ETHIOPIAN FOOD AND DRUG AUTHORITY (EFDA)

GUIDELINE ON VARIATION APPLICATIONS TO REGISTERED MEDICINES

2nd Edition

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CE	European Conformity
CEP	European Pharmacopoeia Certificate of suitability
NDRA	National Drug Regulatory Authority
EFDA	Ethiopian Food and Drug Authority
GMP	Good Manufacturing Practice
FPP	Finished Pharmaceutical Product
ICH	International Conference on Harmonization
INN	International Non-Proprietary Name
'N'	Notification
NDA	New Drug Application
Ph Int	International Pharmacopoeia
JP	Japanese Pharmacopoeia
OOS	Out Of Specification
Ph Eur	European Pharmacopoeia
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
WHO	World Health Organization

1. INTRODUCTION

The Food and Drug Authority (FDA) of Ethiopia is responsible to protect the public health from unsafe, inefficacious and poor quality medicines by insuring effective and efficient pre and post -marketing authorization of medicines systems in the country.

Variations to particulars of a medicine may be made to alter or to improve the medicines, to introduce an additional safeguard due to new scientific knowledge or to meet market demands. The conditions of registration of a medicine are therefore considered dynamic taking into account that variation to the original registered dossier may become necessary during the lifetime of the medicine.

Once a medicine is registered by the EFDA for sale in Ethiopia, an applicant must notify and got approval from the Authority for changes that affect to medicine's quality, safety and efficacy who have got marketing authorization. However, medicines with variation having minimum potential on its quality, safety and efficacy may be marketed provided that the applicant and/or manufacturer who registers the product should notify the Authority of such variation before its implementation in accordance with article 21 of Food and Medicines Administration Proclamation (Proclamation No. 1112/2019).

Changes to the registered products, whether administrative or substantive may be subject to acceptance by the Authority prior to implementation. Technical requirements for the different types of variations are set out in this guideline in order to facilitate the submission of appropriate documentation by applicants and their assessment by the Authority and to ensure that variations to the medicines do not result in health concerns.

The license holder and/or manufacturer is responsible to appoint local agent /representative /consultant who follow-up and notify the authority of post approval changes made to registered medicines before being implemented except those changes that are annual notifiable (AN).

This is, therefore, the second edition of Guideline on Variation applications to the registered medicines is prepared to align with the current international practice and to handle the day-to- day challenges faced to the Authority. It also provide applicants/manufacturers with information concerning documentation to be submitted for approval of variations to the previously registered medicine by the Authority.

2. OBJECTIVE

This guideline is intended to:

- assist applicants with the classification of changes made to the registered finished pharmaceutical product (FPP);
- provide guidance on the technical and administrative data and information requirements to support changes to the quality attributes of the FPP.

3. SCOPE OF THIS GUIDELINE

This guideline is applicable to applications intending to make changes to registered finished pharmaceutical products.

This guideline does not apply to medicines whose application is under assessment or still in a queue for assessment by EFDA and biological products.

This guideline applies to all variations whether from the applicant's initiative or requested by the Authority.

4. DEFINATION

Applicants

The person or entity who submits a registration application of product to the Authority and responsible for the product information.

Authority

Authority means the Ethiopian Food and Drug Authority.

Major Variations

Major variations mean changes that could have major effects on the overall safety, efficacy and quality of the finished pharmaceutical product. They are variations to the documentation which can neither be deemed to be minor variations nor to be variations for which the submission of a new dossier would be necessary.

Minor Variation

Minor variations mean variation to the registered pharmaceutical finished product in terms of administrative data and/or changes that could have minimal or no adverse effects on the overall

safety, efficacy and the quality of finished pharmaceutical product.

Notification

Notifications means 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 the Authority before implementation of the change. e.g Periodic Safety Update Reports.

Variation

Variation means a post approval change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished pharmaceutical product, ingredients, container and container labelling, and product information.

5. Guidance for implementation

5.1. Reporting types

The following reporting types are intended to provide guidance with respect to the classification of changes. Specific examples of changes are provided in these guidelines.

Whenever the applicant is unclear about the classification of a particular change, the Authority should be consulted. 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 of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;
- when the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notification.

5.1.1. 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 the Authority.

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.

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 the Authority within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission.

Example: If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

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 30 calendar days of the date of acknowledgement of receipt of the application.

For both AN & IN , the authority issued letter of no objection or objection to the applicant.

5.1.2. 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. This type of application require prior approval by the Authority.

If the proposed change affect the content of marketing authorization certificate issued by the Authority, the Authority will issued amended certificate. However; if the change does not result in the change of the content of marketing authorization certificate issued by the Authority, acceptance letter shall be issued as evidence of approval.

5.1.3. 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 the Authority is required before the changes can be implemented.

If the proposed change affect the content of marketing authorization certificate issued by the Authority, the Authority will issued the amended certificate. However; if the change does not result in the change of the content of marketing authorization certificate issued by the Authority, acceptance letter shall be issued as evidence of approval.

5.1.4. New applications and extension applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases, applicant should submit as a new applications. Examples of such changes are listed in this guideline. (See section 8 of this guideline).

5.1.5. Labeling Information

For any change to labelling information (SmPC, PIL, labels) must be applied as per the respective section of this guideline. Applicant should consult the recent guideline for registration of medicines (available at EFDA web site) for detail requirements on labeling information.

5.2. Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions

stipulated for these specific circumstances is considered to be a Vmaj.

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 provided. 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.

5.3. Documentation required

For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation. It should be noted that the Authority reserves the right to request further information not explicitly described in these guidelines.

Where applicable, the following should be included in the application:

- a variation application form (as indicated in annex 1 of the guideline). All sections of this form should be completed and the document signed.
- an updated quality and bio-equivalence information summary (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- When a variation leads to a revision of the product information, the updated product information (summary of product characteristics (SmPC), the patient information leaflet (PIL) and labeling) and packaging leaflet should be submitted as part of the application.
- For variations that require generation of stability data to support the changes, stability studies required to be conducted as per guideline for registration of medicine of the Authority, including commitment batches, should always be continued to cover the currently accepted shelf-life period. The Authority should be informed immediately if any problems with the stability issue occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

6. APPROVAL OF VARIATIONS

In principle, all parts of the dossier that are affected by a variation need to be resubmitted according to the structure of Guideline for Registration of Medicines of the Authority.

As the applicant submits an application in the appropriate format and with application form via https://eris.efda.gov.et, EFDA assessors conduct screening of application for completeness and confirmation of type of variation. Incomplete applications and improper categorization of variations will then be notified to applicants at this stage. If the completeness of applications and proper categorization of variation confirmed by EFDA assessor at this stage, applicant will be notified to pay appropriate variation payment as indicated in the current service fee rate regulation of the authority and then be considered as the applications officially submitted to EFDA.

The regulatory approval process of the variations would be:

1) For all minor and major variations(Vmin & Vmaj) as indicated this guidelines, prior approval by EFDA is always necessary before the variations can be implemented.
2) Other Variations as indicated as "AN" shall be notified to the Authority annually while those variations indicated as "IN" need to be notified to the Authority immediately before implementation.

Applicants should present a summary of the intended change in tabular form in which the current state/situation and the situation after the intended change are compared to outline the scope of the change in a transparent manner. A justification for the introduction of the change should always follow.

The titles of the changes are numbered and subcategories are depicted by alphabets. Moreover, the conditions and any further documentation required for a particular change is identified.

The conditions necessary for a given change are outlined for each subcategory and listed below each change.

7. DOSSIER REQUIREMENTS FOR VARIATIONS TO REGISTERED PRODUCTS

This section includes the list of types of variations. These variations are numbered, the conditions and the require documentation are identified and the reporting type indicated below.

7.1. Administrative changes

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1.	Change of local agent (s) and/or consultant	a-b	a-b	**Vmin**

Conditions to be fulfilled

a. Must hold a valid medicine import license and/or consultant certificate.

b. The importer has no pending disciplinary case with the EFDA.

Documentation required

a. Agency agreement made between the local agent or consultant and the manufacturer/Marketing Authorisation Holder as described in the guideline for registration of medicines

b. A copy of import license for local agent or license for consultant.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2.	Change in the name of the finished pharmaceutical product (FPP)	a-c	a-c	**Vmin**

Conditions to be fulfilled

a. There is no change to the product (formulation, release & shelf-life specifications, manufacturing source & process) except for the product name change.

b. No confusion with the International Non-proprietary Name (INN).

c. The first and the last three letters of trade name is not identical with a registered finished pharmaceutical product in Ethiopia

Documentation required

a. Update CPP from the national drug regulatory authority (DRA) in which the new name is approved.
b. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change.
c. Samples of actual package inserts and labelling incorporating the proposed variation.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3.	Change in the name and/ or corporate address of the supplier of the FPP.	a	a	**IN**

Conditions to be fulfilled

a. Confirmation that the supplier of the product remains the same legal entity.

Documentation required

a. 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.

S.N.	**Description of change**	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
4.	Change in the name and/or address naming of the marketing authorization holder of the registered product	a	a-b	**Vmin**

Conditions to be fulfilled

a. The marketing authorization holder of the registered product shall remain the same legal entity.

Documentation required

a. Sample of actual packaging insert and labels incorporating the proposed variation, where applicable
b. A formal document from a relevant official body (e.g. the national drug regulatory authority (NDRA)) in which the new name and/or address is mentioned.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
5.	Addition or replacement of the company or party responsible for batch release of finished pharmaceutical product	a-c	a-c	**Vmin**

Conditions to be fulfilled

a. Only applicable for batch release.

b. The manufacturer of the finished pharmaceutical product remains the same.

c. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.

Documentation required

a. Revised drafts of the package insert and labelling incorporating the proposed variation, where applicable.

b. Proof of the proposed site is appropriately authorized by the Authority to be responsible for batch release such as a Valid GMP certificate.

c. Official letter from FPP manufacturer/marketing authorization holder to be responsible for batch release, where applicable.

S.N.	**Description of change**	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
6.	Change in the name or address of a manufacturer of an API	a	a-b	**IN**

Conditions to be fulfilled

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

Documentation required

a. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.

b. An updated Letter of Access in case of change in the name of the holder of the APIMF.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7.	Change in the name and/or address of a manufacturer of the FPP.	a	a	IN

Conditions to be fulfilled

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

Documentation required

a. 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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8.	Deletion of the manufacturing site or manufacturer involving:			
4a	Production of the API starting material	a	a	**AN**
4b	Production or testing of the API intermediate or API	a-b	a	**IN**
4c	production, packaging or testing of the intermediate or FPP	a-b	a	**IN**

Conditions to be fulfilled

a. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.

b. The deletion of the site is not a result of critical deficiencies in manufacturing.

Documentation required

a. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

7.2. Changes to a CEP or CPQ to a confirmation of API

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
9.	Submission of new or updated CEP or CPQ for an API or starting material or intermediate used in the manufacturing process of the API:			
5a.1	from a currently accepted manufacturer	a-e	a-e	**AN**
5a.2		a-d	a-f	**IN**
5a.3		a, c-d	a-f	**Vmin**
5b.1	from a new manufacturer	a-d	a-f	**IN**
5b.2		a, c-d	a-f	**Vmin**

Conditions to be fulfilled

a. No change in the FPP release and shelf-life specifications.

b. Unchanged (excluding tightening) additional (to Ph. Eur) specification 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.

c. 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.

d. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low soluble APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.

e. No revision of the API manufacturer's API specifications is required.

Documentation required

a. 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 the behalf of the FPP manufacturer

b. A written commitment that the applicant will inform the Authority in the event that the CEP is withdrawn and an acknowledgement that withdrawn of the CEP will require additional consideration of the API data requirements to support product dossier.

c. Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under 3.2.S of the Authority's Guidelines for registration of medicines.

d. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.

e. (P.8.2) In the case of 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 Authority.

f. (S.4.1) Copy of FPP manufacturer's revised API specifications.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
10.	Submission of a new or updated confirmation of API WHO-prepublication document			
10a.1	from a currently accepted manufacturer	a-c	a-c, e	**AN**
10a.2		a-b	a-e	**Vmin**
10b.1	from a new manufacturer	a-c	a-c, e	**IN**
10b.2		a-b	a-e	**Vmin**

Conditions to be fulfilled

a. No change in the FPP release and shelf-life specifications.

b. 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.

c. There is no difference in impurity profile of the proposed API to be supplied including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.

Documentation required

a. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
b. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option (Option 1: confirmation of API Prequalification document) stipulated under section 3.2.S. of the Authority Guideline for Registration of Medicines.
c. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
d. 4. (S.4.1) Copy of FPP manufacturer's revised API specifications.
e. (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 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 Authority.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11	Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	None	a	**AN**

Conditions to be fulfilled

None

Documentation required

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

7.3. Quality changes

7.3.1. S Drug substance (or API)

3.2.S.2 Manufacture

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
12	Replacement or addition of a new manufacturing site or manufacturer of an API involving:			

8a.1	API testing only	a-b, d	a, c-d	**IN**
8a.2		B, d	a, c-d	**Vmin**
8b.1	production of API starting material	c-d	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8b.2		d-e	a-b, l	**IN**
8b.3		None	a-b, e, g-h, l, m	**Vmaj**
8c.1	production of API intermediate		No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8c.2		d-e	a-b, l	**IN**
8c.3		None	a-b, e, g-h, l, m	**Vmaj**
8d.1	production of API (APIMF procedure)	c, g-i	a-b, f, h	**IN**
8d.2		c, g, i	a-b, f-h	**Vmin**
8e.1	production of API (full dossier)	a, i-k	a-b, d, h-i	**IN**
8e.2		None	a-b, d-e, g-h, j-k, m	**Vmaj**

Conditions to be fulfilled

a. The API is non-sterile.
b. The transfer of analytical methods has been successfully undertaken.
c. The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
d. No change in the FPP manufacturer's API specifications.
e. 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.
f. 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.
g. No change in the FPP release and end-of-shelf-life specifications.

h. 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.

i. 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.

j. 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 a new contract manufacturing site with evidence of an acceptable and similar quality system that of the main manufacturer).

k. 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 (www.who.int/biologicals) or EMA's Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or equivalent guidelines of ICH region and associated countries.

Documentation required

a. (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.

b. (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 and a tabulated summary of the differences.

c. (S.4.3) Copies or summaries of validation reports or method transfer reports, which equivalence of analytical procedures to be used at the proposed testing site.

d. (S.4.4) Description of batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.

e. Relevant section of the (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the Authorities Guideline for Registration of Medicines.
f. The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of the requirements for the API option under section 3.2.S of the Authority's Guideline for Registration of Medicines.
g. (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 Authority.
h. (S.4.1) A copy of the FPP manufacturer's API specifications.
i. (S.2) A declaration from the supplier of the prequalified FPP that the route of synthesis, materials, quality control procedures, and the specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
j. A discussion of the impact of the new API on safety, efficacy and quality of the FPP.
k. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low solubility APIs) where there is 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.
l. Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material.
m. 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.

S.N.		Description of change	Conditions to be fulfilled	Documentation required	Reporting type
9.	**a**	change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	a-e	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
9.	**B**		a, c-e	a-d	**IN**

Conditions to be fulfilled

a. The API is non-sterile.

b. The API manufacturing block or unit is currently accepted through the APIMF procedure.

c. The same quality system covers the currently accepted and proposed blocks or units.

d. 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.

e. No change in the route of synthesis, quality control procedures and the specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable.

Documentation required

a. (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.

b. (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 valid GMP compliance if available.

c. (S.4.4) Description of the batches, copies of certificates of analysis, 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 or blocks.

d. (S.2.2) A summary of difference between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
10. a	change in the manufacturing process	a-c, i	a-b, h	**AN**
10. b.1	of the API	a-b, d, f-i	c-d, k-l	**IN**
10. b.2	change in the manufacturing process	a-b, d, f-h, j	c-d, k-l	**Vmin**
10. c	of the API	a-b, d-g	c-d, k-l	**Vmin**
10. d		None	b-n	**Vmaj**

Conditions to be fulfilled

a. No change in the physical state (e.g. crystalline, amorphous) of the API.

b. 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 that of the API lot used in the preparation of the biobatch.

c. The API manufacturing site is currently accepted through the APIMF procedure.

d. 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.

e. 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.

f. No change in qualitative and quantitative impurity profile or physicochemical properties of the API.

g. The change does not affect the sterilization procedures of a sterile API.

h. The change involves only steps before the final intermediate.

i. The change does not require the revision of starting material, intermediate or API specifications.

j. The change does not require revision of the API specifications.

Documentation required

a. A copy of the APIMF amendment acceptance letter.

b. (P.8.2) If the quality characteristics of the API changed in the way that 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 Authority.

c. (S.2.2) A side-by-side comparison of the current process and the new process.
d. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
e. (S.2.2) Information on the quality and controls of the material (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
f. (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 guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (www.who.int/biologicals) or EMA's Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or equivalence guidelines in the ICH region and associated countries.
g. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
h. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
i. (S.3.1) Evidence for elucidation of structure, where applicable.
j. (S.3.2) Information on impurities.
k. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
l. (S.4.4) Description of batches, corticates 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.
m. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
n. 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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11.	Change in the in-process tests or limits applied during the manufacture of the API:			
11. a	any change in the manufacturing process controls	a	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
11. b	tightening of in-process limits	b-d	a	**AN**
11. c	addition of a new in-process test and limit	b, e	a-e	**AN**
11. d	addition or replacement of an in-process test as a result of a safety or quality issue	None	a-e, g, h-j	**Vmin**
11. e.1	deletion of an in-process test	b, f-g	a-c, f	**AN**
11. e.2		None	a-c, g-j	**Vmaj**
11. f	relaxation of the in-process test limits	None	a-c, e, g-j	**Vmaj**

Conditions to be fulfilled

a. API manufacturing site is currently accepted through the APIMF procedure.

b. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits.

c. The change is within the range of currently accepted limits.

d. The analytical procedure remains the same, or changes to the analytical procedure are minor.

e. Any new procedure does not concern a novel non-standard technique, or a standard technique used in a novel way.

f. The affected parameter is non-significant.

g. The change does not affect the sterilization procedures of sterile API.

Documentation required

a. A comparison of the currently accepted and the proposed in-process tests.

b. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).

c. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.

d. Detail of any new non-pharmacopeial analytical method and validation data where relevant.

e. Justification for the new in-process test and/or limits.

f. Justification and/or risk-assessment showing that the parameter is non-significant.

g. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization where applicable.

h. (S.3.2) Information on impurities, if applicable.

i. (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).

j. (S.4.4) description of batches, certificates of analysis, batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
12.	Change in batch size of the API or intermediate involving:			
12. a	up to 10-fold compared to the currently accepted batch size	a-b, d, f	a, c-d	AN
12. b1	Downscaling	a-d	A, c-d	**AN**
12. b2		a-c	a-d	**IN**
12. c	any change in scale (APIMF procedure)	e	a-b, d-e	**AN**
12. d	more than 10-fold increase compared to the currently accepted batch size	a-b, d, f	a, c-d	**Vmin**

Conditions to be fulfilled

a. No changes to the manufacturing process other than those necessitated by change in scale (e.g. use of different size of equipment).

b. The change does not affect the reproducibility of the process.

c. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.

d. The change does not concern a sterile API.

e. The API manufacturing site and batch size is currently accepted through the APIMF procedure.

f. 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

a. (S2.2) A brief narrative description of the manufacturing process.

b. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.

c. (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).

d. (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.

e. A copy of the APIMF amendment acceptance letter.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
13.	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:			
13. a	any change	a	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
13. b	tightening of the specification limits	b-d	a-c	**AN**
13. c	minor change to an analytical procedure	e-g	b-c	**AN**
13. d	addition of a new specification parameter and a corresponding analytical procedure where necessary	b, g-h	a-c	**AN**
13. e	deletion of a specification parameter or deletion of an analytical procedure	b, j	a-d	**AN**

13. f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	a-c, e	**Vmin**
13. g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	d, g, i-j	a, c-d	**IN**
13. h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	a-c, e	**Vmaj**

Conditions to be fulfilled

a. API manufacturing site is currently accepted through the APIMF procedure.
b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
c. Any change is within the range of currently accepted limits.
d. The analytical procedure remains the same.
e. 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 and other parameters, but do not include variations beyond the acceptable range or different type of column or method).
f. 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.
g. No change to the total impurity limits; no new impurities are detected.
h. Any new analytical procedure does not concern a novel non-standard technique, or a standard technique used in the novel way.
i. The change does not concern a genotoxic impurity.
j. The affected parameter is non-significant, or the alternative analytical procedure has been previously accepted.

Documentation required

a. Comparative table of currently accepted and proposed specifications.

b. (S.2.3) information on quality and controls of materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
c. (S.2.4) Information on intermediates, where applicable.
d. Justification and/or risk assessment showing that the parameter is non-significant.
e. (S.3.2) Information on impurities, where applicable.

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

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14.	Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that does not require a change to the FPP manufacturer's API specifications involving:			
14a	API supported through the APIMF procedure.	a-b	No change required. Such changes are handled as amendments to the associated APIMF	
14b	API not supported through the APIMF procedure.	b	a-d	**IN**

Conditions to be fulfilled

a. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF and accepted.
b. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revision 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 maintained.

Documentation required

a. (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
b. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.

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

d. 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

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
15.	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
15a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph (BP, Ph Int, JP, Ph Eur, USP) as a result of an update to this monograph to which the API is controlled.	k	a-e	AN
15b1	deletion of a test parameter	a-b	a, f	**AN**
15b2		J	a, f, h	**IN**
15b3		None	a, f	**Vmaj**
15c1	addition of a test parameter	a, d-h	a-f	**AN**
15c2		a, e-f, j	a-f, h	**IN**
15c3		a, e-f	a-f	**Vmin**
15c4		None	a-g	**Vmaj**
15d1	replacement of a test parameter	a, e-h	a-f	**IN**
15d2		e, g, j	a-f, h	**Vmin**
15d3		None	a-g	**Vmaj**
15e1	tightening of an acceptance criterion	a, c, i	a, f	**AN**
15f1	relaxation of an acceptance criterion	a, e-i	a, f	**IN**
15f2		a, g, j	a, f, h	**Vmin**

15f3	None	a, f-g	**Vmaj**

Conditions to be fulfilled

a. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
b. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
c. The change is within the range of currently accepted acceptance criteria.
d. Any analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
e. 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.
f. No additional impurity found over the ICH identification threshold.
g. The change does not concern sterility testing.
h. The change does not involve the control of a genotoxic impurity.
i. The associated analytical procedure remains the same.
j. The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
k. No change is required in FPP release and shelf life specifications.

Documentation required

a. (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
b. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
c. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
d. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.

e. (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.

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

g. (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 does not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batches used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact WHO/PQP for advice. For changes to the polymorph of an insoluble API the applicant should contact WHO/PQP for advice before embarking upon any investigation.

h. Copy of the APIMF amendment acceptance letter.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
16.	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
16a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	a-c	AN
16b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia	None	a-d	IN

16c1	addition of an analytical procedure	a-c	a-c	AN
16c2		c, h	a-c, e	IN
16c3		h	a-c, e	Vmin
16c4		None	a-c	Vmaj
16d1	modification or replacement of an analytical procedure	a-f	a-d	AN
16d2		b-c, e-f, h	a-e	AN
16d3		a-c, e-f	a-d	Vmin
16d4		e-f, h	a-e	Vmin
16d5		None	a-d	Vmaj
16e1	deletion of an analytical procedure	f-g	a, f	AN
16e2		f-h	a, e-f	IN
15e3		None	a, f	Vmaj

Conditions to be fulfilled

a. Any analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
c. No new impurities have been detected as a result of the use of the new analytical method.
d. 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 and other parameters, but do not include variations beyond the acceptable the acceptable ranges or a different type of column and method), and no new impurities are detected.
e. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
f. The change does not concern sterility testing.
g. The delated analytical procedure is an alternative and is equivalent to the currently accepted method.
h. 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 required

a. (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.
b. (S.4.2) Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
c. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or

significantly modified analytical procedures are used.

d. (S.4.4) Comparative analytical results demonstrating that the proposed analytical Procedures are at least equivalent to the accepted analytical procedures.
e. A copy of the APIMF acceptance letter.
f. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
17.				
17a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	c, d	a-b, d	AN
17b		a-b, d	b-c	IN
17c		d	a-c	**Vmin**

Conditions to be fulfilled

a. Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others).
b. The change does not concern a sterile API.
c. The change has previously been accepted through the APIMF procedure.
d. The change is not the result of stability issues.

Documentation required

a. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.
b. (S.6) Information on the proposed primary packaging (e.g. description and specifications) and data in fulfilment of condition 1.
c. (S.7.1) Results of (or a commitment to the study in the case of demonstrating equivalent or more protective packaging) a minimum of 3-months accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.
d. A copy of the APIMF amendment acceptance letter.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
18.	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
18a	tightening of specification limits	a-b	a	AN
18b	addition of a test parameter	b-c	a-c	AN
18c	deletion of a non-critical parameter	a	a, d	AN
18d	any change (APIMF procedure)	d	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

a. The change is within the range of currently accepted limits.

b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

c. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

d. The change has previously been accepted through the APIMF procedure.

Documentation required

a. (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.

b. (S.4.2) details of method and summary of validation of new analytical procedure.

c. (S.6) Certificate of analysis for one batch.

d. Justification to demonstrate that the parameter is not critical.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
19.	Change to an analytical procedure on the immediate packaging of the API involving:			
19a	minor change to an analytical procedure	a-c	a	AN
19b	other changes to an analytical procedure	b-d	a	AN

	including addition or replacement of an analytical procedure			
19c	deletion of an analytical procedure	e	b	AN
19d	any change (APIMF procedure)	f	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

a. 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 and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method)
b. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
c. Comparative studies indicate the new analytical procedure to be at least equivalent to the currently accepted procedure.
d. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
e. The deleted analytical procedure is an alternative method and is equivalent to currently accepted method.
f. The change has previously been accepted through the APIMF procedure.

Documentation required

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

3.2. S.7 Stability

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
20.	Change in the retest period or shelf-life of the API involving:			
20a	any change (APIMF procedure)	d	d	IN

20b	Reduction	c	a-b	IN
20c	Extension	a-b	a-c	Vmin

Conditions to be fulfilled

a. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
b. Stability data were generated in accordance with the currently accepted stability protocol.
c. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
d. The revised retest period has previously been accepted through the APIMF procedure.

Documentation required

a. (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results.
b. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
c. (S.7.3) Stability data to support the change.
d. A copy of the APIMF acceptance letter.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
21.	Change in the labelled storage conditions of the API involving:			
21a	any change in storage conditions (APIMF procedure)	a	a	**IN**
21b	any change in storage conditions	b	b	**Vmin**

Conditions to be fulfilled

a. The revised storage conditions have previously been accepted through the APIMF procedure.
b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

a. A copy of the APIMF acceptance letter.
b. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.

7.4. 3.2. P Drug product (or FPP)

3.2. P.1 Description and composition of the FPP

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
22a	Change in the composition of a solution dosage form	a-f	b, d, g, i-j	IN
22b		None	a-j	Vmaj

Conditions to be fulfilled

a. The affected excipient(s) does/do not function to affect the solubility and/or absorption of the API.
b. The affected excipient(s) does/do not function as preservative or preservative enhancer.
c. No change in the affected specification of the excipient (s) or the FPP.
d. No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
e. The change does not concern a sterile FPP.
f. 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

a. Supporting clinical or comparative bioavailability data or justification for not submitting new bioequivalence study according to the current Bioequivalence guideline of the Authority
b. (P-1) Description and composition of the FPP.
c. (P-2) Discussion on the components of the proposed product (the choice of excipients, compatibility of API and excipients, suitability study on packaging system for the changed product).
d. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
e. (P.4) Control of excipients, if new excipients are proposed.
f. 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 TSE risk material has been previously assessed the national authority in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following

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

g. (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.

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

i. (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).

j. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
23.	Change in the colouring system or the flavouring system currently used in the FPP involving:			
23a	Reduction or increase of one or more components of the colouring or the flavouring system	a-c, f	a, d, f-g	**AN**
23b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	a-f	a-g	**IN**

Conditions to be fulfilled

a. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.

b. Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.

c. Specifications for the FPP are updated only with respect to appearance, odour and/or taste or if relevant, deletion or addition of a test for identification.
d. Any new component must comply with section 3.2.P.4 of the Guideline for Registration of medicines of the Authority.
e. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required or incompliance 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 guide from ICH region and associated countries.
f. When applicable, the change does not affect the differentiation between strengths and for pediatric formulations it does not require submission of results of taste acceptability studies.

Documentation required

a. Sample of the FPP.
b. (P.2) Discussion on the components of FPP (e.g. compatibility of the API, qualitative composition of colouring and flavouring system if purchased as mixture, with specifications, if relevant).
c. (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 TSE risk material has been previously assessed the national authority in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
d. (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.
e. (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
f. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

g. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
24.	Change in weight of tablet coatings or capsule shells involving:			
24a	Immediate-release oral FPPs	a-c	b-e	**AN**
24b	gastro-resistant, modified or prolonged release FPPs	None	a-e	**Vmaj**

Conditions to be fulfilled

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

Documentation required

a. Justification for not submitting bioequivalence study according to the current Guideline for requirement on invitro biowaiver application of the Authority and as applicable other international guidelines (e.g. WHO, U.S. FDA guidelines).
b. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.
c. (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.
d. (P.8.1) Results of stability testing generated on at least one pilot- or production scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.

e. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
25.	Change in the composition of an immediate-release solid oral dosage form including:			
25a.1	Replacement of a single excipient with a comparable excipient at a similar concentration	a-e	a-j	**Vmin**
25a.2		None	a-j	**Vmaj**
25b.1	Qualitative change in excipients	a-d	a-d, g-j	**Vmin**
25b.2		None	a-d, g-j	**Vmaj**

Conditions to be fulfilled

a. No change in functional characteristics of the pharmaceutical form.
b. Only minor adjustment are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
c. Stability studies have been started under conditions according to Guidelines for registration of medicine of the Authority (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the applicant, and the stability profile is similar to that of the currently accepted product.
d. 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.
e. The change is not the result of stability issues and/or does not result in potential safety concern i.e. differentiation in strength.

Documentation required

a. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current guideline for bioequivalence of the Authority (Annex IV requirement for bioequivalence study of Guideline for Registration of Medicines and Guidance on

Waiver of In-vivo Bio-equivalence Requirements)

b. (P.1) Description and composition of the FPP
c. (P.2) Discussion on the components of the proposed product (e.g. the choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained 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 routine release medium or in multiple media covering the physiological pH range).
d. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
e. (P.4) Control of excipients, if new excipients are proposed.
f. (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 TSE risk material has been previously assessed the national authority in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and its use.
g. (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.
h. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
i. (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).
j. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
26.	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:			
26a	Changes in imprints, embossing or other markings	a-c	a-b, e-f	**IN**
26b	Deletion of a score line	b-e	a, e-f	**IN**
25b.1	addition of a score line	b-d	a, c, e-f	**Vmin**
25b.2		None	a, c-f	**Vmaj**

Conditions to be fulfilled

a. Any ink complies with section 3.2.P.4 of the Guideline for registration of Medicine of the Authority and other international guideline (e.g. WHO guidelines)

b. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.

c. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.

d. Addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product.

e. The scoring is not intended to divide the FPP in to equal doses.

Documentation required

a. Sample of the FPP.

b. (P.1.) Qualitative composition of the ink, if purchased as a mixture.

c. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions where the scoring intended to divide the FPP in to equal doses.

d. (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.

e. (P.5) Copies of revised FPP release and shelf-life specifications.

f. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
27.	Change in dimensions without change in qualitative and quantitative composition and mean mass of:			
27a	Tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	a-b	b-f	**IN**
27b	Gastro-resistant, modified or prolonged-release FPPs and scored tablets	a-b	a-f	**Vmin**

Conditions to be fulfilled

a. Specifications for the FPP are updated only with respect to dimensions of the FPP.

b. Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot or production-scale), are comparable.

Documentation required

a. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new equivalence study according to the current Annex IV requirement for bioequivalence study of Guideline for Registration of Medicines and Guidance on Waiver of In-vivo Bio-equivalence Requirements). For scoring tablets where the scoring is intended to divide the FPP into equal doses demonstration of the uniformity of the tablet portions.

b. Sample of the FPP.

c. (P.2) Discussion on the differences in the manufacturing process(es) between the currently registered and proposed products and the potential impact on product performance.

d. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products.

e. (P.5) Copies of revised FPP release and shelf-life specifications.

f. (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.

3.2. P.3 Manufacture

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
28.	Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:			
28a	Secondary packaging of all types of FPPs	b-c	a	**IN**
28b	Primary packaging site of:			
28b1	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	b-d	a, h	**IN**
28b2	Other liquid FPPs (suspensions, emulsions)	b-e	a, e, h	**IN**
28C	all other manufacturing operations except batch control and/or release testing	a-c, e	a-i	**Vmin**

Conditions to be fulfilled

a. 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.
b. Site accordingly approved for GMP by a NDRA (to manufacture the pharmaceutical form and the product concerned) and satisfactory inspection in the last three years either by WHO or an SRA.
c. Site has approval from EFDA for the packaging or manufacturing of the pharmaceutical form and the product concerned.
d. The change does not concern a sterile FPP.
e. 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

a. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned:
    - a copy of the current manufacturing, a GMP certificate or equivalent document issued by the EFDA.

- a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NDRA & a GMP statement or equivalent issued by WHO or an SRA; and
- date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years.

b. Date and scope (with indication as to whether scope was e.g. product specific or related to a specific pharmaceutical form) of the last satisfactory inspection.

c. (P.2) Where applicable, for semisolid and liquid formulation in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.

d. (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 production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.

e. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.

f. (P.5.1) Copies of release and shelf-life specifications.

g. (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.

h. (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).

i. (R.1) Executed production documents for one batch of the FPP manufactured at the new site.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
29.	Replacement or addition of a site involving batch control testing	a-b	a-c	**AN**

Conditions to be fulfilled

a. Site is appropriately authorized by the NMRA and site has approval from EFDA to conduct quality control testing of finished pharmaceutical product concerned.
b. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

a. Clear identification of the currently registered and proposed quality control site on the letter accompanying the application.
b. Documented evidence that the site is proportionally authorized by the NMRA and approved by EFDA or SRA
c. (P.5.3) Documented evidence of successfully transfer of analytical procedure from the current to the proposed site.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
30.	Change in the batch size of the FPP involving			
30a	up to and including a factor of 10 compared to the biobatch	a-g	b, e-f	**IN**
30b	Downscaling	a-e	a, f	AN
30C	other situations	a-g	a-g	**Vmin**

Conditions to be fulfilled

a. The change does not affect the reproducibility and/or consistency of the product.
b. The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms
c. Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change by the batch size e.g. use of different size equipment.
d. 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.

e. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
f. The change does not require supporting in vivo data
g. The biobatch size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

a. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next full production scale batch should be available on request and should be reported if they do not meet a dissolution profile similarity (f2) requirement. For semi-solid dosage forms (e.g. lotions, gels, creams, 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 available upon request.
b. (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
c. (P.5.1) Copies of release and shelf-life specifications.
d. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently registered and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action).
e. (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).
f. (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) (above) and confirmation that there are no changes to the production documents other than those highlighted.
g. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current guideline for bioequivalence of the Authority (Annex

IV requirement for bioequivalence study of Guideline for Registration of Medicines and Guidance on Waiver of In-vivo Bio-equivalence Requirements)

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
31a	Change in the manufacturing process of the FPP	a-i	a-d, f-g	**AN**
31b		a-c, e-i	a-g	**Vmin**

Conditions to be fulfilled

a. The change does not require supporting in vivo data.
b. No change in qualitative and quantitative impurity profile or in physicochemical properties; dissolution profiles are similar to those of the biobatch.
c. 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 or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process.
d. The same class of equipment, operating procedure, in process controls with no widening or deleting of limits) are used for the currently registered and proposed products; no change in critical process parameters.
e. No change in the specifications of the intermediates or the FPP.
f. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
g. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
h. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
i. The change does not affect the sterilization parameters of the sterile FPP.

Documentation required

a. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current guideline for bioequivalence of the Authority (Annex IV requirement for bioequivalence study of Guideline for Registration of Medicines and Guidance on Waiver of In-vivo Bio-equivalence Requirements) applicable:

b. (P.2) Discussion on the development of manufacturing process, where applicable

- comparative in vitro testing, e.g. multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);
- Comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two Production batches should be submitted or 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 presented in non-dissolved form.

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

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

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

f. (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.

g. (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.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
32.	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
32a	tightening of in-process limits	a-b, e	a	**AN**

32b	deletion of a test	b, d	a, f	**AN**
32c	addition of new tests and limits	b-c	a-f	**AN**
32d	revision or replacement of a test	b-c	a-f	**IN**

Conditions to be fulfilled

a. The change is within the range of acceptance limits.

b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

c. Any new test does not concern a novel, nonstandard technique or standard technique used in a novel way.

d. The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedure (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).

e. No change in the analytical procedure.

Documentation required

a. (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.

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

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

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

e. (P.5.4) Description of the batches, certificate 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.

f. (P.5.6) Justification for the addition or deletion of the tests and limits.

P.4 Control of excipients

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
33.	Change in source of an excipient from TSE risk to	a	a	**AN**

a material of vegetable or synthetic origin.

Conditions to be fulfilled

a. No change in the excipient and FPP release and shelf-life specifications.

Documentation required

a. Declaration from the manufacturer of the excipients that entirely of vegetable or synthetic origin.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
34.	Change in the specifications or analytical procedures for an excipient involving:			
34a	deletion of a non-significant in-house parameter	B	a-c	**AN**
34b	addition of a new test parameter or analytical procedure	b-c	a-b	**AN**
34c	tightening of specification limits	a-b, d	a-b	**AN**
34d	change or replacement of an analytical procedure	b-c	a-b	**Vmin**

Conditions to be fulfilled

a. The change is within the range of currently accepted limits.

b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

c. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way

d. No change in the analytical procedure.

Documentation required

a. Justification for the change.

b. (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).

c. Justification to demonstrate that the parameter is not critical.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
35.	Change in specifications of an excipient to comply with an officially recognized Pharmacopoeia	a	a	**AN**

Conditions to be fulfilled

a. No change to the specifications other than those require to comply with the pharmacopoeia (e.g. no change in particle size distribution).

Documentation required

a. Comparative table of currently accepted and proposed specifications for the excipient.

P.5 Control of FPP

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
36a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	a-c	a-e	**AN**
36b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph (BP, Ph Int, JP, Ph Eur, USP) as a result of an update to this monograph to which the FPP is controlled	None	a, c, e	**AN**

Conditions to be fulfilled

a. The change is made exclusively to comply with the officially recognized pharmacopoeia.

b. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).

c. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation required

a. (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.
b. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claim, results of equivalence study between in house pharmacopoeial methods.
c. (P.5.4) Description of the batches, certificates of analysis 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.
d. (P.5.6) Justification for the proposed FPP specifications.
e. (P.5.3) Demonstration of the suitability of the monograph to control the FPP.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
37.	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
37a	deletion of a test parameter	e	a, f	**AN**
37b	addition of a test parameter	b-d, g	a-f	**AN**
37c	tightening of an acceptance criterion	a-b	a, f	**AN**
37d	relaxation of an acceptance criterion	b, d f-g	a, e-f	**IN**
37e	replacement of a test parameter	b-d, f-g	a-f	**IN**

Conditions to be fulfilled

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

Documentation required

a. (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.
b. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
c. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
d. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial Standard is claim, the results of an equivalence study between the in-house pharmacopoeial methods.
e. (P.5.4) Description of the batches, certificates of analysis for at least one bacth (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.
f. (P.5.6) Justification for the proposed FPP specifications.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
38.	Change in the analytical procedures for the FPP involving:			
38a	deletion of an analytical procedure	e	a, f	**AN**
38b	addition of an analytical procedure	c-d, f-g	a-e	**AN**
38c1	modification or replacement of an analytical procedure	a-d, f-g	a-e	**AN**
38c2		b-d, f-g	a-e	**Vmin**
38d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	a-e	**AN**
38e	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 pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	b, g	a-c, e	**IN**

Conditions to be fulfilled

a. 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 and other parameters, but do not include variations beyond the acceptable ranges or a different type of column, method), and no new impurities are detected.
b. Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
c. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in the novel ways.
d. The change does not concern sterility testing.
e. The detailed analytical procedure is an alternative method and equivalent to the currently accepted analytical procedure.
f. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
g. No new impurities have been detected.

Documentation required

a. (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.
b. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
c. (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
d. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard claimed, results of an equivalence study between an in-house and pharmacopoeial methods.
e. (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.
f. Justification for the deletion of the analytical procedure, with supporting data.

P.7 Container-closure system

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
39a	Replacement or addition of a primary packaging type	a	a-b, d-f	**Vmin**
39b		None	a-f	**Vmaj**

Conditions to be fulfilled

a. The change does not concern a sterile FPP.

Documentation required

a. Samples of the product as packaged in the new container-closure system.

b. (P.2) Data on suitability of the container closure system (e.g. extractable/leachability test, 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.

c. (P.3.5) For sterile FPPs, process validation and/or evaluation studies.

d. (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).

e. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.

f. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
40.	Change in the package size involving:			
40a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	a-b	a-c	**IN**
40b1		a-c	a-c	**IN**

40b2	change in the fill weight or fill volume of non-parenteral multidose products	a-b	a-c	**Vmin**

Conditions to be fulfilled

a. The change is consistent with the posology and treatment duration accepted in the SmPC.
b. No change in the primary packaging material.
c. No increase in the headspace or surface/volume ratio.

Documentation required

a. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
b. 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.
c. (P.8.2) A written commitment that stability studies will be conducted in accordance the guideline for Registration of medicines of the Authority for parameters where the stability parameters could be affected

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
41.	Change in the shape or dimensions of the container or closure for:			
41a	non-sterile FPPs	a-b	a-c	**IN**
41b	sterile FPPs	a-b	a-d	**Vmin**

Conditions to be fulfilled

a. No change in qualitative and quantitative composition of the container and/or closure.
b. 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

a. Samples of the product packaged in the new container-closure system.
b. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
c. P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3

months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies.

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

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
42.	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
42a	solid FPPs	a-c	a-c	**IN**
42b	semisolid and liquid FPPs	a-c	a-c	**Vmin**

Conditions to be fulfilled

a. The change does not concern a sterile FPP.

b. No change in the packaging type and material (an example of an allowable change is blister to blister).

c. The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.

Documentation required

a. (P.2) Data demonstrating the suitability of the proposed packaging materials (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture).

b. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).

c. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in demonstrating equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
43.	Change in the specifications of the immediate packaging involving:			
43a	tightening of specification limits	a-b	A	**AN**
43b	addition of a test parameter	b-c	a-b	**AN**
43c	deletion of a non-critical parameter	b	a, c	**AN**

Conditions to be fulfilled

a. The change is within the range of currently accepted limits.

b. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

c. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Documentation required

a. (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.

b. (P.7) Description of analytical procedure and summary of validation of the new analytical procedure.

c. Documentation to demonstrate that the parameter is not critical.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
44.	Change to an analytical procedure on the immediate packaging involving:			
44a	minor change to an analytical procedure	a-c	a	**AN**
44b	other changes to an analytical procedure including addition or replacement of an analytical procedure	b-d	a	**AN**
44c	deletion of an analytical procedure	e	b	**AN**

Conditions to be fulfilled

a. The method of analysis is based on the same analytical technique or principle (e.g. changes to analytical procedure are with in the allowable adjustments to column length and other parameters,

but do not include variations beyond the acceptable ranges of a different type of column and method).

b. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.

c. Comparative study indicates the new analytical procedure to be at least equivalent to the former procedure.

d. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

e. The deleted analytical procedure is an alternative method and is equivalent to the current accepted method.

Documentation required

a. (P.7) Description of the method and comparative validation results demonstrating the currently accepted and the proposed methods are at least equivalent.

b. Documentation to demonstrate the equivalence of the delated method and the currently accepted method.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
45.	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, or change of needle shield).	a	a-b	**AN**

Conditions to be fulfilled

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

Documentation required

a. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).

b. Amendment of the relevant section(s) of the dossier as per the guideline for Registration of Medicines including revised product labelling as appropriate.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
46.	Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:			
46a	addition or replacement	a-b	a-b	**IN**
46b	Deletion	c	c	**IN**

Conditions to be fulfilled

a. 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.
b. The proposed device is compatible with the FPP.
c. The FPP can be accurately delivered in the absence of the device.

Documentation required

a. (P.2) Data to demonstrate the accuracy, precision and compatibility of the device.
b. Sample of the device.
c. Justification for the deletion of the device.

3.2. P.8 Stability

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
47.	Change in the shelf-life of the FPP (as packaged for sale) involving:			
47a	Reduction	c	a-c	**IN**
47b	Extension	a-b	a-c	**Vmin**

Conditions to be fulfilled

a. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.
b. Stability data were generated in accordance with the currently accepted stability protocol.
c. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

a. (P.5.1) Copy of the currently accepted shelf-life specifications.

b. (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 for a period sufficient to support the proposed shelf-life.

c. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
48.	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):			
48a	Reduction	a	a	**IN**
48b	Extension	None	a-b	**Vmin**

Conditions to be fulfilled

a. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

a. (P 8) Proposed in-use period, test results and justification of change.

b. (P 5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
49.	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	a	a	**IN**

Conditions to be fulfilled

a. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

a. (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage

conditions.

b. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

7.5. Clinical Indication

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
50.	Change and/or additional indications/dosing regimen/patient population/inclusion of clinical information extending the usage of the product)	a-c	a-e	**Vmaj**

Conditions to be fulfilled

a. Product labelling refers to package insert (PI). Patient Information Leaflet (PIL) outer carton and immediate labels are the same except for additional claim.

b. As subsequent change due to revision of summary of product Characteristics (SmPC) or equivalent document are the same except for additional claim.

c. Potential benefits of the product, when used to treat the identified disease or condition, outweigh the known and potential risks of the product.

Documentation required

a. Justification for the change proposed.

b. Approved PI/SmPC/PIL and product labels from an approved reference regulatory authority or the country of origin containing the proposed changes

c. Proposed product labelling, a clean and annotated version highlighting the change made

d. Data on safety and effectiveness for recommended indication under the recommended conditions of use such as dosage and dosage, status and age of patients e.g. pregnancy paediatric, liver or kidney insufficiency or other co-morbidities.

e. Clinical study reports as per module 5 of the guideline for registration of medicines.

7.6. Labeling Information

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
51.	Correction and/or statements of the label or Periodic update prescribing information	a-b	a-c	**AN**

Conditions to be fulfilled

a. The correction and statements of the label do not have any modification to the content of the message.

b. There is no change in the indication and safety of the product.

Documentation required

a. The summary of the change made in comparison with the previous approved package labelling.

b. Reason for making such changes.

c. The new prescribing information.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
52.	Other minor variations such as (Change logo of applicant/manufacturer, change in the design or layout of packaging, Change in the colour of design of the package.	a-c	a-c	**Vmin**

Conditions to be fulfilled

a. There is no change in the content of finished pharmaceutical product.

b. The change in colour design of the package is not affect the legibility of the label.

c. There is no change in the indication and safety of the product.

Documentation required

a. The summary of the change made in comparison with the previous approved package labelling.

b. Reason for making such changes.

c. Actual sample and/or colour print out of the new and the present package labelling.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
53.	Packaging of pharmaceutical product.	a-d	a-d	**Vmin**

Conditions to be fulfilled

a. The products are registered by the Authority separately.
b. There is no change in the primary container closure of the products to be repacked.
c. The products are packed together secondary container closure system
d. The proposed secondary container closure is able to protect the product from external environment

Documentation required

a. Evidence of registration of the products to be repacked
b. Reason for making such changes.
c. Actual sample of the new and the present package labelling.
d. Manufacturing License or authorization certificate or GMP certificate of the sites involved in repacking of products.

8. VARIATIONS THAT MAKE A NEW APPLICATION/ EXTENSION APPLICATION NECESSARY

Variations that make a new application necessary include:

1. **Changes to the API**

   a. Change of the API to a different API.

   b. Inclusion of an additional API to a multi-component product.

   c. Removal of one API from a multi-component product.

   d. Change in the dose of one or more APIs.

2. **Changes to the pharmaceutical form/dosage form**

   a. Change from an immediate-release product to a slow- or delayed release dosage form and vice versa.

   b. Change from a liquid to a powder for reconstitution, or vice versa.

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

9. CONSIDERATION OF SRA PROCEDURE FOR VARIATION APPLICATION

An applicant claiming to have a certificate and/or acceptance letter of approval for variation application (under consideration) by Stringent Regulatory Authority (SRA) as defined in Guideline for Registration of Medicines of the Authority, 2020, need to fulfill conditions and submit all documentations as per the respective sections of variation indicated in this guideline. However, the applicant may not requested to submit samples for laboratory analysis at EFDA facility.

Applicant requesting to follow this procedure requires:

- To provide evidence of approval of such variation(s) by the regulatory authority in the SRA regions.
- To provide a certificate of analysis by GMP approved laboratories and/or independent ISO accredited laboratories.

ANNEX I-APPLICATION FORM

APPLICATION FORM FOR REGISTRATION

Food and Drug Authority of Ethiopia P.O.Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

Variation to existing marketing authorization	
• Previous registration number	
• Previous registration condition	
• Brief description of the change intended	
• Reasons for variations	

B. Details of the product

Proprietary name (trade name)	
Approved generic name (s) (use INN if any)	
Standard claimed (BP, Ph.In, EP, USP, IH etc)	
Strength (s) per dosage unit	
Dosage form	
Route of administration	
Shelf Life (months)	
Storage condition	
Visual Description	
Description of container closure	
Packaging and pack size	
Therapeutic category of the product	
Use category	Scheduled Narcotic ☐
	Prescription only ☐
	Hospital use only ☐

	Pharmacy ☐		
	Over the counter (OTC) ☐		
Complete qualitative and quantitative composition (indicate per unit dosage form like per tablet, per 5ml etc)** ** Add/delete as much rows and columns as required	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L etc)	Composition	Strength	Function

Statement of similarity and difference of clinical, bio batch, stability, validation and commercial batch sizes			
Regulatory situation in other country. (Provide a list of the countries in which this product has been granted a marketing authorization, the restrictions on sale or distribution, withdrawn from the market etc..)			

C. Details of the Applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number

	E-mail:
Details of Manufacturer if different from above	<<Insert the required information as indicated above>>>

D. Details of active pharmaceutical(s) ingredient(s) Manufacturer

Name of manufacturer	
Street and postal address	
Telephone/Fax number	
E-mail	
Retest period/Shelf life	

E. Details of Local Agent (Representative) in Ethiopia

Name of the local agent	
Sub city and postal address	
Telephone/Fax number	
E-mail	
Contact person in a company and address	

F. Details of dossiers submitted with the application

Section of the dossier	**Annex, page number etc**
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I the undersigned certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name (s) (INN)	
Strength (s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO guideline on "Good manufacturing practices for pharmaceutical products" Guideline, is applied in full in all premises involved in the manufacture of this product.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.

4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications *before it is released for manufacturing purposes.*

5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*

8. Each batch of the finished pharmaceutical product is either tested, or certified, against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training".

10. The procedures for control of the finished Pharmaceuticals product have been validated for this formulation.

11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.

12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.

13. All the documentation referred to in this certificate is available for review during a GMP inspection.

14. Any clinical trials including BE study were conducted according to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products" .

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

ANNEX II-TYPES OF POST APPROVAL VARIATIONS REQUIRING SAMPLES FOR LABORATORY ANALYSIS

Category of variations listed below and other variation considered as major variation by the authority require samples of actual product for the analysis at EFDA laboratory and hence, the applicant should refer to Annex V: Sample of actual product of Guideline for Registration of Medicines 2020 edition for the quantities of samples, types and quantities of reference substances and the accompanied documents.

1. Replacement or addition of manufacturing site of primary packing process for finished pharmaceutical product.
2. Replacement or addition of manufacturing site for manufacturing process of finished pharmaceutical product.
3. Change in manufacturer of API(s): sample of finished product manufactured using the API(s) sourced from the new API manufacturer, if deemed necessary.
4. Change in composition of the finished product including replacement excipients, coloring system, flavoring system, change in coating weight of the tablet.
5. Change in the primary container closure having the direct contact with the product including qualitative and/or quantitative composition of immediate packing materials, change in shape and dimension of container closure.
6. Change in batch size of the finished product of more than 10 fold up scaling.
7. Change in the manufacture procedure of the finished pharmaceutical Product.
8. Change in the dimension of the tablets, capsule, suppository, peccaries.
9. Change in fill weight and/or fill volume of multi-dose product.
10. Extension of shelf life of the finished pharmaceutical product.

ANNEX III-PAYMENTS FOR POST APPROVAL VARIATIONS

The post approval variation application should be accompanied by the appropriate payments as per the current Authority regulation to service fee.

REFERENCE

1. WHO guidelines on variations to a prequalified product, In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh report, Geneva, World Health Organization, 2013, Annex 3 (WHO Technical Report Series No. 981).
2. Guidelines for Submission of Post Approval Variation Medicine Applications, 1st Edition, Ethiopia Food and Drug Authority (EFDA), Dec, 2015, Addis Ababa, Ethiopia.
3. ASEAN Variation Guidelines for pharmaceutical Products 2013(Final draft 7.2) Available at: http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western Medicine/Overview Framework Policies/Guidelines on Drug Registration/ASEAN Variation Guideline for Pharmaceutical Products 7.2 cleandraft.pdf
4. Guidance for Variation to a Prequalified Product Dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report,* Geneva, World Health Organization, 2007, Annex 6(WHO Technical Report Series, No. 943). Available at: http://whqlibdoc.who.int/trs/WHO TRS 943 eng.pdf
5. WHO Guidelines for Variation to a Prequalified Product Dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report,* Geneva, World Health Organization, 2013, Annex 3(WHO Technical Report Series, No. 981). Available at: http://apps.who.int/prequal/info general/documents/variations/2013/TRS981 Annex3 draft.pdf
6. Guidelines on dossier requirements for type 1A and 1B notification 2006. Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/var/type 1a1b guideline 06-2006 en.pdf
7. WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva, World Health Organization, 2003. Available at: http://www.who.int/biolicals/publications/en/whotse2003.pdf
8. ICH Q2(R1): Validation of analytical procedures: Text and Methodology. November 2005. Available at: http://www.ich.org/fileadmin/public web site/Guidelines/Quality/Q2 R1/Step4/Q2 R1 Guideline.pdf