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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 supportive information on how to present an application to implement a change to a prequalified product.

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

Where a variation requires consequential revision of the Summary of Product Characteristics (SmPC), labelling and package leaflet/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 biological finished products are assessed as major changes. In this case the applicant should refer to guidance documents that specifically address biological APIs, excipients and finished products (e.g. ICH Q5A (R1), Q5B, Q5C, Q5D, Q5E, Q6B)[2].

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[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

[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

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 variation applications are also to be approved by these drug regulatory authorities and WHO should be notified about 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 only a temporary status given for a defined period of time as precised in the general procedure[1]. It is renewable upon application before expiry, resulting in a submission and a review of an updated dossier within the prequalification project.

Irrespective of these regular reviews by WHO a prequalified supplier is responsible for the prequalifed product throughout its life (time) and is, therefore, 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 prequalified dossier 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 in order 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.

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[1] Procedure for Assessing the Acceptability, in Principle, of Pharmaceutical Products for Purchase by United Nations Agencies [http://mednet3.who.int/prequal/info_general/documents/ppdoc2.pdf] . Revised Procedure in: *Forty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2007, Annex 4 (in press).

The following definitions may be given to classify changes:

A minor change is a variation which can be found listed in Annex I of the present document.

A major change is a change to the documentation which can neither be deemed to be a minor variation within the meaning of preceding definition (therefore exceeding the frame of a minor change) nor to be a change for which the submission of a new dossier would be necessary (Annex II).

Approval of changes

Among minor changes as listed in Annex I of this document, some are classified by the letter N and can be considered as notifications. Applications for minor changes that are classified notifications (N) must provide evidence to fulfil the conditions and documentation requirements as listed. Within a period of three months these notifications will be evaluated by WHO and can be considered approved if no correspondence by WHO with the applicant has been initiated within that time. If the validity of the notification cannot be acknowledged by WHO correspondence with the applicant will be started and a new period of three months must be awaited by the applicant upon submission of his response documents, accordingly.

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. For these cases a new dossier must be submitted (Annex III).

In order to facilitate the classification of the various types of changes the following annexes explicitly define the various changes:

ANNEX I lists minor changes. These are classified by the type of change as such and the conditions which frame this type of change. Whenever the conditions are not kept, the change may either become a major change or may even make a new application necessary.

ANNEX II lists examples of major changes.

ANNEX III lists types of changes which make a new application necessary.

ANNEX IV lists stability requirements for variations and changes to prequalified FPPs

ANNEX I

DOSSIER REQUIREMENTS FOR MINOR CHANGES TO PREQUALIFIED PRODUCTS

This guide was prepared in order to clarify what documentation should be submitted with 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. In case the change also implies a change in the pharmaceutical particulars in the Summary of Product Characteristics (SmPC), labelling and/or package leaflet/insert, this also forms part of the change.

The titles of the changes are numbered and subcategories 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 are to be resubmitted according to the structure of the Pharmaceutical Quality Information Form (PQIF)[1] [structure/relevant parts of the dossier is/are also reflected 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"[2]]. Moreover, any further documentation required along with the change is identified.

Applicants should present a summary of the intended change in tabulated format in which the current state/situation and the situation after the intended change are compared in order to outline the scope of the change in a transparent manner. A justification should always follow why the change needs to be introduced.

Applicants should be aware that submitting redundant or irrelevant information does not facilitate rapid procedures. Deficient documentation can lead to non-validation/rejection of the change.

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

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

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**

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 (NDRA)) 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 (NDRA) 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[1].

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	Documen-tation to be supplied	
		1	1, 2	**N**

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

Conditions

1. The manufacturing site shall remain the same.

Documentation

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

4	**Change in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP)**	Conditions to be fulfilled	Documen-tation 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. NDRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.

5	**Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP**	Conditions to be fulfilled	Documen-tation 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	

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

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	

Conditions

1. Satisfactory inspection in the last three 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 NDRA (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 NDRA.
   – 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 concerning the packaging facilities by WHO or drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries, in the last three 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 should be indicated and validation protocol (scheme) to be submitted.

5. The variation application should clearly outline the "prequalified" and "proposed" finished product manufacturers.
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 semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
9. For solid dosage forms data of comparative dissolution tests [refer to Supplement 1[1] 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 dissolution profile similarity, performed on the last three batches from the previous site and the first three batches of the new site should be submitted.

6	**Change to quality control testing of the finished product**	Conditions to be fulfilled	Documen-tation 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 NDRA.
2. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Documentation

1. The corresponding letter should clearly outline the "prequalified" and "proposed" quality control sites.
2. Documented evidence that the site is appropriately authorized by the NDRA.

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

3. Documented evidence that the Method transfer from the old to the new site or 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	Documen-tation to be supplied	
		None	1	**N**

Conditions

None

Documentation

1. The corresponding letter 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 as listed in the PQIF[1] and of the prequalified Drug Master File (where applicable), including a direct comparison of the prequalified process and the new process.
2. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the prequalified and the proposed process.
3. Copy of prequalified specifications of the API.

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

9	**Change in batch size of API or intermediate**	Conditions to be fulfilled	Documen-tation to be supplied	
a)	Up to 10-fold 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 compared to the prequalified batch size	1, 2, 3	1, 3, 4	

Conditions

1. Any changes to the manufacturing methods are only 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 as listed in the PQIF[1].
2. The batch numbers of the tested batches having the proposed batch size.
3. Batch analysis data (in a comparative tabulated 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 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	Document-ation to be supplied	

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

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	

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 non-standard 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[1].
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 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.

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

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.[1]

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	Documen-tation 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, but not a different type of column or method); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard 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[2], which includes a description of the analytical methodology, a summary of validation data, 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)[3]).

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

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

[3] 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 Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products[1] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[2] 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 as listed in the PQIF[3].

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 TSE European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to

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

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

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

comply with the current WHO guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products[1] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[2] 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.

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

[2] (EMEA/410/01rev2; please 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 as listed in the PQIF[1].
3. Where applicable a document providing information of any materials falling within the scope of the WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products[2] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[3] 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 a derivative, 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 physiochemical 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 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.

14	**Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an API**	Conditions to be fulfilled	Documen-tation to be	**N**

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

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

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

	or starting chemical material/reagent/ intermediate in the manufacturing process of the API for a prequalified manufacturer and prequalified manufacturing process		supplied	
		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 as listed in the PQIF[1].
3. A document providing information of 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[2] 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

Conditions

1. Stability studies have been done to the prequalified protocol (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[3], Section 2.7.2]. The studies must show that the agreed relevant specifications are still met.

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

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

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

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 as listed in the PQIF[1]. 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[2]
3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data.
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 three months (accelerated and real time) satisfactory stability data are at the disposal of the applicant and 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 proposed action).

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

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

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[1] (as applicable).
2. Justification for the change/choice of excipients, etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
3. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition.
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[2].
5. Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by 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[3] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[4] 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 a derivative, 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.

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

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

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

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

17	**Change in specification of an excipient**	Conditions to be fulfilled	Documen-tation 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 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 non-standard 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[1].
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)[2]).
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

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

[2] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

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.[1]

18	**Change in test procedure for an excipient**	Conditions to be fulfilled	Documen-tation 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, but not a different type of column or method); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard 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[2] which includes a description of the analytical methodology, a summary of validation data, 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)[3]).

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

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

[3] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

19	**Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient**	Conditions to be fulfilled	Documen-tation 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.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[1].
3. Where applicable, a document providing information of any materials falling within the scope of the WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products[2] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[3] 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

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

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

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

manufacturer, species and tissues from which the material is a derivative, 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	Documen-tation 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 as listed in the PQIF[1].
3. A document providing information of 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[2] 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 a derivative, 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	Documen-tation to be supplied	N
		1	1, 2	

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

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

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, PhInt, JP , PhEur, USP)**	Conditions to be fulfilled	Documentation to be supplied
Change of specifications of a former non-major pharmacopoeial substance 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.
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 as listed in the PQIF[1].
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.

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

5. Where appropriate, batch analysis data (in a comparative tabulated 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 on at least one pilot batch.

23	**Change in the specifications of the immediate packaging of the finished product**	Conditions to be fulfilled	Documen-tation 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 non-standard 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[1].
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)[2]).
4. Batch analysis data on two batches for all tests in the new specification.

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

[2] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

24	**Change to a test procedure of the immediate packaging of the finished product**	Conditions to be fulfilled	Documen-tation 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, but not a different type of column or method).
2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard 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[1], which includes a description of the analytical methodology and a summary of validation data.
2. Comparative validation results showing that the prequalified test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)[2]).

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 (different plastic used)]**	Conditions to be fulfilled	Documen-tation to be supplied	
		1	1	**N**

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

[2] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

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 as listed in the PQIF[1].

26	**Change in the qualitative and/or quantitative composition of the immediate packaging material**	Conditions to be fulfilled	Documen-tation 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. blister to blister).
3. The proposed packaging material must be at least equivalent to the prequalified material in respect of its relevant properties.
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 three 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 proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2,

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

CO_2 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/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 as listed in the PQIF[1].
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this extent.
3. Comparative table 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	Documen-tation to be	

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

			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 non-standard 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[1].
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)[2]).
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	Documen-tation to be supplied	
a)	Up to10-fold compared to the prequalified batch	1, 2, 3, 4	1, 4	**N**

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

[2] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

size			
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 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. 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)[1].
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 three 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 proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[2].
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the prequalified and the proposed sizes. Batch data on the

[1] http://www.who.int/medicines/publications/pharmprep/TRS_937.pdf#page=119

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

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 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 of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside 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.
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 three 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 proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[1].
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; comparative size distribution data by an appropriate method.
3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process. 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 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.[2]
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 tabulated format) on a minimum of one batch manufactured to both the prequalified and the 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 specification (with propose 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	Documen-tation to be supplied	

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

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

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 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 three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data shall be provided immediately to WHO if outside specifications or potentially outside specification at the end of the prequalified shelf life (with proposed action). In addition, where relevant, photostability testing should be performed.
5. Any new proposed 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[1].
6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and

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

Pharmaceutical Products[1] or the NfG on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[2] or an equivalent guide of the ICH region and associated countries.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[3] (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 of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by 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, 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	Documen-tation 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	

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

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

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

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 three months' satisfactory stability data are at the disposal of the applicant and 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 proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[1].
2. Comparative dissolution profile data of 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 Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report,* 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices.[2]
3. Justification for not submitting a new bioequivalence study according to the current WHO Guideline 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	Documen-tation to be supplied	
a) Sterile pharmaceutical forms		1, 2, 3	1, 2, 3	

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

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

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 affects the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three 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 proposed action).

Documentation

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

34	**Change in the specification of the finished product**	Conditions to be fulfilled	Documen-tation 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).

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

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 non-standard 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.[1]
2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guidelines ICH Q2 (R1)[2]).
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	Documen-tation 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	

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.

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

[2] 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 non-standard 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[1], which includes a description of the analytical methodology, a summary of validation data, 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)[2]).

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	Documen-tation to be supplied	
		1, 2	1, 2	**N**

Conditions

1. Finished product release and end-of-shelf-life specifications have not been changed (except for appearance).
2. Any ink must comply with the relevant section 3.8 excipients 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[3].

Documentation

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

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

[2] ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology
http://www.ich.org/LOB/media/MEDIA417.pdf

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

37	**Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass**	Conditions to be fulfilled	Documen-tation 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 as listed in the PQIF[1] (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 (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.[2]
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 and commitment to submit data on breakability at the end of shelf-life.

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

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

38	**Change in pack size of the FPP**	Conditions to be fulfilled	Documen-tation 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. 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 as listed in the PQIF[1].
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 to be reported immediately if outside specifications (with 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

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

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 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 five years.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF[1]. Replaced pages must contain 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, results of appropriate microbiological testing should be included.
2. Copy of prequalified end-of-shelf-life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

40	**Addition or replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded)**	Conditions to be fulfilled	Documen-tation 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.

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

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 as listed in the PQIF[1] (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.

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

ANNEX II

MAJOR CHANGES (EXAMPLES)

Major changes exceed the scope of minor changes as listed in Annex I, e.g. they exceed/do not comply with the conditions to be fulfilled along with the change, but still do not cover the changes listed in Annex III.

They most likely consist of a:

Change in the manufacturing process of the API

Change in the composition of the finished product

Change of immediate packaging of the product

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

ANNEX III

CHANGES THAT MAKE A NEW APPLICATION/EXTENSION APPLICATION NECESSARY

Changes that make a new application necessary consist of:

Changes to the API

Change of the API to a different API.

Inclusion of an additional API to 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

ANNEX IV

STABILITY REQUIREMENTS FOR VARIATIONS AND CHANGES TO PREQUALIFIED FINISHED PHARMACEUTICAL PRODUCTS (FPPs)

It is the purpose of this Annex document 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 must be taken into account such as:

For APIs:

- the stability profile including the results on stress testing
- the supportive data
- the primary data of accelerated and long-term testing.

For FPPs:

- the supportive data
- the primary data of 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 APIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Annex document 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[1], 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

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

Technical Report Series, No. 908) and amended stability testing conditions (WHO Technical Report Series, No. 937)[1] as well as Stability Testing of New Drug Substances and Products (ICH Q1A (R2)).[2]

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 approved shelf-life and WHO should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

Minor changes

In cases of minor changes as listed in Annex I of this variation 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 Annex I. The results of these studies covering the requested time period as defined in Annex I, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/FPP in order to ensure that the change does not negatively impact the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed retest 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

In cases of major changes the following are widely encountered examples:

Change in the manufacturing process of the API

Change in composition of the FPP

Change of immediate packaging of the FPP.

[1] 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

[2] ICH Q1A (R2) Stability Testing of New Drug Substances and Products http://www.ich.org/LOB/media/MEDIA419.pdf

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 in accelerated and long term testing conditions, on the API before and after the change:

APIs known to be stable[1]	three months on one batch of at least pilot scale
APIs known to be unstable	six 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 impact the stability of the FPP, additional stability data on the FPP, in accelerated and long term testing conditions, three months on two batches on at least pilot scale, may be required.

Physical quality characteristics: crystallinity and/or polymorphic state, if applicable, and characteristics derived from crystallinity such as solubility, hygroscopicity, etc.

Chemical quality characteristics: impurity profile, 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, six months duration, long-term and accelerated testing conditions on two pilot scale batches[2] are required.

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

[2] The pilot scale batch size should correspond to at least 10% of the production scale batch size, i.e. such that the multiplication factor for the scale-up does not exceed 10. For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater [GuideGeneric, section 3.7.1, http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

For critical dosage forms (e.g. prolonged release form) or when the API is known to be unstable, comparative stability data, six months duration long-term and accelerated stability testing conditions on three pilot scale batches are required.

Change on 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 using accelerated and long-term testing conditions of six months duration 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 be placed on long-term stability testing using the same stability testing protocol as described above unless it has 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 appear with the stability studies.

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 physico-chemical-biological testing and the production process and its control is needed for its characterization and the determination of its quality.

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].

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].

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].

Test procedure

= Analytical procedure.

Limits

= Acceptance criteria.

Validation protocol

= Validation scheme, validation plan.

ABBREVIATIONS and ACRONYMS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CEP	European Pharmacopoeia Certificate of suitability
DRA	Drug Regulatory Authority
FPP	Finished Pharmaceutical Product
	The acronym FPP always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release)
ICH	International Conference on Harmonisation
PhInt	International Pharmacopoeia
JP	Japanese Pharmacopoeia
NDRA:	National Drug Regulatory Authority
OoS	Out of specification (outside specification)
PhEur	Pharmacopoeia Europae (European Pharmacopoeia)
SmPC	Summary of Product Characteristics
USP	United States Pharmacopeia

WEB LINKS

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

Pharmaceutical Quality Information Form (PQIF)

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

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 [GuideGeneric]

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

Supplement 1 of the GuideGeneric

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

Supplement 2 of the GuideGeneric

http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement2.pdf

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report, 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices

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

ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology

http://www.ich.org/LOB/media/MEDIA417.pdf

ICH Q 5A (R1) Quality of Biotechnological Products: Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin (CPMP/ICH/295/95)

http://www.ich.org/LOB/media/MEDIA425.pdf

ICH Q 5B 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)

http://www.ich.org/LOB/media/MEDIA426.pdf

ICH Q 5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (CPMP/ICH/138/95)

http://www.ich.org/LOB/media/MEDIA427.pdf

ICH Q 5D Quality of Biotechnicological Products: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products (CPMP/ICH/294/95)

http://www.ich.org/LOB/media/MEDIA429.pdf

ICH Q 5E Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)

http://www.ich.org/LOB/media/MEDIA1196.pdf

ICH Q 6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96)

http://www.ich.org/LOB/media/MEDIA432.pdf

WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products

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)

http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf

Good manufacturing practices for pharmaceutical products: main principles. Annex 4, WHO Technical Report Series, No. 908, 2003

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Supplementary guidelines on good manufacturing practices: validation. Annex 4, WHO Technical Report Series, No. 937, 2006

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, Volume 2, 2nd updated edition, 2006 (in press)

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

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, 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

http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf

and modification of storage conditions (WHO Technical Report Series, No. 908) and amended stability testing conditions (WHO Technical Report Series, No. 937)

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)

http://www.ich.org/LOB/media/MEDIA419.pdf