative; this change is treated as administrative change with accordance to Tanzania Food, Drugs and Cosmetics Fees and Charges Regulations, 2015.

If amendments to the dossier only concern **editorial changes**, such changes should generally not be submitted as a separate variation, but they can be included in a variation relating to that part of the dossier. In such cases the changes should be clearly identified in the application form as **editorial changes** and a declaration that the content of the concerned part of the dossier has not been changed by the **editorial changes** beyond the scope of the variation submitted should be provided. It should be noted that **editorial changes** include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

General Information

The requirements specified in these guidelines have been adapted from the current WHO Guidance on Variations to a Prequalified Product, the European Union Institutions and Bodies Commission's Guideline on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and Health Canada's Guidance Document Post-Notice of Compliance (NOC) Changes: Quality. It is intended to provide supportive information on how to present an application to implement a change to a product.

1.2 Objectives

These guidelines are intended to:-

(a) Assist applicants with the classification of changes made to a registered FPP and API;
(b) Provide guidance on the technical and other general data requirements to support changes to the quality, safety and efficacy attributes of the active pharmaceutical ingredient (API) or Finished Pharmaceutical Products (FPP).

2.0 General Guidance

The notification requirements for API-related changes differ depending on the manner in which API information was submitted with the original FPP application, namely: use of a WHO prequalified API, use of a European Pharmacopoeia Certificate of Suitability (CEP), use of the EAC APIMF procedure or as provided in full within the dossier.

The conditions and documentation stipulated in these guidelines for API-related variations focus primarily on those FPPs that relied upon the provision of full API information within the FPP dossier. When an FPP relies upon a CEP or a prequalified API, FPP applicants are required to notify the Authority only when the associated CEP or Confirmation of API WHO Prequalification document has been revised.

Whenever FPPs have been registered on the basis of approval by a stringent regulatory authority (SRA) (innovator products or generic products) or WHO prequalification, subsequent applications for variations should also be approved by the same SRA and WHO PQP, respectively, and the Authority shall be notified of the approval of the changes and the applicant shall submit proof of approval of such changes from the respective agency, if applicable. All **AN** and**IN** will be subjected to payment as per current Fees and Charges Regulations. For the products registered under collaborative procedures, the changes may be submitted as an **IN.**

When a variation leads to a revision of the summary of product characteristics (SmPC), patient information leaflet (PIL) and labelling, updated product information should be submitted as

part of the application. For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches should always be continued to cover the currently accepted retest or shelf-life period. TMDA should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

Applicants should be aware that some variations may require the submission of additional consequential variations. Therefore, for any given change the applicant should consider if one or more variations may be required to be submitted.

4.0 Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

Authority
Means Tanzania Medicines and Medical Devices Authority

Active pharmaceutical ingredient (API)
Any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.
(USFDA Glossary of terms, it can be found online at Drugs@FDA Glossary of Terms).

Active pharmaceutical ingredient (API) starting material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

Biobatch
The FPP batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or bio-waiver studies, respectively.

Editorial changes
Include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

Finished pharmaceutical product (FPP)
A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling

In-process control
Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

Marketing Authorization Holder (MAH)
Is a person resident/domiciled to any of the EAC Partner States who holds authorization to place a medicinal product in the EAC Partner Sates and is responsible for that product.

Manufacturer
A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Officially recognized pharmacopoeia (or compendium)
Those pharmacopoeias recognized by TMDA (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (USP)).

Pilot scale batch
A batch of an API or FPP manufactured, by a procedure fully representative of and simulating that to be applied to a full production scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

Production batch
A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application

Stringent regulatory authority (SRA)
A National Medicines Regulatory Authority which is strict, precise, exact with effective and well-functioning systems. Among others, it includes regulatory authorities which are: -

- Members or observers or associates (prior to 2015) of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

  Members:
  - European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom
  - Japan
  - United States

  Observers:
  - European Free Trade Association (EFTA) represented by Swiss Medic of Switzerland, and Health Canada (as may be updated from time to time).

  Associates: through mutual recognition agreements: Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).
- For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognized as stringent approval: -
  - Article 58 of European Union Regulation (EC) No. 726/2004
  - Canada S.C. 2004, c. 23 (Bill C-9) procedure

- United States FDA tentative approval (for antiretroviral under the PEPFAR programme)

- A regulatory Authority that has been agreed by the Authority to have an effective and well-functioning medicines regulation systems.

5.0 Guidance for implementation

5.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of administrative, quality, safety and efficacy -related changes. Specific change examples are provided in these guidelines. However, it is to be noted that a change not cited in these guidelines, should be decided on a case-by-case basis. Whenever the applicant is unclear about the classification of a particular change, the Authority should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure.
For the purpose of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.
Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although individual changes may be classified as a particular reporting type, classification at a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact the Authority prior to submission of the variation application in order to obtain guidance in classifying such changes.

5.2 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to Authority immediately after implementation (immediate notification (**IN)**), or within 12 months following implementation (annual notification (**AN**)) of the change.
It should be highlighted that an **IN** or **AN** may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

5.3 Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for **ANs** should be available on request or at the time of inspection. ANs should be submitted to TMDA within 12 months of implementation of the changes.

Annual notifications submitted at once in one calendar year will be considered as one minor variation and will be charged as such as per TMDA's Fees and Regulations which are in force at the time of submission.

5.4 Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by the Authority within two (2) months of the date of acknowledgement of receipt of the application.

Submitted immediate notification will be considered as one minor variation and will be charged as such as per TMDA's Fees and Regulations which are in force at the time of submission.

5.5 Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.
Such variations can be implemented if no objection letter has been issued within three (3) months from the date of acknowledgement of receipt. Should questions arise during the specified period; the change can only be implemented on receipt of a letter of acceptance from the Authority.

5.6 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by TMDA is required before the changes can be implemented. A letter of acceptance will be issued for all major variations when the variation is considered acceptable. These variations will be handled within a time period of six (6) months from the date of acknowledgement of receipt.

5.7 New applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. For these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

5.8 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, TMDA must be notified and submission of the revised labelling information is expected as per the Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products, 1st Edition, and January, 2015.

5.9 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements **(IN, AN orVmin)** are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a major variation.
In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be considered to be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

5.10 Documentation required

For each variation certain documents have been identified and the change categories are organized according to CTD structure as supporting data. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation:

(a) a variation application form (a template can be downloaded from the website). All sections of this form shall be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF file, shall be provided;
(b) replacement of the relevant sections of the dossier as per CTD format;
(c) Copies of SmPC, PIL and labels, if relevant.

Note: Implementation of some changes such as multiple manufacturing sites and multiple pack sizes of sterile products should only commence after amendment of TMDA (Registrations of Medicinal Products) Regulations, 2015 and TMDA (Fees and Charge) Regulations, 2015 to align them with the changes proposed in the various guidelines.

6.0 Administrative changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1	Change of the of the Marketing Authorization Holder (MAH) of the FPP			
a	Change in the name and/or corporate address of the (MAH)	1	1, 3	IN
b	Change of MAH from one company to another	2	2-3	IN
Conditions to be fulfilled				
1) Confirmation that the supplier of the product remains the same legal entity 2) All legal requirements for change of MAH have been met & Legal transfer of change has been completed				
Documentation required				
1) A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned. 2) Notarized transfer documents 3) Company registration certificate from the relevant jurisdiction				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name or address of a manufacturer of an API	1	1-2	IN
Conditions to be fulfilled				
1) No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required				
1) A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2) An updated Letter of Access in the case of a change in the name of the APIMF Holder.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
3	Change in the name and/or address of a manufacturer of the FPP	1	1-2	IN
Conditions to be fulfilled				
1) No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required				
1) Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2) Two (2) commercial samples of the product				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
4	Deletion of a manufacturing site or manufacturer involving:			
4a	production of the API starting material	1	1,3	AN
4b	production or testing of the API intermediate or API	1-2	1,3	IN
4c	production, packaging or testing of the intermediate or FPP	1-2	1-3	IN
Conditions to be fulfilled				
1) At least one other site continues to perform the same function(s) as the site(s) intended to be deleted. 2) The deletion of site is not a result of critical deficiencies in manufacturing.				
Documentation required				
1) Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application. 2) Two (2) commercial samples of the product required **ONLY** if deleted manufacturing site				

appears on registered product label. 3) Updated manufacturers information and their roles

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
5	Change of Proprietary name of the Product	1-4	1-2	Vmin
Conditions to be fulfilled				
1) The brand name should not have been accepted for another product. 2) There is no change to the product (formulation, release and end-ofshelflife specifications, manufacturing source and process) except forthe product name change. 3) No confusion with another drug product either when spoken or written. 4) The new name does not (i) suggest greater safety or efficacy thansupported by clinical data (ii) imply a therapeutic use (iii) implysuperiority over another similar product and (iv) imply the presence ofsubstance(s) not present in the product.				
Documentation required				
1) Revised product information 2) Two (2) commercial samples of the product				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
6	a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication. c) Change of distributor's/manufacturers details.	1 – 2	1 - 3	Vmin
Conditions to be fulfilled				
1) Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2) The change does not contain promotional information.				
Documentation required				
1) Current approved product labelling. 2) Proposed product labelling, a clean and annotated version highlighting the changes made. 3) Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change.				

Changes to a CEP or to a confirmation of API-prequalification document

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
7	Submission of a new or updated European Pharmacopoeia Certificate of Suitability for an API or starting material or intermediate used in the manufacturing process of the API:			
7a	Updated CEP	1-5	1-7	IN
7b	from a new manufacturer	1, 3-5	1-7	Vmin

Conditions to be fulfilled

1) No change in the FPP release and shelf-life specifications.
2) Unchanged (excluding tightening) additional (to Ph.Eur.) specifications for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements.
3) The manufacturing process of the API, starting material or 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 low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
5) The site must be GMP compliant

Documentation to be supplied

1) Copy of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the EAC Partner State's NMRAs who refers to the CEP.
2) A written commitment that the applicant will inform the EAC Partner State's NMRAs in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3) Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under section 3.2.S of EAC Partner States' NMRAs "*Guidelines on Submission of Documentation for Marketing Authorization of a Registered Pharmaceutical Product for Human Use*".
4) For sterile APIs, data on the sterilization process of the API, including validation data.
5) In the case of the submission of a CEP for an API, 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 batch of the FPP of at least pilot scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to the EAC Partner State's NMRA.
6) Copy of FPP manufacturer's revised API specifications and standard test procedure.
7) Proof of GMP compliance

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8	Submission of a new or updated WHO Confirmation of API -Prequalification Document (CPQ)			
8a	Updated CPQ	1-3	1-3, 5	IN
8b	from a new manufacturer	1-2	1-5	Vmin

Conditions to be fulfilled

1) No change in the FPP release and shelf-life specifications.
2) For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3) There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, to the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.

Documentation to be supplied

1) Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box on the name of the applicant or FPP manufacturer seeking to use the document.
2) Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option
3) For sterile APIs, data on the sterilization process of the API, including validation.
4) Copy of FPP manufacturer's revised API specifications and standard test procedure.
5) 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 batch of at least pilot scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to the EAC Partner State's NMRAs.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
9	Submission of a new or updated transmissible spongiform encephalopathy European Pharmacopoeia Certificate of Suitability for an excipient or API (addition or replacement)	None	1	AN

Conditions to be fulfilled

None

Documentation required

1) 1. Copy of the current (updated) TSE CEP.

Note: For all changes involve submission of samples that are not readily available at the time of variation applications submission to the Authority, commitment to submit and artwork for the same should be accepted in place of the physical sample.

7.0 Quality changes

3.2. S Drug substance (or API)

3.2. S.2 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10	Replacement or addition of a new manufacturing site or manufacturer of an API involving:			
10a	API testing only	1, 2,4	1, 3-4	IN
10b.1	Production of API starting material	3-4	No variation is required such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC APIMF procedure	
10b.2		4-5	1-2, 12	IN
10b.3		None	1,2,5, 7-8,12, 13	Vmaj
10c.1	Production of API intermediate	3-4	No variation is required such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC APIMF procedure	
10c.2		4, 6	1-2, 12	IN
10c.3		None	1,2,5, 7-8,12	Vmaj
10d.1	Production of API	1, 7-11	1-2, 4, 8-9	IN
10d.2		None	1,2,4,6,5,7-8, 10-11, 13	Vmaj

Conditions to be fulfilled

1) The API is non-sterile.
2) The transfer of analytical methods has been successfully undertaken.
3) The new site is supported by an APIMF that has been currently accepted through the EAC Partner States' APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4) No change in the FPP manufacturer's API specifications.
5) The impurity profile of the API starting material is essentially the same as other accepted

sources. The introduction of the new supplier does not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.

6) Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications.
7) No change in the FPP release and end-of-shelf-life specifications.
8) No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
9) For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
10) Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or new contract manufacturing site with evidence of an acceptable and similar quality system to the main manufacturer).
11) 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 WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or EMA's Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products or an equivalent guideline of the ICH region and associated countries.

Documentation required

1) (S.2.1)Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s). A valid testing authorization or a certificate of GMP compliance, if applicable.
2) (S.2.2)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.
3) (S.4.3)Copies or summaries of validation reports or method transfer reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.
4) (S.4.4)Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed manufacturers/sites.
5) Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier

6) The open part of the new APIMF (with a Letter of Access provided in Module 1)
7) (P.8.2)If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to the EAC Partner State's NMRAs.
8) (S.4.1) A copy of the FPP manufacturer's API specifications.
9) (S.2) A declaration from the supplier of the registered FPP that the route of synthesis, materials, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
10) A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
11) For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low solubility APIs) where there is a significant difference in particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.
12) Certificates of analysis for at least one batch of API starting material/intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material/intermediate (as applicable) from the new source and from a previously accepted source.
13) An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
11a	change or addition of a manufacturing block/unit at a currently accepted site of API manufacture	1-5	1-4	IN
11b		1,3-5		

Conditions to be fulfilled

1) The API is non-sterile.
2) API manufacturing block/unit is currently accepted by the EAC Partner State's APIMF procedure.
3) The same quality system covers currently accepted and proposed units/blocks.
4) For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the biobatch.
5) No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable).

Documentation required

1) (S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2) (S.2.1)Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3) (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed units/blocks.
4) (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units/blocks

Description of change		**Conditions to be fulfilled**	**Documentation to be supplied**	**Reporting type**
12a	Change in the manufacturing process of the API	1-3, 9	1-2, 8	AN
12b		1-2, 4, 6-9	3-4, 11-12	IN
12c		1-2, 4-7	3-4, 11-12	Vmin
12d		None	2-14	Vmaj

Conditions to be fulfilled

1) No change in the physical state (e.g. crystalline, amorphous) of the API.
2) For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to the API lot used in the preparation of the biobatch.
3) API manufacturing site is currently accepted through the EAC Partner State's APIMF procedure.
4) Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5) No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
6) No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
7) The change does not affect the sterilization procedures of a sterile API.
8) The change involves only steps before the final intermediate.
9) The change does not require revision of the starting material, intermediate or API specifications

Documentation to be supplied

1) A copy of the EAC partner state's letter of acceptance for APIMF amendment
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 EAC Partner State's NMRAs.

3) (S.2.2)A side-by-side comparison of the current process and the new process.
4) (S.2.2)A flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
5) (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.
6) (S.2.3)Either a TSE CEP for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current *WHO guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products* or EMA's *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* or an equivalent guideline of the ICH region and associated countries.
7) (S.2.4)Information on controls of critical steps and intermediates, where applicable.
8) (S.2.5)Evidence of process validation and/or evaluation studies for sterilization, if applicable.
9) (S.3.1)Evidence for elucidation of structure, where applicable.
10) (S.3.2)Information on impurities.
11) (S.4.1)A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12) (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.
13) (S.7.1)Results of two batches of at least pilot scale with a minimum of three (3) months of accelerated (and intermediate as appropriate) and three (3) months of long-term testing of the proposed API.
14) 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

Description of change		**Conditions to be fulfilled**	**Documentation to be supplied**	**Reporting type**
13	Change in the in-process tests or limits applied during the manufacture of the API:			
13a	any change in the manufacturing process controls	1	No variation is required, such changes are handled as amendments to the	

			APIMF by the APIMF holder as part of the EAC APIMF procedure	
13b	tightening of in-process limits	2-4	1	AN
13c	addition of a new in-process test and limit	2, 5	1-5	AN
13d	addition or replacement of an in-process test as a result of safety or quality issue	None	1-5,7, 8-10	Vmin
13e.1	deletion of an in-process test	2,6-7	1-3, 6	AN
13e.2		None	1-3, 7-10	Vmaj
13f	relaxation of the in-process test limits	None	1-3, 5,7-10	Vmaj

Conditions to be fulfilled

1) API manufacturing site is currently accepted through the EAC Partner State's APIMF procedure.
2) The change is not necessitated by unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3) The change is within the range of currently accepted limits.
4) The analytical procedure remains the same, or changes to the analyticalprocedure are minor.
5) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6) The affected parameter is non-significant. ("*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.")*
7) The change does not affect the sterilization procedures of a sterile API.

Documentation to be supplied

1) A comparison of the currently accepted and the proposed in-process tests.
2) (S.2.2)Flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
3) (S.2.4)Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
4) Details of any new non-pharmacopoeial analytical method and validation data where relevant.
5) Justification for the new in-process test and/or limits.
6) Justification/risk-assessment showing that the parameter is non-significant.
7) (S.2.5)Evidence of process validation and/or evaluation studies for sterilization, where applicable.
8) (S.3.2)Information on impurities, if applicable.
9) (S.4.1)Copy of currently accepted specifications of API (and intermediates, if applicable).
10) (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) for all specification parameters.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
14	Change in batch size of the API involving:			
14a	up to 10-fold compared to the currently accepted batch size	1-2,4,6	1,3-4	AN
14b	Downscaling (to at least pilot batch size)	1-4	1,3-4	AN
14c	any change in scale (APIMF procedure)	5	1-2, 4-5	AN
14d	more than 10-fold increase compared to the currently accepted batch size	1-2,4,6	1,3-4	Vmin

Conditions to be fulfilled

1) No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of different size of equipment).
2) The change does not affect the reproducibility of the process.
3) The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4) The change does not concern a sterile API.
5) API manufacturing site and batch size is currently accepted through the EAC Partner State's APIMF procedure.
6) The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

Documentation required

1) (S2.2)A brief narrative description of the manufacturing process.
2) (S.2.5)Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3) (S.4.1)Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4) (S.4.4)Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5) A copy of the EAC partner state's letter of acceptance for APIMF amendment.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
15	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
15a	any change	1	No variation is required, such changes are handled	

			as amendments to the APIMF by the APIMF holder as part of the EAC APIMF procedure	
15b	tightening of the specification limits	2-4	1-3	AN
15c	minor change to an analytical procedure	5-7	2-3	AN
15d	addition of a new specification parameter and a corresponding analytical procedurewhere necessary.	2,7-9	1-3	AN
15e	deletion of a specification parameter or deletion of an analyticalprocedure	2,10	1-4	AN
15f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1-7	Vmin
15g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4,7,9-10	1,3-4	IN
15h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1-3,5,6,7	Vmaj

Conditions to be fulfilled

1) API manufacturing site is currently accepted through the EAC Partner State's APIMF procedure.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any change is within the range of currently accepted limits.
4) The analytical procedure remains the same.
5) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
6) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7) No change to the total impurity limits; no new impurities are detected.
8) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9) The change does not concern a genotoxic impurity.
10) The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation to be supplied

1) Comparative table of currently accepted and proposed specifications.
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) (S.2.4)Information on intermediates, where applicable.
4) Justification/risk-assessment showing that the parameter is non-significant.
5) (S.3.2)Information on impurities, where applicable.
6) Batch analysis data on two production batches
7) Where appropriate, comparative dissolution profile data for the FPP on at least one pilot batch containing the API complying with current and proposed specifications.

3.2. S.4 Control of the API by the API manufacturer

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
16	Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:			
16a	API supported through the EAC APIMF procedure.	1-2	No variation is required, such changes are handled as amendments to the associated APIMF	
16b	API not supported through the EAC APIMF procedure.	2	1-4	IN

Conditions to be fulfilled

1) The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF (EAC APIMF procedure) and accepted.
2) The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.

Documentation to be supplied

1) (S.4.1)Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2) (S.4.2)Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3)Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4) Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
17a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	11	1-5	AN
17b.1	deletion of a test parameter	1-2	1,6	AN
17b.2		10	1, 6, 8	IN
17b.3		None	1, 6	Vmaj
17c.1	addition of a test parameter	1, 4-8	1-6	AN
17c.2		1, 5-7, 10	1-6,8	IN
17c.3		1,5-7	1-6	Vmin
17c.4		None	1-7	Vmaj
17d.1	replacement of a test parameter	1, 5-8	1-6	IN
17d.2		5, 7, 10	1-6,8	Vmin
17d.3		None	1-7	Vmaj
17e.1	tightening of an acceptance criterion	1, 3, 9	1,6	AN
17f.1	relaxation of an acceptance criterion	1, 5-9	1,6	IN
17f.2		5, 7, 10	1, 6,8	Vmin
17f.3		None	1,6-7	Vmaj

Conditions to be fulfilled

1) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2) The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3) The change is within the range of currently accepted acceptance criteria.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no change in particle size

distribution acceptance criteria.

6) No additional impurity found over the ICH identification threshold.
7) The change does not concern sterility testing.
8) The change does not involve the control of a genotoxic impurity.
9) The associated analytical procedure remains the same.
10) The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
11) No change is required in FPP release and shelf-life specifications.

Documentation to be supplied

1) (S.4.1)A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (S.4.2)Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3)Copies or summaries of validation/verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4) (S.4.3)Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (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) (S.4.5)Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7) (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 2 batches. of FPP manufactured using API controlled to the proposed criteria; 2 batches of FPP manufactured using API controlled to the currently accepted criteria; and data on the FPP 2 batches. used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact EAC partner states NMRAs for advice. For changes to the polymorph of an insoluble API the applicant should contact EAC partner states NMRAs for advice before embarking upon any investigation.
8) Copy of the EAC Partner State's letter of acceptance for APIMF amendment

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
18	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
18a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1-3	AN
18b	change from a currently accepted house analytical procedure to an analytical procedure in a officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another officially recognized pharmacopoeia	None	1-4	IN
18c.1	addition of an analytical procedure	1-3	1-3	AN
18c.2		3, 8	1-3, 5	AN
18c.3		8	1-3, 5	Vmin
18c.4		None	1-3	Vmaj
18d.1	modification or replacement of an analytical procedure	1-6	1-4	AN
18d.2		2-3, 5-6, 8	1-5	AN
18d.3		1-3, 5-6	1-4	Vmin
18d.4		5-6, 8	1-5	Vmin
18d.5		None	1-4	Vmaj
18e.1	deletion of an analytical procedure	6-7	1,6	AN
18e.2		6, 8	1, 5-6	IN
18e.3		None	1, 6	Vmaj
Conditions to be fulfilled				

1) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3) No new impurities have been detected as a result of the use of the new analytical method. 4) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected. 5) Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure. 6) The change does not concern sterility testing. 7) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method. 8) The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.
Documentation to be supplied
1) (S.4.1)Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. 2) (S.4.2)Copies or summaries of analytical procedures, if new or significantly modified analytical procedures are used. 3) S.4.3)Copies or summaries of validation/verification reports issued by the FPP manufacturer, if new or significantly modified analytical procedures are used. 4) (S.4.4)Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures. 5) A copy of the EAC Partner State's letter of acceptance for APIMF amendment 6) (S.4.5)Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
19a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3-4	1-2,4	AN
19b		1-2, 4	2-3	IN
19c		4	1-3	Vmin
Conditions to be fulfilled				

1) Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, moisture permeability etc.). 2) The change does not concern a sterile API. 3) The change has previously been accepted through the EAC Partner State's APIMF procedure. 4) The change is not the result of stability issues.
Documentation required
1) (S.2.5)Evidence of process validation and/or evaluation studies for sterilization if different from the current process. 2) (S.6)Information on the proposed primary packaging (e.g. description, specifications etc.) and data in fulfillment of condition 1. 3) (S.7.1)Results of a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing of the API in the proposed primary packaging type. 4) A copy of the EAC Partner State's letter of acceptance for APIMF amendment

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
20	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
20a	tightening of specification limits	1-2	1	AN
20b	addition of a test parameter	2-3	1-3	AN
20c	deletion of a non-critical parameter	2	1,4	AN
20d	addition or replacement of a specification parameter as the result of a safety or quality issue	1,3	1-4	Vmin
20e	any change EAC Partner State's APIMF procedure	4	No variation is required, such changes are handled as amendments to the associated APIMF	
Conditions to be fulfilled				
1) The change is within the range of currently accepted limits. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 4) The change has previously been accepted through the EAC Partner State's APIMF procedure.				
Documentation required				

1) (S.4.5)Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2) (S.4.2)Details of method and summary of validation of new analytical procedure.
3) (S.6)Certificate of analysis for two batches.
4) Justification to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Report-ing type
21	Change to an analytical procedure on the immediate packaging of the API involving:			
21a	minor change to an analytical procedure	1-3	1	AN
21b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1	AN
21c	deletion of an analytical procedure	5	2	AN
21d	any change (EAC Partner State's APIMF procedure)	6	No variation is required, such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.
6) The change has previously been accepted through the EAC Partner State's APIMF procedure.

Documentation required

1) (S.6)Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.
2) Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of change		Conditions to be fulfilled	Documentation required	Report-ing type
22	Change in the retest period/shelf-life of the API involving:			
22a	any change EAC Partner State's APIMF procedure	4	4	IN
22b	Reduction	3	1-2	IN
22c	Extension	1-2	1-3	Vmin
Conditions to be fulfilled				
1) No change to the primary packaging in direct contact with the API or to the recommended condition of storage. 2) Stability data was generated in accordance with the currently accepted stability protocol. 3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns. 4) The revised retest period has previously been accepted through the EAC Partner State's APIMF procedure.				
Documentation required				
1) (S.7.1)Proposed retest period/shelf-life, summary of stability testing according to currently accepted protocol and test results. 2) (S.7.2)Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable. 3) (S.7.3)Stability data to support the change 4) A copy of the EAC Partner State's letter of acceptance for APIMF amendment.				

Description of change		Conditions to be fulfilled	Documentation required	Report-ing type
23	Change in the labelled storage conditions of the API involving:			
23a	any change in storage conditions EAC Partner State's APIMF procedure	1	1	IN
23b	any change in storage conditions	2	2	Vmin
Conditions to be fulfilled				
1) The revised storage conditions have previously been accepted through the EAC Partner State's APIMF procedure. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.				
Documentation required				
1) A copy of the EAC Partner State's letter of acceptance for APIMF amendment. 2) (S.7.1)Stability and/or compatibility test results to support the change to the storage conditions.				

3.2. P Drug product (or FPP)

3.2. P.1 Description and composition of the FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
24a	Change in the composition of a solution of dosage form	1-6	2,4,7,9-10	IN
24b		None	1-11	Vmaj

Conditions to be fulfilled

1) The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API.
2) The affected excipient(s) does/do not function as a preservative or preservative enhancer.
3) No change in the specifications of the affected excipient(s) or the FPP.
4) No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
5) The change does not concern a sterile FPP.
6) The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally registered product.

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current Authority Guidelines on Bioequivalence.
2) (P.1)Description and composition of the FPP.
3) (P.2)Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, preservative effectiveness, suitability studies on the packaging system for the changed product).
4) (P.3)Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5) (P.4)Control of excipients, if new excipients are proposed.
6) (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 SRA and shown to comply with the scope of the current guideline in the SRA. 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 its use.
7) (P.5)Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8) (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.
9) (P.8.2)Updated post-acceptance stability protocol and stability commitment to place the first

production scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).

10) (R.1)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.
11) Two (2) commercial samples of the product

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
25	Change in the colouring system or the flavouring system currently used in the FPP involving			
25a	reduction or increase of one or more components of the colouring or the flavouring system	1-3,6	1,4,6-7	AN
25b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1-7	1-7	IN

Conditions to be fulfilled

1) No change in the functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile etc.
2) Any minor adjustment to the formulation to maintain the total weight is made by an excipient which currently makes up a major part of the FPP formulation.
3) Specifications for the FPP are updated only with respect to appearance/odour /taste or if relevant, deletion or addition of a test for identification.
4) Any new component must comply with the relevant section of EAC Partner State's NMRAs "*Guidelines on Submission of Documentation for Marketing Authorization of a Registered Pharmaceutical Product for Human Use*", and "*Guidelines for registration of Veterinary drugs*".
5) 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 is in compliance with the current *WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products* or EMA's *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* or an equivalent guide of the ICH region and associated countries.
6) For paediatric products, the change does not require submission of results of palatability studies.
7) *The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.*

Documentation required

1) Two (2) commercial samples of the product
2) (P.2)Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant).
3) (P.4.5)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 SRA and shown to comply with the scope of the current guideline of the SRA. 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 its use.
4) (P.5)Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches.
5) (P.5.3)If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6) (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.
7) (R.1)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**	**Reporting type**
26	Change in weight of tablet coatings or capsule shells involving			
26a	immediate-release oral FPPs	1-3	2-5	AN
26b	gastro-resistant, modified or prolonged release FPPs	None	1-5	Vmaj

Conditions to be fulfilled

1) Multipoint in vitrodissolution profiles of the proposed version of the product (determined in the release medium on at least two batches of pilot or production scale), are similar to the dissolution profiles of the biobatch.
2) Coating is not a critical factor for the release mechanism.
3) Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1) Justification for not submitting a new bioequivalence study according to the current *EAC Guideline on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*.
2) (P.2)Comparative multipoint in vitrodissolution profiles in the release medium (or media), on at least two batches of pilot or production scale of the proposed product versus the biobatch.

3) (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) (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. In addition, a written commitment, that the stability studies will be finalized should be provided
5) (R.1)Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batchand confirmation that there are no changes to the production documents other than those highlighted.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
27	Change in the composition of an immediate-release solid oral dosage form including			
27a.1	replacement of a single excipient with a comparable excipient at a similar level	1-5	1-10	Vmin
27a.2		None	1-10	Vmaj
27b.1	quantitative changes in excipients	1-4	1-4, 7-10	Vmin
27b.2		None	1-4, 7-10	Vmaj

Conditions to be fulfilled

1) No change in functional characteristics of the pharmaceutical form.
2) Only minor adjustments (see appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made by an excipient which currently makes up a major part of the FPP formulation.
3) Stability studies have been started under conditions according to *EAC Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)* (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot or production scale batches and at least three months satisfactory stability data are at the disposal of the applicant and the stability profile is similar to the currently accepted product.
4) 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.
5) The change is not the result of stability issues and/or does not result in potential safety concerns i.e. differentiation between strengths.

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current *EAC Guideline on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*.
2) (P.1)Description and composition of the FPP.
3) (P.2)Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles on at least two batches of pilot or production scale of the proposed product and the biobatch

(depending on the solubility and permeability of the drug, dissolution in the release medium or in multiple media covering the physiological pH range).

4) (P.3)Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5) (P.4)Control of excipients, if new excipients are proposed.
6) (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 SRA and shown to comply with the scope of the current guideline of the SRA. 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 its use.
7) (P.5)Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8) (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.
9) (P.8.2)Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10) (R.1)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**	**Reporting type**
28	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
28a	changes in imprints, embossing or other markings	1-3	1-2, 5-6	IN
28b	deletion of a scoreline	2-5	1,5-6	IN
28c.1	addition of a scoreline	2-4	1, 3, 5-6	Vmin
28c.2		None	1, 3-6	Vmaj
Conditions to be fulfilled				
1) Any ink must comply with the pharmacopeial requirements of EU, Japan, US or any other recognised pharmacopeia and must be food grade 2) The change does not affect the stability or performance characteristics (e.g. release rate) of the				

FPP.

3) Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4) Addition or deletion of a score line to a generic product is consistent with a similar change in the comparator product.
5) The scoring is not intended to divide the FPP into equal doses.

Documentation required

1) Two (2) commercial samples of the Product.
2) (P.1.)Qualitative composition of the ink.
3) (P.2)Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses.
4) (P.2)Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.
5) (P.5)Copies of revised FPP release and shelf-life specifications.
6) (R.1)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 and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
29	Change in dimensions without change in qualitative or quantitative composition and mean mass of::			
29a	tablets, capsules, suppositories and pessaries other than those stated in change #29b	1-2	2-6	IN
29b	gastro-resistant, modified or prolonged release FPPs and scored tablets	1-2	1-6	Vmin

Conditions to be fulfilled

1) Specifications for the FPP are updated only with respect to dimensions of the FPP.
2) Multipoint in vitrodissolution profiles of the current and proposed versions of the product (determined in the release medium, on at least one batch of pilot or production scale), are comparable.

Documentation required

1) For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current *EAC Guideline on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.
2) Two (2) commercial samples of the Product.
3) (P.2)Discussion on the differences in manufacturing process(es) between the currently

accepted and proposed products and the potential impact on product performance.

4) (P.2)Comparative multipoint in vitrodissolution profiles in the release medium, on at least one batch of pilot or production scale of the current and proposed products.
5) (P.5)Copies of revised FPP release and shelf-life specifications.
6) (R.1)Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation 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**	**Reporting type**
30	Deletion of the solvent/diluent container from the pack	None	1-3	Vmin
	addition of solvent/diluent container in the pack"		2-5	Vmajor
Documentation required				
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 pharmaceutical product. 2) Revised product information 3) Two (2) commercial samples of the product 4) Necessary information required for a new application (refer to EAC guidelines on registration of medicines) 5) Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected by EAC.				

3.2. P.3 Manufacture

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
31	Addition or replacement of a manufacturing site for part or all of the manufacturing process for a FPP involving			
31a	secondary packaging of all types of FPPs	2-3	1	IN
31b	primary packaging site of:			
31b.1	solid FPPs (e.g. tablets, capsules) , semisolid (e.g. ointments, creams) and solution liquid FPPs	2-4	1,8	IN
31b.2	other liquid FPPs (suspensions, emulsions)	2-5	1,5,8	IN
31c	all other manufacturing operations except batch control/release testing	1-3,5	1-9	Vmin

Conditions to be fulfilled

1) No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications.
2) Satisfactory joint inspection in the last three years by EAC Partner States.
3) Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).
4) The change does not concern a sterile FPP.
5) Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production scale batches in accordance with the current protocol.

Documentation required

1) Evidence that the proposed site is appropriately authorized in the last 3 years, for the pharmaceutical form and the product concerned:
    a. a copy of the current manufacturing authorization, a GMP certificate or equivalent issued by the NMRA
    b. a GMP certificate issued by EAC after joint inspection; or as required in the EAC GMP compendium
    c. date of the last satisfactory inspection concerning the packaging facilities by Authority
2) Date and scope of the last satisfactory inspection.
3) (P.2)Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4) (P.2)For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one (1) production scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two (2) more production scale batches.
5) (P.3.5)Process validation reports or validation protocol (scheme) for three (3) batches of the proposed batch size that includes comparative dissolution against the biobatch results with f2 calculation as necessary.
6) (P.5.1)Copies of FPP release and shelf-life specifications from the proposed manufacturing site.
7) (P.5.4)Batch analysis data on one production scale batch from the proposed site and comparative data on the last three batches from the previous site.
8) (P.8.2)Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the FPP produced at the new site, into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9) (R.1)Executed production documents for one batch of the FPP manufactured at the new site.

Note: Two (2) commercial samples of the product should be submitted where the manufacturing site appears on the product label

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
32	Replacement or addition of a site involving batch control testing	1-2	1-3	AN

Conditions to be fulfilled

1) Site is appropriately authorized by the EAC Partner State's NMRA and should be GMP compliant
2) Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

1) Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2) Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected by EAC.
3) (P.5.3)Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
33	Change in the batch size of the FPP involving			
33a	up to and including a factor of ten (10) compared to the biobatch	1-7	2, 5-6	IN
33b	downscaling (to at least pilot batch size)	1-5	2,6	AN
33c	other situations	1-7	1-7	Vmin

Conditions to be fulfilled

1) The change does not affect the reproducibility and/or consistency of the product.
2) The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3) 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 size equipment.
4) A validation protocol is available or validation of the manufacture of three production scale batches has been successfully undertaken in accordance with the current validation protocol.
5) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6) The change does not require supporting *in vivo* data.
7) The biobatch was at least of 100,000 units in case of solid oral dosage forms.

Documentation required

1) (P.2)For solid dosage forms: dissolution profile data on a minimum of one representative production scale batch performed in routine release medium and comparison of the data with the biobatch results and one production scale batch from the previous batch size. Data on the

next two (2) full production scale batches should be available on request and should be reported if outside 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) (P.3.5)Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3) (P.5.1)Copies of release and shelf-life specifications.
4) (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 (2) full production scale batches should be available on request and should be reported immediately if outside specifications (with proposed remedial action).
5) (P.8.2)Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6) (R.1)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) and confirmation that there are no changes to the production documents other than those highlighted.
7) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current *EAC Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*..

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
34a	Change in the manufacturing process of the FPP	*1-9*	*1-4, 6-7*	*AN*
34b		1-3, 5-9	1-7	Vmin
	Substancial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of a medicinal product	none	1-8	Vmajor

Conditions to be fulfilled

1) The change does not require supporting in vivo data.
2) No change in qualitative and quantitative impurity profile or in physico-chemical properties; dissolution profiles are similar with those of the biobatch.
3) The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet/dry granulation or vice versa would be considered a change in manufacturing principle), same processing intermediates and there are no changes to any manufacturing solvent used in the process.

4) The same classes of equipment, operating procedures, in-process controls (no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5) No change in the specifications of the intermediates or the FPP.
6) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
7) The change does not involve packaging or labeling where the primary packaging provides a metering and/or delivery function.
8) The change does not concern a gastro-resistant, modified or prolonged release FPP.
9) The change does not affect the sterilization parameters of a sterile FPP.

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO Guidelines on Bioequivalence.
2) (P.2)Discussion on the development of the manufacturing process; where applicable:
   - comparative in vitro testing, e.g. multipoint dissolution profiles in the release medium for solid dosage units (one production batch and comparative data of one batch from the previous process and the biobatch results, data on the next two production batches should be available on request or reported if outside specification);
   - comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data of one batch from the previous process and the biobatch results, data on the next two production batches) should be submitted or be available on request;
   - microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.
3) (P.3)Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4) (P.5)Specification(s), certificate of analysis for one production scale batch each manufactured according to the currently accepted and the proposed processes.
5) 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.
6) P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the proposed product into the long-term stability programme.
7) (R.1)Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.
8) Updated quality, safety and efficacy data

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
35	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
35a	tightening of in-process limits	1-2,5	1	AN
35b	deletion of a test	2,4	1, 6	AN
35c	addition of new tests and limits	2-3	1-6	AN
35d	revision or replacement of a test	2-3	1-6	IN

Conditions to be fulfilled

1) The change is within the range of acceptance limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5) No change in the analytical procedure.

Documentation required

1) (P.5.1)Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2)Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3)Copies or summaries of validation reports, if new analytical procedures are used.
4) (P.5.3)Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (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) (P.5.6)Justification for the addition/deletion of the tests and limits.

3.2. P.4 Control of excipients

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
36	Change in source of an excipient from a transmissible spongiform encephalopathy risk to a material of vegetable or synthetic origin.	1	1	AN
	Change or introduction of a TSE risk			Vmajor

	material or replacement of a TSE risk material from a different TSE risk material			
Conditions to be fulfilled				
1) No change in the excipient and FPP release and shelf-life specifications.				
Documentation required				
1) Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin. 2) A TSE/BSE certificate of suitability				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
37	Change in the specifications or analytical procedures of an excipient involving:			
37a	deletion of a non-significant in-house parameter	2	1-3	AN
37b	addition of a new test parameter or analytical procedure	2-3	1-2	AN
37c	tightening of specification limits	1-2,4	1-2	AN
37d	change or replacement of an analytical procedure	2-3	1-2	Vmin
Conditions to be fulfilled				
1) The change is within the range of currently accepted limits. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 4) No change in the analytical procedure.				
Documentation required				
1) Justification for the change. 2) (P.5)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). 3) Justification to demonstrate that the parameter is not critical.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
38	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN

Conditions to be fulfilled
1) No change to the specifications other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution).
Documentation required
1) Comparative table of currently accepted and proposed specifications for the excipient.

3.2. P.5 Control of FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
39a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard.	1-3	1-5	AN
39b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled	1	1, 3, 5	AN
Conditions to be fulfilled				
1) The change is made exclusively to comply with the officially recognized pharmacopoeia. 2) No change to the specifications that result in a potential impact on the performance of the FPP (e.g. dissolution test). 3) No deletion of or relaxation to any of the tests, analytical procedures or acceptance criteria of the specifications.				
Documentation required				
1) (P.5.1)Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. 2) (P.5.3)Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods. 3) (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 procedures, if new analytical procedures are implemented. 4) (P.5.6)Justification for the proposed FPP specifications. 5) (P.5.3)Demonstration of the suitability of the monograph to control the FPP.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
40	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
40a	deletion of a test parameter	5	1,6	AN
40b	addition of a test parameter	2-4, 7	1-6	AN
40c	tightening of an acceptance criterion	1-2	1,6	AN

40d	relaxation of an acceptance criterion	2,4,6-7	1,5-6	IN
40e	replacement of a test parameter	2-4,6-7	1-6	IN

Conditions to be fulfilled

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) No additional impurity found over the ICH identification threshold.
5) The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6) The change to the specifications does not affect the stability and the performance of the product.
7) The change does not concern sterility testing.

Documentation required

1) (P.5.1)Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2)Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3)Copies or summaries of validation reports, if new analytical procedures are used.
4) (P.5.3)Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (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) (P.5.6)Justification for the proposed FPP specifications.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
41	Change in the analytical procedures for the FPP involving:			
41a	deletion of an analytical procedure	5	1,6	AN
41b	addition of an analytical procedure	3-4,6-7	1-5	AN
41c.1	modification or replacement of an analytical procedure	1-4, 6-7	1-5	AN
41c.2		2-4, 6-7	1-5	Vmin
41d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to this monograph	None	1-5	AN
41e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized	2,7	1-3, 5	IN

	pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph			
Conditions to be fulfilled				
1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected. 2) Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure. 3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 4) The change does not concern sterility testing. 5) The deleted analytical procedure is an alternate method and is equivalent to another currently accepted analytical procedure. 6) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 7) No new impurities have been detected.				
Documentation required				
1) (P.5.1)A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. 2) (P.5.2)Copies or summaries of analytical procedures, if new analytical procedures are used. 3) (P.5.3)Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used. 4) (P.5.3)Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods. 5) (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 analytical procedures. 6) Justification for the deletion of the analytical procedure, with supporting data.				

3.2. P.7 Container-closure system

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
42a	Replacement or addition of a primary packaging type	1	1-2,4-6	Vmin
42b		None	1-6	Vmaj
Conditions to be fulfilled				
1) The change does not concern a sterile FPP.				
Documentation required				

1) Two (2) commercial samples of the product as packaged in the new container-closure system.
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.
3) (P.3.5)For sterile FPPs, process validation and/or evaluation studies.
4) (P.7)Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, results of transportation studies, if appropriate).
5) (P.8.1)Stability summary and conclusions, results for a minimum of two (2) 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 photo stability studies.
6) (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 was provided in documentation 5.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
43	Change in the package size involving:			
43a	change in the number of units (e.g. tablets, ampoules etc.) in a package	1-2	1-3	IN
43b	change in the fill weight/fill volume of non-parenteral multidose products	1-2	1-3	Vmin
Conditions to be fulfilled				
1) The change is consistent with the posology and treatment duration accepted in the SmPC. 2) No change in the primary packaging material.				
Documentation required				
1) Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC. 2) (P.8.2)A written commitment that stability studies will be conducted in accordance with EAC harmonized guidelines for products where stability parameters could be affected. 3) Two (2) commercial samples of the product				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
44	Change in the shape or dimensions of the container or closure for:			
44 a	non-sterile FPPs	1-2	1-3	IN
44 b	sterile FPPs	1-2	1-4	Vmin

44c	The change does concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP			Vmajor
Conditions to be fulfilled				
1) No change in the qualitative or quantitative composition of the container and/or closure. 2) The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP.				
Documentation required				
1) Two (2) commercial samples of the product. 2) (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, specifications etc.). 3) (P.8.1)In the case of a change in the headspace, a change in the surface/volume ratio or a change in the thickness of a packaging component: 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 photo stability studies. 4) (P.3.5)Evidence of re-validation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
45	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
45a	solid FPPs	1-3	1-3	IN
45b	semisolid and non-sterile liquid FPPs	1-3	1-3	Vmin
45c	Sterile medicinal products and biological/immunological medicinal products	None		Vmajor
Conditions to be fulfilled				
1) The change does not concern a sterile FPP. 2) No change in the packaging type and material (e.g. a different blister, but same type). 3) The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.				
Documentation required				

1) (P.2)Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, moisture etc.).
2) (P.7)Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.).
3) (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 photo stability studies.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
46	Change in the specifications of the immediate packaging involving:			
46a	tightening of specification limits	1-2	1	AN
46b	addition of a test parameter	2-3	1-2	AN
46c	deletion of a non-critical parameter	2	1,3	AN
Conditions to be fulfilled				
1) The change is within the range of currently accepted limits. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.				
Documentation required				
1) (P.7)Comparative table of currently accepted and proposed specifications, justification of the proposed specifications. 2) (P.7)Description of the analytical procedure and summary of validation of the new analytical procedure. 3) Documentation to demonstrate that the parameter is not critical.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
47	Change to an analytical procedure on the immediate packaging involving:			
47a	minor change to an analytical procedure	1-3	1	AN
47b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1	AN
47c	deletion of an analytical procedure	5	2	AN
Conditions to be fulfilled				

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method). 2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines. 3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure. 4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.
Documentation required
1) (P.7)Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent. 2) Documentation demonstrating that condition #5 is met.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
48	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, change of needle shield), and change of secondary pack			
48a	Change in any part of the (primary) packaging material not in contact with the finished pharmaceutical product formulation (e.g. colour of flip-off caps, colour code rings on ampoules, change of needle shield)	1	1-2	IN
48b.1	Change of secondary packaging components	2	2-3	IN
48b.2		None	1-4	Vmin
Conditions to be fulfilled				
1) The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP. 2) The registered and proposed secondary packaging components are non-functional				
Documentation required				
1) (P.7) Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.). 2) Two (2) commercial samples of the product. 3) Brief description of the secondary packaging components 4) Discussion on suitability with respect to, for example, protection from moisture and light, and provide supportive data e.g. moisture permeability, photo-degradation, stability studies				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
49	Change to an administration or measuring device			
49a	addition or replacement of a device which is not an integral part of the primary packaging	1-2	1-2	IN
49b	deletion of a device	3	3	IN
49c	Change to an administration or measuring device that is an integral part of the primary packaging			Vmajor
49d	addition or replacement of spacer devices for metered dose inhalers			Vmajor
Conditions to be fulfilled				
1) The proposed measuring device is designed to accurately deliver the required dose for the product concerned, in line with the posology and results of such studies are available. 2) The proposed device is compatible with the FPP. 3) The FPP can be accurately delivered in the absence of the device.				
Documentation required				
1) (P.2)Data to demonstrate accuracy, precision and compatibility of the device. 2) Two (2) samples of the device. 3) Justification for the deletion of the device.				

3.2. P.8 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
50	Change in the shelf-life of the FPP (as packaged for sale) involving:			
50a	reduction	3	1-4	IN
50b	extension	1-2	1-4	Vmin
Conditions to be fulfilled				
1) No change to the primary packaging type in direct contact with the FPP and to the recommended condition of storage. 2) Stability data was generated in accordance with the currently accepted stability protocol. 3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.				
Documentation required				

1) (P.5.1) Copy of the currently accepted shelf-life specifications. 2) (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot or production scale batches. 3) (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change. 4) Two (2) commercial samples of the product

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
51	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):			
51a	Reduction	1	1, 3-4	IN
51b	Extension	None	1-4	Vmin
Conditions to be fulfilled				
1) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.				
Documentation required				
1) (P 8) Proposed in-use period, test results and justification of change. 2) (P5.1) Copy of currently accepted end of shelf-life FPP specifications and where applicable, specifications after dilution/reconstitution. 3) The revised label information 4) Two (2) commercial samples of the product				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
52	Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1-3	Vmin
Conditions to be fulfilled				
1) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.				
Documentation required				
1) (P.8.1)If applicable, stability and/or compatibility test results to support the change to the storage conditions. 2) (P.8.2)Updated post-acceptance stability protocol and stability commitment and justification of change. 3) Two (2) commercial samples of the product				

8.0 Safety and Efficacy changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
53	Change in the Summary of product Characteristics, Labelling or Package Leaflet of a generic pharmaceutical product following assessment of the same change for the reference (innovator) product			
53a	Implementation of change(s) for which no new additional data are submitted by the MAH		1	Vmin
53b	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)		1-2	Vmaj
Documentation required				
1) Revised product information 2) Current approved product labelling. 3) Proposed product labelling, a clean and annotated version highlighting the changes made. 4) Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 5) Relevant document/reference to support the changes (where applicable).				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
54	Implementation of change(s) requested by the Authority following assessment of an Urgent safety restriction, class labelling or periodic safety update report			
54a	Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		1-2	Vmin
54b	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			Vmaj
Documentation required				
1) EAC Partner State's NMRAs request with attached relevant assessment report 2) Revised product information				

Description of change	Conditions to be fulfilled	Documentation required	Reporting type

55	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data.			
				Vmaj

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
56	Change(s) to therapeutic indication(s)			
56a	Addition of a new therapeutic indication or modification of an approved one			Vmaj
56b	Deletion of a therapeutic indication			Vmin
Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of changes to the product information of a generic/hybrid/biosimilar product following assessment of the same change for the reference (innovator) product, variations 54 applies.				

9.0 Appendix 1: Examples of changes that make a new application necessary

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1. Change of the API to a different API 2. Inclusion of an additional API to a multicomponent product 3. Removal of one API from a multicomponent product 4. Change in the dose/strength of one or more APIs 5. Change from an immediate-release product to an extended or delayed-release dosage form or vice versa 6. Change in dosage form 7. Changes in the route of administration	None	1	New application
Conditions to be fulfilled			
None			
Documentation required			
1) Documents in fulfillment of the requirements outlined in Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products, 1st Edition, January, 2015**(Doc. No. TMDA/DMC/HVR/G/001).**			

10.0 Appendix 2: Changes to excipients

Excipient	**Percent excipient (w/w) out of total target dosage form core weight**
Filler	±5.0
Disintegrant • Starch • Other	 ±3.0 ±1.0
Binder	±0.5
Lubricant • Ca or Mg Stearate • Other	 ±0.25 ±1.0
Glidant • Talc • Other	 ±1.0 ±0.1

(a) These percentages are based on the assumption that the API in the FPP is formulated to 100.0% of label/potency. The total additive effect of all excipient changes should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).

(b) If an excipient serves multiple functions (e.g. microcrystalline cellulose as filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ±1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

11.0 References

(a) Guidelines on variations to a prequalified product, In: *WHO ExpertCommittee on Specifications for Pharmaceutical Preparations. Forty-seventh report.* Geneva, World Health Organization, 2013, Annex 3 (WHO Technical Report Series, No. 981).

(b) EU Guidelines on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products, 12 December 2008.