# Annex 6

## Guidance on variations to a prequalified product dossier

### Preface

This guidance document was technically and structurally inspired by the *Guideline on dossier requirements for type IA and IB notifications*.[1] It is intended to provide information on how to present an application to implement a change to a prequalified product.

References to compendial monographs (*British Pharmacopoeia* (BP), *International Pharmacopoeia* (Ph Int), *Japanese Pharmacopoeia* (JP), *European Pharmacopoeia* (Ph Eur) or *United States Pharmacopeia* (USP)) or to guidelines (WHO, International Conference on Harmonisation (ICH)-region and associated countries) are included to assist applicants. However, it remains the applicant's responsibility to ensure that the most recent revisions of all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier. The guidelines referred to in each section provide useful information on the content expected in that section. However, this list should not be regarded as exhaustive.

Where a variation requires consequential revision of the summary of product characteristics (SmPC), labelling and package leaflet or insert, this is considered as part of the variation.

This guidance document is applicable only to active pharmaceutical ingredients (APIs) and excipients manufactured by chemical synthesis or semisynthetic processes and finished pharmaceutical products (FPPs) containing such APIs and excipients. Variations to a biological API and/or biological excipient, or to biological finished products are assessed as major changes. In such a case the applicant should refer to guidance documents

[1] Guideline on dossier requirements for type IA and IB notifications (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf).

that specifically address biological APIs, excipients and finished products (e.g. ICH Q5A (R1), Q5B, Q5C, Q5D, Q5E, Q6B).[2]

This guidance document applies to multisource (generic) FPPs that have been prequalified by WHO. Whenever FPPs have been prequalified on the basis of approval by a drug regulatory authority of the ICH region and associated countries (innovator products or generic products) subsequent applications for variations also need to be approved by the same drug regulatory authorities and WHO should be notified of the approval of the changes. Applicants are advised to refer to the Letters of Prequalification.

## Introduction

The listing of a product on the list of prequalified products that have been found acceptable, in principle, for procurement by United Nations agencies, is a temporary status given for a defined period of time as described in detail in the general procedure.[3] An application for renewal is required before expiry, resulting in a submission and a review of an updated dossier as part of the procedure within the prequalification project.

Irrespective of these regular reviews by WHO a prequalified supplier is responsible for the prequalifed product throughout its life and is, therefore,

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[2] ICH Q5A (R1): *Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin* (http://www.ich.org/LOB/media/MEDIA425.pdf).

ICH Q5B: *Quality of biotechnological products: analysis of the expression construct in cells used for production of r-DNA derived protein products* (http://www.ich.org/LOB/media/MEDIA426.pdf).

ICH Q5C: *Quality of biotechnological products: stability testing of biotechnological/biological products* (http://www.ich.org/LOB/media/MEDIA427.pdf).

ICH Q5D: *Derivation and characterisation of cell substrates used for production of biotechnological/biological products* (http://www.ich.org/LOB/media/MEDIA429.pdf).

ICH Q5E: *Comparability of biotechnological/biological products subject to changes in their manufacturing process* (http://www.ich.org/LOB/media/MEDIA1196.pdf).

ICH Q6B: *Specifications: test procedures and acceptance criteria for biotechnological/biological products* (http://www.ich.org/LOB/media/MEDIA432.pdf).

[3] *Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies* Revised Procedure. in: *Forty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2007, Annex 4. (http://mednet3.who.int/prequal/info_general/documents/ppdoc2.pdf).

required to take into account technical and scientific progress. He or she is required to make any amendment that may be required to enable the prequalified product to be manufactured and checked by means of generally accepted scientific methods. Suppliers of prequalified products may also wish to alter or to improve the medicinal product or to introduce an additional safeguard.

The prequalification project is, therefore, considered dynamic, taking into account that changes to the original dossier that was used for prequalification of the product may become necessary during the lifetime of the product. Any changes to prequalified products (variations) may involve administrative and/or more substantial changes and are subject to approval by WHO.

Procedures for the implementation of the different types of variations need to be set out to facilitate the task of both suppliers and WHO and to guarantee that variations to the medicinal product do not give rise to public health concerns.

The following definitions may be used to classify changes:

- A *minor change* is one of the variations listed in Appendix 1 of this guidance.
- A *major change* is a change to the documentation which can neither be deemed to be a minor variation within the meaning of the above definition (being of greater significance than a minor change) nor to be a change for which the submission of a new dossier would be necessary (Appendix 2).

## Approval of changes

Of the minor changes listed in Appendix 1 of this document, some are classified by the letter N and can be considered as notifications. Applications for minor changes that are so classified must provide evidence to fulfil the conditions and documentation requirements listed. These notifications will be evaluated by WHO within a period of 3 months and can be considered approved if no correspondence with the applicant has been initiated by WHO within that time. If the validity of the notification cannot be acknowledged by WHO, correspondence with the applicant will be started and a further period of 3 months must be allowed to elapse by the applicant upon submission of his or her response documents.

*For all other change applications that are not considered as notifications, prior approval by WHO* is always necessary *before the changes can be implemented.*

Certain changes are so fundamental that they alter the terms of the prequalified dossier and consequently cannot be considered as a "change". In such cases a new dossier must be submitted (Appendix 3).

In order to facilitate the classification of changes, the appendices explicitly define the various types of changes:

- Appendix 1 lists minor changes classified by the type of change and the conditions which frame the type of change. When the conditions are not met, the change may either be classified as a major change or may make a new application necessary.
- Appendix 2 lists examples of major changes.
- Appendix 3 lists the types of changes which make a new application necessary.
- Appendix 4 lists the stability requirements for variations and changes to prequalified FPPs.

## Glossary

### *Biological pharmaceutical product*

A product, the API of which is a biological substance.

### *Biological API*

A substance that is produced by or extracted from a biological source and for which a combination of physicochemical–biological testing and the production process and its control is needed for its characterization and the determination of its quality.

### *Finished pharmaceutical product (FPP)*

The acronym FPP always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

### *GuideGeneric*

Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGenericRev1_Final.doc). Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

*GuideGeneric supplement 1*

Supplementary, separate document 1 (dissolution requirements) to the Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGeneric-Dissolution_ Suppl1.doc). Available at: http://mednet3.who.int/prequal/info_applicants/ Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

*GuideGeneric supplement 2*

Supplementary, separate document 2 (stability implications) to the Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGeneric_Suppl2.doc). Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/ GuideGenericSubmitDocFPPs_Supplement2.pdf

## *Test procedure*

Analytical procedure.

## *Limits*

Acceptance criteria.

## *Validation protocol*

Validation scheme, validation plan.

# Appendix I

## Dossier requirements for minor changes to prequalified products

This guide has been prepared to clarify what documentation should be submitted with regard to each type of minor change. The applicant is also asked to check whether other guidance documents (Prequalification guidelines, WHO guidelines, guidelines of the ICH region and associated countries) are also applicable. If the change also implies a change in the pharmaceutical particulars in the SmPC, labelling and/or package leaflet or insert, this also forms part of the change.

The titles of the changes are numbered and subcategories are depicted by letters and numbers. The conditions necessary for a given change are outlined for each subcategory and listed below each change.

In principle, all parts of the dossier that are affected by a variation need to be resubmitted according to the structure of the pharmaceutical quality information form (PQIF)[4] (the structure/relevant parts of the dossier is/ are also covered in the *"Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis")*[5]. Moreover, any further documentation required for a particular change is identified.

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.

Applicants should be aware that submitting redundant or irrelevant information may hamper approval procedures. Deficient documentation can lead to non-validation or rejection of the change.

| 1 | Change in the name and/or address of the supplier of the prequalified product | Conditions to be fulfilled | Documen-tation to be supplied | |
|---|---|---|---|---|
| | | 1 | 1 | N |

[4] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[5] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

## Conditions

1. The supplier of the prequalified product shall remain the same legal entity.

## Documentation

1. A formal document from a relevant official body (e.g. the national drug regulatory authority (DRA)) in which the new name and/or address is mentioned.

| 2 | Change in the name of the finished pharmaceutical product (FPP) | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| | | 1 | 1, 2 |

## Conditions

1. No confusion with the International Nonproprietary Name (INN).

## Documentation

1. A formal document from the national drug regulatory authority (DRA) in which the new name is approved.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.[6]

| 3 | Change in the name and/or address of a manufacturer of the active pharmaceutical ingredient (API) where no European Pharmacopoeia certificate of suitability (CEP) is available | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| | | 1 | 1, 2 | N |

## Conditions

1. The manufacturing site shall remain the same.

## Documentation

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

[6] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.

| 4 | Change in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP) | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| | | 1 | 1, 2 | N |

## Conditions

1. The manufacturing site shall remain the same.

## Documentation

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. DRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[7]

| 5 | Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Secondary packaging for all types of pharmaceutical forms | 1, 2 | 1, 2, 5 | N |
| b) | Primary packaging site | | | |
| | 1. Solid pharmaceutical forms, e.g. tablets and capsules | 1, 2, 3 | 1, 2, 5 | N |
| | 2. Semisolid or liquid pharmaceutical forms | 1, 2, 3 | 1, 2, 5 | |
| | 3. Liquid pharmaceutical forms (suspensions, emulsions) | 1, 2, 3, 4 | 1, 2, 4, 5 | |
| c) | All other manufacturing operations except batch release | 1, 2, 4 | 1, 3, 4, 5, 6, 7, 8, 9 | |

[7] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

## Conditions

1. Satisfactory inspection in the last 3 years either by WHO or a drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries.
2. Site appropriately authorized by a DRA (to manufacture the pharmaceutical form and the product concerned).
3. Product concerned is not a sterile product.
4. Validation protocol is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production-scale batches.

## Documentation

1. Proof that the proposed site is appropriately authorized for the pharmaceutical form and the product concerned:
   - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the DRA; and
   - a GMP statement or equivalent issued by WHO or a drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries.
2. The date of the last satisfactory inspection of the packaging facilities by WHO or the drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries must have taken place within the last 3 years.
3. Date and scope (indicate if product-specific, if related to a specific pharmaceutical form, etc.) of the last satisfactory inspection.
4. The batch numbers of batches (≥ 3) used in the validation study and the validation protocol (scheme).
5. Clear identification of the "prequalified" and "proposed" finished product manufacturers in the variation application.
6. Copy of prequalified release and end-of-shelf-life specifications.
7. Batch analysis data of three production batches and comparative data on the last three batches from the previous site.
8. For semi-solid and liquid formulations in which the API is present in a non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.

9. For solid dosage forms, data from comparative dissolution tests (refer to Supplement 1[8] of the *Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*) with demonstration of similarity of dissolution profile, performed on the last three batches from the previous site and the first three batches from the new site should be submitted.

| 6 | Change to quality control testing of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| Replacement or addition of a site where batch control/testing takes place | | 1, 2 | 1, 2, 3 | N |

## Conditions

1. The site is appropriately authorized by the DRA.
2. Transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

## Documentation

1. The letter that accompanies the application for approval should clearly outline the "prequalified" and "proposed" quality control sites.
2. Documented evidence that the site is appropriately authorized by the DRA.
3. Documented evidence that the transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

| 7 | Deletion of any manufacturing site (including for an API, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place) | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| | | None | 1 | N |

## Conditions

None

[8] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

## Documentation

1. The letter that accompanies the application for approval should clearly name the manufacturer to be deleted.

| 8 | Minor change in the manufacturing process of the API | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| | | 1, 2 | 1, 2, 3 |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF[9] and of the prequalified drug master file (where applicable), including a direct comparison of the prequalified process with the new process.
2. Batch analysis data (in comparative tabular format) from at least two batches (minimum pilot scale) manufactured according to the prequalified and the proposed process.
3. Copy of prequalified specifications of the API.

| 9 | Change in batch size of API or intermediate | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Up to 10-fold increase compared to the prequalified batch size | 1, 2, 3 | 1, 2 | N |
| b) | Downscaling | 1, 2, 3, 4 | 1, 2 | N |
| c) | More than 10-fold increase compared to the prequalified batch size | 1, 2, 3 | 1, 3, 4 | |

[9] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

## Conditions

1. No changes to the manufacturing methods other than those necessitated by scale-up, e.g. use of different sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The change does not affect the reproducibility of the process.
4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[10]
2. The batch numbers of the tested batches that have the proposed batch size.
3. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the prequalified and the proposed size. Batch data on the next two full production batches should be available on request and reported immediately to WHO if outside specifications (OoS) with details of proposed action.
4. Copy of prequalified specifications of the API (and of the intermediate, if applicable).

| 10 | Change in the specification of an API, a starting chemical material/ intermediate/reagent used in the manufacturing process of the API | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Tightening of specification limits | 1, 2, 3 | 1, 2 | N |
| | | 2, 3 | 1, 2 | |
| b) | Addition of a new test parameter to the specification of: | | | |
| | 1. an API | 2, 4 | 1, 2, 3, 4, 5, 6 | |
| | 2. a starting chemical material/ intermediate/reagent | 2, 4 | 1, 2, 3, 4 | |

[10] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[11]
2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data (in a comparative tabular format) on a minimum of two production batches of the relevant substance for all tests in the new specification manufactured to both the prequalified and the proposed specifications. (Batch data on the next two full production batches should be available on request or reported if outside specification (OoS) with details of the proposed action.)
5. Where appropriate, comparative dissolution profile data for the finished product on at least one batch containing the API complying with the prequalified and the proposed specification.
6. Justification for not submitting a new bioequivalence study according to the current WHO guideline, in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices.[12]

[11] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[12] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359.

| 11 | Change in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Minor changes to a prequalified test procedure | 1, 2, 3 | 1 | N |
| b) | Other changes to a test procedure, including replacement or addition of a test procedure | 2, 3, 4 | 1, 2 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF,[13] which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
2. Comparative validation results showing that the prequalified test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).[14]

[13] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[14] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

| 12 | Change in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the API | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| a) | Change in site of the already prequalified manufacturer (replacement or addition) | 1, 2 | 1, 2, 3, 4, 5 |
| b) | New manufacturer (replacement or addition) | 1, 2 | 1, 2, 3, 4, 5 |

## Conditions

1. The specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already prequalified.
2. 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*[15] or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*[16] or an equivalent guideline of the ICH region and associated countries.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. A declaration from the supplier of the prequalified 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 prequalified.
3. Either a transmissible spongiform encephalopathy (TSE) European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary 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

[15] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[16] (EMEA/410/01rev 2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

*Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*[17] or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*[18] or an equivalent guideline of the ICH region and associated countries.

4. Batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the prequalified and proposed manufacturers/sites.
5. The application should clearly outline the "prequalified" and "proposed" manufacturers.

| 13 | Submission of a new or updated European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/ intermediate in the manufacturing process of the API | Conditions to be fulfilled | Documen-tation to be supplied | |
|---|---|---|---|---|
| a) | From a prequalified manufacturer | 1, 2, 4 | 1, 2, 3, 4 | N |
| b) | From a new manufacturer (replacement or addition) | | | |
| | 1. Sterile substance | 1, 2, 3, 4 | 1, 2, 3, 4 | |
| | 2. Other substances | 1, 2, 3, 4 | 1, 2, 3, 4 | N |

## Conditions

1. The finished product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for impurities and product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The API will be tested immediately prior to use if no retest period is included in the European Pharmacopoeia certificate of suitability or if data to support a retest period is not provided.
4. The manufacturing process of the API, starting material/reagent/ intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

[17] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[18] (EMEA/410/01rev 2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

## Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[19]
3. Where applicable, a document providing information on any materials falling within the scope of the WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacture of the API. The following information should be included for each such material:
   – name of manufacturer;
   – species and tissues from which the material is derived;
   – country of origin of the source animals; and
   – its use.
4. The variation application should clearly outline the "prequalified" and "proposed" manufacturers.

*Note*

The reference to unchanged specifications for impurities, if applicable, in condition no. 2 should refer to new additional impurities. In change no. 8: minor change in the manufacturing process of the API, condition no. 1 stipulates that there is no change in the qualitative and quantitative impurity profile or in the physicochemical properties. In change no. 10: change in specification of API tightening of specification limits or addition of new test parameters are allowed. One of the conditions to be met for these changes to qualify as a minor change is that the change should not be the result of unexpected events during manufacture. The conditions of these changes should be borne in mind in the fulfilment of the conditions of change no. 13.

[19] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

| 14 | Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/ intermediate in the manufacturing process of the API for a prequalified manufacturer and prequalified manufacturing process | Conditions to be fulfilled | Documen-tation to be supplied | N |
|---|---|---|---|---|
| | | None | 1, 2, 3 | |

## Conditions

None

## Documentation

1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[20]
3. A document providing information on any materials falling within the scope of the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*[21] including those which are used in the manufacture of the API. The following information should be included for each such material:
   - name of manufacturer;
   - species and tissues from which the material is a derivative;
   - country of origin of the source animals; and
   - its use.

| 15 | Change in: | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| a) | the re-test period of the API | 1, 2 | 1, 2 |
| b) | the storage conditions for the API | 1, 2 | 1, 2 |

[20] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[21] (EMEA/410/01rev 2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

## Conditions

1. Stability studies have been done according to the prequalified protocol (*Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*,[22] Section 2.7.2). The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[23] These must contain results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two pilot or production-scale batches of the API in the prequalified packaging material and covering the duration of the requested re-test period or requested storage conditions.
2. Copy of approved specifications of the API.

| 16 | Replacement of an excipient with a comparable excipient | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| | | 1, 2, 3, 4 | 1, 2, 3, 4, 5, 6, 7 |

## Conditions

1. Same functional characteristics of the excipient.
2. The dissolution profile of the new product determined on a minimum of two pilot-scale batches is comparable to the old one (no significant differences regarding comparability according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.[24]

[22] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

[23] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[24] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

3. The new excipient does not include the use of materials of human or animal origin for which assessment of viral safety data is required.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and satisfactory stability data for at least 3 months (accelerated and real-time) are at the disposal of the applicant together with the assurance that these studies will be finalized. Data will be provided immediately to WHO if outside specifications or potentially outside specification at the end of the prequalified shelf-life (with details of proposed action).

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF (as applicable).
2. Justification for the change/choice of excipients, etc. must be given by appropriate information from pharmaceutical development including stability aspects and antimicrobial preservation where appropriate).
3. For solid dosage forms, comparative dissolution profile data on at least two pilot-scale batches of the finished product in the new and old composition.
4. Justification for not submitting a new bioequivalence study according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.[25]
5. Either a European Pharmacopoeia certificate of suitability for any new component of animal origin susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA of the ICH region and associated countries and shown to comply with the scope of the current WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*[26] or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*[27]

[25] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[26] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[27] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

or an equivalent guide of the ICH region and associated countries. The information should include the following:
- name of manufacturer;
- species and tissues from which the material is derived;
- country of origin of the source animals;
- its use; and
- evidence of its previous acceptance.

6. Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).

7. The batch numbers of the batches used in the stability studies should be given.

| 17 | Change in specification of an excipient | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Tightening of specification limits | 1, 2, 3 | 1, 2 | N |
| | | 2, 3 | 1, 2 | |
| b) | Addition of a new test parameter to the specification | 2, 4 | 1, 2, 3, 4, 5, 6 | |

## Conditions

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

2. The change should not be the result of unexpected events arising during manufacture.

3. Any change should be within the range of prequalified limits.

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.[28]

[28] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Comparative table of prequalified and proposed specifications.

3. Details of any new analytical method and summary of validation data (please refer to guideline ICH Q2 (R1)).[29]

4. Batch analysis data on two production batches for all tests in the new specification.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot-scale batch containing the excipient complying with the prequalified and proposed specification.

6. Justification for not submitting a new bioequivalence study according to the current WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices.[30]

| 18 | Change in test procedure for an excipient | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Minor changes to an approved test procedure | 1, 2, 3 | 1 | N |
| b) | Other changes to a test procedure, including replacement of a prequalified test procedure by a new test procedure | 2, 3, 4 | 1, 2 | |

## Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature is acceptable, but a different type of column or method is not); no new impurities are detected.

2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.

3. Results of method validation show the new test procedure to be at least equivalent to the former procedure.

[29] (EMEA/410/01rev2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

[30] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF[31] which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
2. Comparative validation results showing that the current test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).[32]

| 19 | Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | From a manufacturer prequalified | 1, 2, 3 | 1, 2, 3 | N |
| b) | From a new manufacturer (replacement or addition) | | | |
| | 1. Sterile substance | 1, 2, 3 | 1, 2, 3 | |
| | 2. Other substances | 1, 2, 3 | 1, 2, 3 | N |

## Conditions

1. The finished product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

## Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.

[31] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

[32] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.

3. Where applicable, a document providing information on any materials falling within the scope of the WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*[33] or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*[34] or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacture of the excipient. 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.

| 20 | Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient | Conditions to be fulfilled | Documentation to be supplied | N |
|---|---|---|---|---|
| From a manufacturer prequalified or a new manufacturer (replacement or addition) | | None | 1, 2, 3 | |

## Conditions

None.

## Documentation

1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.

2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[35]

3. A document providing information on any materials falling within the scope of the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary*

[33] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

[34] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[35] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

*medicinal products*[36] including those which are used in the manufacture of the excipient. 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.

| 21 | Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material | Conditions to be fulfilled | Documentation to be supplied | N |
|---|---|---|---|---|
| | | 1 | 1, 2 | |

## Conditions

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

## Documentation

1. Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the pharmaceutical product.

| 22 | Change to comply with a major international pharmacopoeia (BP, Ph Int, JP, Ph Eur, USP) | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| Change of specifications of a substance from a former non-major pharmacopoeia to comply with a monograph of a major international pharmacopoeia | | | |
| a) | API | 1, 2 | 1, 2, 3, 4, 5 |
| b) | Excipient | 1, 2 | 1, 2, 3, 4, 5 |

## Conditions

1. The change is made exclusively to comply with a major international pharmacopoeia.

[36] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Unchanged specifications (additional to the pharmacopoeia) for product-specific properties (e.g. particle size profiles, polymorphic form), if applicable.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[37]
2. Comparative table of prequalified and proposed specifications.
3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
4. Analysis of the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities.
5. Where appropriate, batch analysis data (in a comparative tabular format) on two production batches of the finished product containing the substance complying with the prequalified and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product obtained on at least one pilot batch.

| 23 | Change in the specifications of the immediate packaging of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Tightening of specification limits | 1, 2, 3 | 1, 2 | N |
| | | 2, 3 | 1, 2 | |
| b) | Addition of a new test parameter | 2, 4 | 1, 2, 3, 4 | |

## Conditions

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

[37] (EMEA/410/01rev 2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).[38]
4. Batch analysis data on two batches for all tests in the new speci-fication.

| 24 | Change to a test procedure on the immediate packaging of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Minor change to a prequalified test procedure | 1, 2, 3 | 1 | N |
| b) | Other changes to a test procedure, including replacement or addition of a test procedure | 2, 3, 4 | 1, 2 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF,[39] which includes a description of the analytical methodology and a summary of validation data.

[38] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[39] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

2. Comparative validation results showing that the prequalified test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

| 25 | Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (i.e. different plastic used)) | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| | | 1 | 1 | N |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[40]

| 26 | Change in the qualitative and/or quantitative composition of the immediate packaging material | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Semisolid and liquid pharmaceutical forms | 1, 2, 3, 4 | 1, 2, 3, 4, 5 | |
| b) | All other pharmaceutical forms | 1, 2, 3, 4 | 1, 4, 5 | N |
| | | 1, 3, 4 | 1, 2, 3, 4, 5 | |

## Conditions

1. The product concerned is not a sterile product.
2. The packaging type and material remain the same (e.g. a different blister, but same type).

[40] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

3. The relevant properties of the proposed packaging material must be at least equivalent to those of the prequalified material.
4. Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches, and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for oxygen, carbon dioxide and moisture).
3. Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack).
4. The batch numbers of batches used in the stability studies should be indicated.
5. Comparison of the prequalifed and proposed specifications, if applicable.

| 27 | Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded | Conditions to be fulfilled | Documen-tation to be supplied | |
|---|---|---|---|---|
| a) | Deletion of a supplier | 1 | 1 | N |
| b) | Replacement or addition of a supplier | 1, 2, 3, 4 | 1, 2, 3 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[41]
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this effect.
3. Tabulated comparison of prequalified and proposed specifications, if applicable.

| 28 | Change to in-process tests or limits applied during the manufacture of the product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Tightening of in-process limits | 1, 2, 3 | 1, 2 | N |
| | | 2, 3 | 1, 2 | |
| b) | Addition of new tests and limits | 2, 4 | 1, 2, 3, 4, 5 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Tabulated comparison of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).[42]

[41] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[42] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

4. Batch analysis data on two production batches of the finished product for all tests in the new specification.
5. Justification for addition of new tests and limits.

| 29 | Change in the batch size of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Up to10-fold compared to the prequalified batch size | 1, 2, 3, 4 | 1, 4 | N |
| b) | Downscaling to 10-fold | 1, 2, 3, 4, 5 | 1, 4 | N |
| c) | Other situations | 1, 2, 3, 4, 5, 6 | 1, 2, 3, 4, 5, 6 | |

## Conditions

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change relates only to standard immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different sized equipment.
4. A validation protocol is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the WHO guideline on validation of manufacturing processes (Supplementary guideline on good manufacturing practices for Pharmaceutical Products: validation. Annex 4, WHO Technical Report Series, No. 937, 2006).[43]
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or

[43] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf)

potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[44]
2. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the prequalified and the proposed sizes. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).
3. Copy of prequalified release and end-of-shelf-life specifications.
4. The batch numbers (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5. The batch numbers of batches used in the stability studies should be indicated.
6. For solid dosage forms: dissolution profile data on a minimum of one representative production batch and comparative data on the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside dissolution profile similarity requirements.

| 30 | Minor change in the manufacture of the finished product | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| | | 1, 2, 3, 4 | 1, 2, 3, 4, 5, 6, 7, 8 |

## Conditions

1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. In case of a change in the sterilization process, the change is to a standard pharmacopoeial cycle only.

[44] http://whqlibdoc.who.int/trs/WHO_TRS_937.pdf#page=119

4. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[45]
2. *For semisolid and liquid products in which the API is present in non-dissolved form*: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology, and comparative size distribution data obtained by an appropriate method.
3. *For solid dosage forms*: dissolution profile data on one representative production batch and comparative data on the last three batches from the previous process. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).
4. Justification for not submitting a new bioequivalence study according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices.[46]
5. In case of a change to the sterilization process, validation data should be provided.
6. Copy of prequalified release and end-of-shelf-life specifications.
7. Batch analysis data (in a comparative tabular format) on a minimum of one batch each, manufactured according to the prequalified and the

[45] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[46] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

proposed process. Batch data on the next two full production batches should be made available upon request and reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).

8. The batch numbers of batches used in the stability studies should be indicated.

| 31 | Change in the colouring system or the flavouring system currently used in the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Reduction or deletion of one or more components of the | | | |
| | 1. colouring system | 1, 2, 3, 4 | 1, 2, 3 | N |
| | 2. flavouring system | 1, 2, 3, 4 | 1, 2, 3 | N |
| b) | Increase, addition or replacement of one or more components of the | | | |
| | 1. colouring system | 1, 2, 3, 4, 5, 6 | 1, 2, 3, 4, 5 | |
| | 2. flavouring system | 1, 2, 3, 4, 5, 6 | 1, 2, 3, 4, 5 | |

## Conditions

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

5. Any proposed new components must comply with section 3.8 of the *Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*.[47]
6. Any new component does not involve the use of materials of human or animal origin which requires:
   - assessment of viral safety data; or
   - compliance with the current WHO Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products;[48] or
   - compliance with the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products;[49] or
   - compliance with an equivalent guide of the ICH region and associated countries.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF[50] (if appropriate, where the end-of-shelf-life specifications have been updated).
2. The batch numbers of the batches used in the stability studies should be indicated.
3. Sample of the new product.
4. Either a European Pharmacopoeia certificate of suitability for any new component originating from an animal susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA in the ICH region or associated countries and shown to comply with the scope of the current guideline 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 a derivative;

[47] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

[48] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

[49] http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

[50] (EMEA/410/01rev2; note that rev 3 is in the consultation phase) http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

– country of origin of the source animals; and
– its use.

5. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

| 32 | Change in coating weight of tablets or change in weight of capsule shells | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Immediate-release oral pharmaceutical forms | 1, 3, 4 | 1, 4 | N |
| b) | Gastroresistant, modified or prolonged release pharmaceutical forms | 1, 2, 3, 4 | 1, 2, 3, 4 | |

## Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot-scale batches is comparable to the old one.
2. The coating is not a critical factor for the release mechanism.
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and at least 3 months' satisfactory stability data are at the disposal of the applicant with assurance that these studies will be finalized. Data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[51]
2. Comparative dissolution profile data on at least two pilot-scale batches of the new formulation and two production batches of the prequalified formulation (no significant differences regarding comparability to WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO*

[51] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

*Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.[52]

3. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
4. The batch numbers of the batches used in the stability studies should be indicated.

| 33 | Change in shape or dimensions of the container or closure | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Sterile pharmaceutical forms | 1, 2, 3 | 1, 2, 3 | |
| b) | Other pharmaceutical forms | 1, 2, 3 | 1, 2, 3 | N |

## Conditions

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

## Documentation

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

[52] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

| 34 | Change in the specification of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Tightening of specification limits | 1, 2, 3 | 1, 2 | N |
| | | 2, 3 | 1, 2 | |
| b) | Addition of a new test parameter | 2, 4 | 1, 2, 3, 4 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[53]
2. Tabulated comparison of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).[54]
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.

| 35 | Change in test procedure of the finished product | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Minor change to a prequalified test procedure | 1, 2, 3, 4 | 1 | N |
| b) | Other changes to a test procedure, including replacement or addition of a test procedure | 2, 3, 4 | 1, 2 | |

[53] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

[54] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure in the PQIF,[55] which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
2. Comparative validation results showing that the prequalified test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).[56]

| 36 | Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| | | 1, 2 | 1, 2 | N |

## Conditions

1. Finished product release and end-of-shelf-life specifications have not been changed (except those for physical appearance).
2. Any ink must comply with the relevant section (3.8 excipients) of the Guideline on submission of documentation for prequalification of

[55] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

[56] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis.[57]

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF (including a detailed drawing or written description of the current and proposed new appearance).
2. Submit a sample of the product.

| 37 | **Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass** | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Gastroresistant, modified or prolonged release pharmaceutical forms and scored tablets | 1, 2 | 1, 2, 3, 4, 5 | |
| b) | All other tablets, capsules, suppositories and pessaries | 1, 2 | 1, 4 | N |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF[58] (including a detailed drawing of the current and proposed situation).
2. Comparative dissolution data on at least one pilot-scale batch of the current and proposed dimensions (with no significant differences regarding comparability according to the WHO Multisource (generic)

[57] ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

[58] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report*, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.[59]

3. Justification for not submitting a new bioequivalence study according to the current WHO Guideline on bioequivalence.
4. Samples of the finished product.
5. Where applicable, data on breakability test of tablets at release must be given together with a commitment to submit data on breakability at the end of the shelf-life.

| 38 | Change in pack size of the FPP | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) | Change in the number of units (e.g. tablets, ampoules, etc.) in a pack | | | |
| 1. | Change within the range of the prequalified pack sizes | 1, 2 | 1, 3 | N |
| 2. | Change outside the range of the prequalified pack sizes | 1, 2 | 1, 2, 3 | |
| b) | Change in the fill weight/fill volume of non-parenteral multidose products | 1, 2 | 1, 2, 3 | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.[60]

[59] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[60] http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as prequalified in the SmPC.
3. Written commitment that stability studies will be conducted in accordance with the WHO guidelines for products where stability parameters could be affected. Data are to be reported immediately if outside specifications (with details of proposed action).

| 39 | Change in: | Conditions to be fulfilled | Documentation to be supplied |
|---|---|---|---|
| a) | the shelf-life of the finished product | | |
| | 1. As packaged for sale | 1, 2, 3 | 1, 2 |
| | 2. After first opening | 1, 2 | 1, 2 |
| | 3. After dilution or reconstitution | 1, 2 | 1, 2 |
| b) | the storage conditions of the finished product or the diluted/reconstituted product | 1, 2 | 1, 2 |

## Conditions

1. Stability studies have been done according to the prequalified protocol. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf-life does not exceed 5 years.

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF. Replacement pages must contain the results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two production-scale batches of the finished product in the prequalified packaging material and/or after first opening or reconstitution, as appropriate; where applicable, the results of appropriate microbiological testing should be included.
2. A copy of the prequalified end-of-shelf-life finished product specification and, where applicable, specifications after dilution/reconstitution or first opening.

| 40 | Addition, replacement or deletion of a measuring or administration device that is not an integrated part of the primary packaging (spacer devices for metered-dose inhalers are excluded) | Conditions to be fulfilled | Documentation to be supplied | |
|---|---|---|---|---|
| a) Addition or replacement | | 1, 2 | 1, 2, 3 | N |
| b) Deletion | | 3 | | |

## Conditions

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

## Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF[61] (including description, detailed drawing and composition of the device material and supplier where appropriate).
2. Reference to CE marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
3. Samples of the new device.

[61] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

# Appendix 2

## Major changes (examples)

Major changes exceed the scope of the minor changes listed in Appendix 1, e.g. they exceed or do not comply with the conditions to be fulfilled along with the change, but are not covered by the changes listed in Appendix 3.

They most likely consist of:
- a change in the manufacturing process of the API;
- a change in the composition of the finished product; or
- a change to the immediate (primary) packaging of the product.

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

# Appendix 3

## Changes that make a new application or an extension application necessary

Changes that make a new application necessary are as follows:

### Changes to the API
- change of the API to a different API;
- inclusion of an additional API in a multicomponent product;
- removal of one API from a multicomponent product;
- change in the dose of one or more APIs.

### Changes to the pharmaceutical form/dosage form
- change from an immediate-release product to a slow- or delayed-release dosage form and vice versa;
- change from a liquid to a powder for reconstitution, or vice versa.

### Changes in the route of administration

# Appendix 4

## Stability requirements for variations and changes to prequalified finished pharmaceutical products (FPPs)

It is the purpose of this Appendix to outline the stability data which have to be generated in case of changes.

The scope and design of stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs. The available information that must be taken into account includes:

- For APIs:
  - the stability profile including the results of stress testing;
  - the supportive data;
  - the primary data on accelerated and long-term testing.
- For FPPs:
  - the supportive data;
  - the primary data on accelerated and long-term testing.

In all cases of variations and changes, the prequalified supplier has to investigate whether or not the intended change will have an impact on the quality characteristics of the APIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Appendix refers to the *Guideline on the submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*,[62] the Guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms, Annex 5, *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth Report.* Geneva, World Health Organization, 1996: 65–79 (WHO Technical Report Series, No. 863); modification of storage conditions (WHO Technical Report Series, No. 908) and amended stability testing conditions (WHO Technical Report Series, No. 937)[63] as well as *Stability testing of new drug substances and products* (ICH Q1A (R2)).[64]

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[62] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

[63] http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

[64] http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=23; http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=24

In all cases of variations which require generation of stability data on the FPP, the stability studies required, including commitment batches, should always be continued up to the end of the prequalified shelf-life and WHO should be informed immediately if any problems with the stability occur during storage, e.g. if outside specifications or potentially outside specifications.

## Minor changes

In the case of minor changes, as listed in Appendix 1 of this guide, which require generation of stability data on the FPP, the minimum set of data to be submitted with the variation application is defined in Appendix 1. The results of these studies covering the requested time period as defined in Appendix 1, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/FPP to ensure that the change does not have any negative impact on the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed re-test period/shelf-life. The comparison data may come from earlier studies and need not necessarily be collected in combination with the study on the unchanged product.

## Major changes

The following are commonly encountered examples of major changes:

- change in the manufacturing process of the API;
- change in composition of the FPP;
- change of immediate packaging of the FPP.

### *Change in the manufacturing process of the API*

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are changed in such a way, that stability may be compromised, comparative stability data are required from studies under accelerated and long-term testing conditions conducted on the API before and after the change:

| | |
|---|---|
| APIs known to be stable[65] | 3 months on one batch of at least pilot-scale |
| APIs known to be unstable | 6 months on three batches of at least pilot-scale |

If the quality characteristics of the API are changed in such a way that it may have an impact on the stability of the FPP, additional stability data on the FPP, obtained in studies under accelerated and long-term testing conditions, over 3 months on two batches on at least pilot-scale, may be required.

[65] ICH Q1A (R2) *Stability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA419.pdf)

Physical quality characteristics: crystallinity and/or polymorphic state, if applicable, and characteristics derived from crystallinity such as solubility and hygroscopicity. Chemical quality characteristics: impurity profile and degradation products.

*Change in composition of the finished product*

- *For conventional dosage forms* (e.g. conventional release solid dosage forms, solutions) *and* when the *API is known to be stable*, comparative stability data from a study of 6 months duration, under long-term and accelerated testing conditions on two pilot-scale batches[66] are required.
- *For critical dosage forms* (e.g. prolonged release form) *or* when the *API is known to be unstable*, comparative stability data, from a study of 6 months duration, under long-term and accelerated stability testing conditions on three pilot-scale batches are required.

### *Change to immediate packaging of the finished product*

In the case of less protective packaging or when a risk of interaction occurs, mainly for semisolid or liquid dosage forms, comparative stability data are required from a study of 6 months duration, using accelerated and long-term testing conditions, on three pilot-scale batches of the finished product.

## Commitment batches

### Minor changes

For all minor changes that require the generation of stability data on the FPP, adequate follow-up studies on commitment batches need to be performed.

### Major changes

For all major changes that require the generation of stability data on the FPP, at least the first production-scale batch manufactured according to the prequalified variation should undergo long-term stability testing using the same stability testing protocol as described above unless the respective data on stability testing have already been submitted as part of the variation application.

Stability studies need to be continued to cover the entire shelf-life. The results of these stability studies should be made available on request and WHO should be informed immediately if any problems occur during the stability studies.

[66] *Definition of stable APIs:* An API is considered as stable if it is within the initial specifications when stored at 25 °C at 60% relative humidity (RH) or 30 °C/60% RH or 65% RH, respectively, for 2 years and at 40 °C/75% RH for 6 months, and such data are available from the API manufacturer that is applying for approval of change in the manufacturing process. Please refer also to Supplement 2 of the GuideGeneric for a specific list of stable APIs.

## Web links

*Guideline on dossier requirements for type IA and IB notifications*. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf

*Pharmaceutical quality information form (PQIF)*. Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

*Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis* [GuideGeneric]. Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

Supplement 1 of the GuideGeneric. Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

Supplement 2 of the GuideGeneric. Availabl e at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement2.pdf

*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

ICH Q2 (R1) *Validation of analytical procedures: text and methodology*. Available at: http://www.ich.org/LOB/media/MEDIA417.pdf

ICH Q5A (R1) *Quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin* (CPMP/ICH/295/95). Available at: http://www.ich.org/LOB/media/MEDIA425.pdf

ICH Q5B *Quality of biotechnological products: analysis of the expression construct in cell lines used for production of r-DNA derived protein products* (CPMP/ICH/139/95). Available at: http://www.ich.org/LOB/media/MEDIA426.pdf

ICH Q5C *Quality of biotechnological products: stability testing of biotechnological/biological products* (CPMP/ICH/138/95). Available at: http://www.ich.org/LOB/media/MEDIA427.pdf

ICH Q5D *Quality of biotechnological products: derivation and characterization of cell substrates used for production of biotechnological/biological products* (CPMP/ICH/294/95). Available at: http://www.ich.org/LOB/media/MEDIA429.pdf

ICH Q5E *Guidance on biotechnological/biological products subject to changes in their manufacturing process* (CPMP/ICH/5721/03). Available at: http://www.ich.org/LOB/media/MEDIA1196.pdf

ICH Q6B *Specifications: test procedures and acceptance criteria for biotechnological/biological products* (CPMP/ICH/365/96). Available at: http://www.ich.org/LOB/media/MEDIA432.pdf

*WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*. Geneva, World Health Organization, 2003. Available at: http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

*Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (EMEA/410/01 rev2). Available at: http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

*Good manufacturing practices for pharmaceutical products: main principles*. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908), Available at: http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

*Supplementary guidelines on good manufacturing practices: validation*. Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937). Available at: http://www.who.int/medicines/publications/pharmprep/TRS_937.pdf#page=119

and *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Good manufacturing practices and inspection,* Vol. 2, 2nd updated edition, Geneva, World Health Organization, 2006 (in press). Available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html

*Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies.* Geneva, World Health Organization, 2004. Available at: http://mednet3.who.int/prequal/info_general/documents/ppdoc2.pdf

*Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth Report.* Annex 5. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863): 65–79. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf

and modification of storage conditions in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh Report*. Geneva, World Health Organization 2003 (WHO Technical Report Series, No. 908) and amended stability testing conditions in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report*. Geneva, World Health Organization 2006 (WHO Technical Report Series, No. 937). Available at: http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=23 http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=24

*ICH guidance on stability testing of new drug substances and products* (ICH Q1A (R2), CPMP/ICH/2736/99). Available at: http://www.ich.org/LOB/media/MEDIA419.pdf