Medicines Control Authority of Zimbabwe

GUIDELINE FOR SUBMITTING APPLICATIONS FOR VARIATIONS TO REGISTERED MEDICINES

PREFACE

This guideline provides the necessary information that must be submitted by all applicants to the Medicines Control Authority of Zimbabwe (MCAZ). Please note that this guideline also refers to changes or variations to a registered medicine.

The better part of this guideline was derived from the EU "Guideline on dossier requirements for type IA and IB notifications"[1], the World Health Organisation (WHO) "Guidance on variations in a dossier submitted within the prequalification program"[2] , FDA "Guidance for Industry: Changes to an approved NDA or ANDA", and Scale-Up and Post-approval Changes(SUPAC) guidelines.

References to compendial monographs [British Pharmacopoeia (BP), International Pharmacopoeia (Ph. Int.), Japanese Pharmacopoeia (JP), European Pharmacopoeia (Ph. Eur.) or United States Pharmacopoeia (USP)] or to guidelines (WHO, ICH-region and associated countries) are inserted to assist applicants on compiling their applications for submission. 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.

MCAZ adopted the Common Technical Document (CTD) guidelines for submissions of applications for registration of medicines in March 2013. Applicants are encouraged to refer to the MCAZ Guideline on Submission of Documentation for Registration of a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part of the (CTD) Format"

Applicants are urged to note the requirements for submission of applications in this guideline as failure to comply fully will lead to rejection of the application. As per MCAZ regulations, applicants are required to submit the application for variation and the applicant should be representative of the principal.

No requests for refunds to rejected applications will be entertained. Any failure to submit additional information requested on evaluation of the variation within the stipulated period (usually not more than 30 days) will lead to rejection of the application. The MCAZ will not accept any responsibility for the safekeeping of incomplete applications.
Any documents accompanying applications received by the Authority, whether accepted or rejected, will become the property of the Authority and their storage will fall under the applicable legislative control and confidentiality clauses.

[1] Guideline on dossier requirements for type IA and IB notifications July 2003" http://pharmacos.eudra.org/F2/eudralex/vol -2/C/G dV arTypIA B_rev0_200307.pdf

[2] WHO "Guidance on variations to a prequalified dossier"

SCOPE

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].

This guideline applies to all variations whether from the applicant's initiative or requested by the Authority. This guideline does not apply to medicines whose application for registration is still under consideration by the MCAZ.

INTRODUCTION

Once a medicine is registered by the MCAZ for sale in Zimbabwe, any variations to the original information submitted with the application or set as conditions for registration must be submitted for approval. Variations to details of a medicine may be made to alter or to improve the medicinal product, to introduce an additional safeguard due to new scientific knowledge or to meet market demands.

The conditions of registration of a medicine are therefore considered dynamic taking into account that variations to the original registered dossier may become necessary during the lifetime of the medicine.

Procedures for the implementation of the different variations are presented here to assist applicants and MCAZ evaluators.

Variations are classified as follows:

> ***Minor Variation*** – this is a variation which can be found listed in Appendix I of the present document. These are classified by the type of variation as such and the applicable

conditions. Whenever the conditions are not kept, the variation may either become a major variation or may even make a new application necessary.

Major Variation **-** is a variation to the documentation which can neither be deemed to be a minor variation nor to be a variation for which the submission of a new dossier would be necessary. See Appendix II.

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

APPENDIX I lists minor variations.

APPENDIX II lists major variations.

APPENDIX III lists types of variations which make a new application necessary.

APPENDIX IV lists stability requirements for variations to registered medicines

FEES

Applicable fees are defined in the MCAZ fee schedule. Note that the MCAZ reserves to determine the correct interpretation of the fee payable based on the published schedule. Please note that relevant variation application fees apply to all variations. Any submission not accompanied by the relevant application fee will not be considered as an application.

PROCEDURE FOR APPROVAL OF VARIATIONS

1. The applicant submits an application in the appropriate format accompanied by the appropriate forms and fees.
2. MCAZ evaluators conduct screening of application for completeness and confirmation of type of variation and fee payable. Incomplete applications will then be rejected at this stage.
3. The application is assessed by MCAZ evaluators and matter considered at a meeting of the MCAZ Committee where a decision on the application is made.
4. The applicant is notified of the Authority's decision and any applicable conditions or request for more information.

DOSSIER REQUIREMENTS FOR VARIATIONS TO REGISTERED PRODUCTS

Although this guideline was prepared in order to clarify what documentation should be submitted with each type of variation, the applicant is advised to ensure compliance with other MCAZ guidelines.

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

In principle, all parts of the dossier that are affected by a variation should be resubmitted according to the structure of the MC8 Form (Application for registration of a medicine) or CTD format.

Applicants should present a summary of the intended variation in tabulated format in which the current state/situation and the situation after the intended variation are compared in order to outline the scope of the variation in a transparent manner. Each variation application should be accompanied by a justification.

Promotional materials are treated as variations and require approval by the Pharmacovigilance and Clinical Trials Committee. For promotional material please refer to the link below: http://www.mcaz.co.zw/index.php/downloads/file/117-draft-guidelines-for-advertising-and-promotion-of-medicines

List of Variations

1	**Variation in the name and/or address of the Applicant/Principal for the registered product**	Conditions to be fulfilled	Required documentation
		1,2	1,2,3,4

1. Variation in the name and/or address of the applicant or principal

Condition

1. The applicant shall remain the same legal entity.
2. Application fee as indicated on the fee schedule accompanies the application

Documentation

1. A formal document from a relevant official body in which the name and or the new address is mentioned. **Where applicable, information on legal status e.g. evidence of merger, sale of formulation, variation of name etc must be submitted.**
2. Completed page 1 of the M C8 Form
3. Written declaration confirming correctness of information submitted and that no other administrative variations have been made to those already approved by the MCAZ
4. A copy of the current medicine registration certificate

2	**Variation in the name of the Finished Pharmaceutical Product (FPP)**	Conditions to be fulfilled	Required documentation
		1	1, 2,3,4

2. Variation in the name of the Finished Pharmaceutical Product (FPP)

Conditions
No confusion with the names of existing registered products or with the international non-proprietary 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 of the M C8 form or CTD format.

3. Revised label and package insert reflecting the proposed name of the FPP.

4. A copy of the current medicine registration certificate

3	**Variation 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	Required documentation to
		1	1, 2

3. Variation 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

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 Form MC8 or MCAZ CTD Guideline

4	**Variation in the name and/or address of a manufacturer of the Finished Pharmaceutical Product (FPP)**	Conditions to be fulfilled	Required Documentation
		1	1, 2,3,4

4. Variation in the name and/or address of a manufacturer of the Finished Pharmaceutical Product (FPP)

Conditions

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. N DRA) 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 MC8 form.
3. Revised label and package insert reflecting the proposed name of the FPP
4. A copy of the current medicine registration certificate

5. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP	Conditions to be fulfilled	Required Documentation

1. Secondary packaging site		
For all types of pharmaceutical forms	1, 2	1, 3, 8, 9, 11,12
2. Primary packaging site		
Solid pharmaceutical forms, e.g. tablets and capsules	1, 2, 3, 4	1, 3, 5, 8, 9, 11,12
Semi-solid or liquid pharmaceutical forms	1, 2, 3, 4	1, 3, 5, 8, 9, 11,12
Liquid pharmaceutical forms(suspensions, emulsions)	1, 2, 3,4	1, 2, 3, 9, 11 ,12 , 5,
3. All other manufacturing site		
All operations except quality control for batch release	1, 2, 3,4	12, 3, 4, 5, 6, 7,9,10,1 10, 11 , 1,12

5. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP

Conditions

1. Site has authority from M CAZ for the packaging or manufacturing of the pharmaceutical form and product concerned.
2. New site must be approved by M CAZ or a stringent regulatory authority as complying with current GMP, and/or a satisfactory inspection of the manufacturing site has been performed in the last three years by the M CAZ
3. Product concerned is not a sterile product.
4. Validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

Documentation

1. Proof that the proposed site is licensed and has been approved by MCAZ or a stringent regulatory authority as complying with current GM P for the packaging or manufacturing of the pharmaceutical form and product concerned.
2. The batch numbers of not less than 3 production batches used in the validation study should be indicated and related validation protocol (scheme) to be submitted. In the case where no production has started a proposed validation protocol must be submitted.
3. The variation application should clearly outline the “present” and “proposed” finished product manufacturers.
4. Copy of approved release and end-of-shelf life (where applicable) specifications.
5. Batch analysis data on three production batch and comparative data on the last three batches from the previous site.
6. For semi-solid 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.
7. For solid dosage forms a comparative dissolution test data on the last 3 batches from the previous site and the 3 first batches for the new site including not less than 6 time points should be provided. In

cases where batches from the previous site are not available, applicants who are unable to fulfil this requirement are required to an application for registration as a new product.

8. Statement as when the variation will be effective should be submitted.
9. Submit updated MC8 form with special emphasis on the name and street address of each facility where *any aspect of* manufacture occurs, including production, sterilization, packaging and quality control. Indicate the activity performed at each site. Provide phone number(s); fax number(s) and e-mail addresses.
10. Comparative schedule of manufacturing process at the two locations. The example below guides on the presentation of the information
11. Written confirmation that no variations have been made to specifications, test methods or sources of API and excipients for the two sites.
12. A copy of the current medicine registration certificate

Example of a comparative schedule for variation of manufacturing site for a tablet formulation:

	Currently approved product details	**Proposed product details**	**Comments**
Product name	ABC 50mg tablets	ABC 50mg tablets	No variation
Batch size	One batch size 30 000 tablets (30kg)	Two batch sizes 150 000 tablets (150kg) and 300 000 tablets (300kg)	Two batch sizes both higher than previous
Unit composition	• Specifications for API in-house • Excipient specifications International Pharmacopoeia and in-House	• API specifications now USP • Excipient specifications now B P/Ph. Eur	• API specifications now in official pharmacopoeia • Excipients specifications variation due to new markets in UK and Europe
Material Sifting	• Sifting of excipients X and Y in mechanical sifter • Sifting of extra granular material in mechanical sifter	Sifting in two lots (A and B) in Co-mill	• Equipment variation due to increased batch size and unavailability of same equipment. • The sifting process is however using the same principle. See attached Description
Granulation	In single lot	In two lots (A and B)	Equipment variation due to increased batch size

Drying	Drying at 50 – 55ºC for 10 –15mins, till LOD is NMT 2.5% w/w	Wet mass dried at 60 - 65ºC for 10 minutes, till LOD at not more than 2.5% w/w for both lots	• Equipment variation with new achieving optimum at higher temperature in a shorter time. • Process under validation • Higher drying temperature acceptable based on previously submitted pharmaceutical development data
Blending	Single cone blender for 20 Minutes	Cage blender and blended for 5 minutes	• Equipment variation. • The principles of operation of both blenders basically similar. See drawings and description of process. • Under validation
Compression	• 16 station rotary press • Oval shaped, biconvex tablets with single break line and plain on the other	• 32 station card press compression machine • Oval shaped, biconvex tablets with single break line on one side and embossed "ABC"	• Similar equipment only increased number of stations • Process validated (see attached report) • New embossing included.

6	**Variation to quality control testing of the finished product**	Conditions to be fulfilled	Required Documentation supplied	
Replacement or addition of a site where batch		1, 2	1, 2, 3	**N**

6. Variation to quality control testing of the finished product

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 "registered" and "proposed" quality control sites.
2. Documented evidence that the site is appropriately authorized by the NDRA.

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	Required Documentation	
		None	1,2,3	**N**

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
None

Documentation
1. The corresponding letter should clearly name the manufacturer to be deleted.

2. Submit updated page 1 of the MC8 form

3. Copy of the current medicine registration certificate

8	**Minor variation in the manufacturing process of the API**	Conditions to be fulfilled	Required Documentation
		1, 2	1, 2, 3

8. Minor variation in the manufacturing process of the API

Conditions
No variation in qualitative and quantitative impurity profile or in physico-chemical properties.
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 M C8 Form or MCAZ CTD Guidelines, including a direct comparison of the registered 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 registered and the proposed process.

3. Copy of registered specifications of the API.

4. Comparative profile of physicochemical properties of the API manufactured with proposed process and that manufactured with the registered process

9	**Variation in batch size of API or intermediate**	Conditions to be fulfilled	Required Documentation	
a)	Up to 10-fold compared to the registered batch Size	1, 2, 3	1, 2,3	**N**
b)	Downscaling	1, 2, 3, 4	1, 2, 3	**N**
c)	More than 10-fold compared to the registered batch size	1, 2, 3	1, 3, 4	

9. Variation in batch size of API or intermediate

Conditions

Any variations to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment.
Test results of at least two batches according to the specifications should be available for the proposed batch size.
The variation does not affect the reproducibility of the process.
The variation 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 MC8 Form or MCAZ CTD Guidelines
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 registered and the proposed size. Batch data on the next two full production batches should be available on request and reported immediately to MCAZ if out of specification (OoS) results are noted with proposed action
4. Copy of registered specifications of the API (and of the intermediate, if applicable).

10	**Variation in the specification of an API, a starting chemical material/ intermediate/reagent used in the manufacturing process of the API**	Conditions to be fulfilled	Required Documentation	

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. Variation in the specification of an API, a starting chemical material/ intermediate/reagent used in the manufacturing process of the API

Conditions

1. The variation is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration or a major variation procedure after registration).
2. The variation should not be the result of unexpected events arising during manufacture.
3. Any variation should be within the range of registered 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 MC8 Form or MCAZ CTD Guidelines
2. Comparative table of registered 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 registered and the proposed specifications. (Batch data on the next two full production batches should be available on request or reported if out of specification (OoS) results are noted 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 registered and the proposed specification.
6. Justification for not submitting a new bio-equivalence study according to the current guideline.

11	**Variation in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API**	Conditions to be fulfilled	Required Documentation	

a)	Minor variations to a registered test procedure	1, 2, 3	1	**N**
b)	Other variations to a test procedure, including	2, 3, 4	1, 2	

11. Variation in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API

Conditions

1. The method of analysis should remain the same (e.g. a variation 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 MC8 Form or MCAZ CTD Guidelines , 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 registered test and the proposed one are equivalent (Please refer to guidelines ICH Q2A[3] and ICH Q2B[4]).

[3]ICH Q2A: Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPM P/IC H/381/95) [www.emea.eu.i nt/pdf s/human/ich/0381 95en.pdf]

[4]ICH Q2B: Note for Guidance on Validation of Analytical Procedures: Methodology (CPM P/ICH/281/95) [www.emea.eu.i nt/pdf s/human/ich/0281 95en.pdf]

12	**Variation in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the API**	Conditions to be fulfilled	Required Documentation
a)	Variation in site of the already registered manufacturer (replacement or addition)	1, 2	1, 2, 3, 4, 5

b) New Manufacturer (replacement or addition)	1,2	1,2,3,4,5,6,7

12. Variation in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the API

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 registered.
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[5]

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC* Form or MCAZ CTD Guidelines (Section 3.2.S.1 to 3.2.S.7)
2. A declaration from the applicant of the registered 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 registered.
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 a competent authority and shown to comply with the current WHO-guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products[6]
4. Batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the registered and proposed manufacturers/sites.
5. The application should clearly outline the “registered” and “proposed” manufacturers.
6. Comparative profile of physicochemical properties of the API manufactured at the proposed site and the API manufactured at the registered site
7. Submission of the drug master file from the proposed manufacturer

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

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	Required Documentation	
a)	From a registered 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**

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

1. The finished product release and end of shelf life specifications remain the same.
2. Unamended (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.

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 MC8 FORM or MCAZ CTD Guidelines
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 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 a derivative, country of origin of the source animals and its use.
4. The variation application should clearly outline the “registered” and “proposed” manufacturers.

Note

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

14	**Submission of a new or updated BSE/TSE European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/intermediate in the manufacturing process of the API for a registered manufacturer and registered manufacturing**	Conditions to be fulfilled	Required Documentation	**N**
		None	1, 2, 3	

14. Submission of a new or updated BSE/TSE European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/ intermediate in the manufacturing process of the API for a registered manufacturer and registered manufacturing process

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 MC8 Form MCAZ CTD Guidelines
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[7] 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	**Variation in retest period and storage conditions for the API**	Conditions to be fulfilled	Required Documentation
a)	the re-test period of the API	1, 2	2
b)	the storage conditions for the API	1, 2	2

15. Variation in retest period and storage conditions for the API

Conditions

1. Stability studies have been done to the registered protocol [MCAZ CTD Guidelines on submission of application for registration of a medicine]. The studies must show that the agreed relevant specifications are still met.
2. The variation 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 MC8 form or MCAZ CTD Guidelines. 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 registered 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

16. Replacement of an excipient with a comparable excipient

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 guideline on bioequivalence
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 MCAZ if outside specifications or potentially outside specification at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM (as applicable).
2. Justification for the variation/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 M CAZ Guideline on bioequivalence
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[8] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[9] 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

[8] http://www.who.int/entity/bloodproducts/publications/en/W HO_TSE_2003.pdf

[9] (EM EA/41 0/01 rev2; please note that rev 3 is in the consultation phase) http://www .emea.eu.int/pdfs/human/bwp/TSE%20N FG%2041 0-rev2.pdf

17	**Variation in specification of an excipient**	Conditions to be fulfilled	Required Documentation	
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	

17. Variation in specification of an excipient

Conditions

1. The variation is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to registration of the product or a major variation procedure after registration).
2. The variation should not be the result of unexpected events arising during manufacture.
3. Any variation should be within the range of registered 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 MC8 FORM or MCAZ CTD Guidelines
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and summary of validation data (Please refer to guidelines ICH Q2A[10] and ICH Q2B[11]).
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 a least one pilot scale batch containing the excipient complying with the registered and proposed specification.

6. Justification for not submitting a new bioequivalence study according to the current MCAZ-guideline on bioequivalence.

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[10] ICH Q2A: Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPM P/IC H/381/95) [www.emea.eu.int/pdfs/human/ich/0381 95en.pdf]

[11] ICH Q2B: Note for Guidance on Validation of Analytical Procedures: Methodology (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

18	**Variation in test procedure for an excipient**	Conditions to be fulfilled	Required Documentation	
a)	Minor variations to an approved test procedure	1, 2, 3	1	**N**
b)	Other variations to a test procedure, including replacement of a registered test procedure by a new test procedure	2, 3, 4	1, 2	

18. Variation in test procedure for an excipient

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 MC8 FORM or MCAZ CTD Guidelines 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 guidelines ICH Q2A[12] and ICH Q2B[13]).

19	**Submission of a new or updated European Pharmacopoeia certificate of suitability for an Excipient**	Conditions to be fulfilled	Required Documentation	
a)	From a registered manufacturer	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**

19. Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient

Conditions

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

[12]ICH Q2A: Note for Guidance on Validation of Analytical Methods: (C PM P/IC H/381 /95) [www .emea.eu.i nt/pdfs/human/ich/0381 95en.pdf]
[13]ICH Q2B: Note for Guidance on Validation of Analytical Procedures: Methodology: (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

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 MC8 FORM.
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[14] or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[15] 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 o 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 BSE/TSE European Pharmacopoeia certificate of suitability for an Excipient**	Conditions to be fulfilled	Required Documentation	**N**
From a registered manufacturer or a new manufacturer (replacement or addition)		None	1, 2, 3	

20. Submission of a new or updated BSE/TSE European Pharmacopoeia certificate of suitability for an excipient

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 MC8 FORM or MCAZ CTD guidelines
3. A document providing information of any materials failing within the scope of the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[16] 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.

[14] http://www.who.int/entity/bloodproducts/publications/en/W HO_TSE_2003.pd
[15] (EM EA/410/01rev2; please note that rev 3 is in the consultation phase) http://www .emea.eu.int/pdfs/human/bwp/TSE%20N FG%2041 0-rev2.pdf
[16] (EMEA/410/01rev2; please note that rev 3 is in the consultation phase) http://www .emea.eu .i nt/pdfs/human/bwp/TSE%20N FG%2041 0-rev2.pdf

21	**Variation in source of an excipient or reagent from a BSE/TSE risk to a vegetable or synthetic material**	Conditions to be fulfilled	Required Documentation	N
		1	1, 2	

21. Variation in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material

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	**Variation to comply with a major international pharmacopoeia (BP, PhInt, JP , PhEur, USP)**	Conditions to be fulfilled	Required Documentation
	Variation 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

22. Variation to comply with a major international pharmacopoeia (BP, PhInt, JP , PhEur, USP)

Conditions

1. The variation 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 MC8

FORM or MCAZ CTD Guidelines

2. Comparative table of registered 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 tabulated format) on two production batches of the finished product containing the substance complying with the registered and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch.

23	**Variation in the specifications of the immediate packaging of the finished product**	Conditions to be fulfilled	Required Documentation	
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	

23. Variation in the specifications of the immediate packaging of the finished product

Conditions

1. The variation is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration of the product or a major variation procedure after registration).
2. The variation should not be the result of unexpected events arising during manufacture.
3. Any variation should be within the range of registered 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 MC8 FORM or MCAZ CTD Guidelines.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and validation data (Please refer to guidelines ICH Q2A[17] and ICH Q2B[18]).
4. Batch analysis data on two batches for all tests in the new specification.

[17] ICH Q2A: Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (C PM P/IC H/381 /95) [www .emea.eu.i nt/pdf __ s/human/i ch/0381 95en .pdf]

[18] ICH Q2B: Note for Guidance on Validation of Analytical Procedures: Methodology (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

24	**Variation to a test procedure of the immediate packaging of the finished product**	Conditions to be fulfilled	Required Documentation	
a)	Minor variation to a registered test procedure	1, 2, 3	1	**N**
b)	Other variations to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

24. Variation to a test procedure of the immediate packaging of the finished product

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 M C8 FORM, which includes a description of the analytical methodology and a summary of validation data.
2. Comparative validation results showing that the registered test and the proposed one are at least equivalent (please refer to guidelines ICH Q2A and Q2B).

25	**Variation in any part of the (primary) packaging material not in contact with the finished product formulation [such as colour of flipoff caps, colour code rings on ampoules, variation of needle shield (different plastic used)]**	Conditions to be fulfilled	Required Documentation	
		1	1	**N**

25. Variation 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, variation of needle shield (different plastic used)]

Conditions

1. The variation 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 MC8 FORM or MCAZ CTD Guidelines, including specifications of packaging material, test methods, and certificate of analysis

26	**Variation in the qualitative and/or quantitative composition of the immediate packaging material**	Conditions to be fulfilled	Required Documentation	
a)	Semi-solid 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	

26. Variation in the qualitative and/or quantitative composition of the immediate packaging material

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 registered 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 MCAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, 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. 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).
5. Comparison of the registered and proposed specifications.

27	**Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); excluding spacer devices for metered dose inhalers**	Conditions to be Fulfilled	Required Documentation	
a)	Deletion of a supplier	1	1	**N**
b)	Replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	

27. Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); excluding spacer devices for metered dose inhalers

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 MC8 FORM or MCAZ CTD Guidelines.
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this extent.
3. Comparative table of registered and proposed specifications, if applicable.

28	**Variation to in-process tests or limits applied during the manufacture of the product**	Conditions to be Fulfilled	Required Documentation	
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	

28. Variation to in-process tests or limits applied during the manufacture of the product

Conditions

1. The variation is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to registration of the product or a major variation procedure after registration).
2. The variation should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any variation should be within the range of registered 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 MC8 FORM.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guidelines ICH 2QA[19] and ICH Q2B[20]).
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.

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[19]ICH Q2A: Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPM P/IC H/381/95) [www.emea.eu.int/pdfs/human/ich/0381 95en.pdf]

[20]ICH Q2B: Note for Guidance on Validation of Analytical Procedures: Methodology (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

29. Variation in the batch size of the finished product

29	**Variation in the batch size of the finished Product**	Conditions to be fulfilled	Required Documentation	
a)	Up to10-fold compared to the registered batch Size	1, 2, 3, 4	1, 4	**N**
b)	Downscaling down to 10-fold	1, 2, 3, 4, 5	1, 4	**N**
c)	More than 10-fold compared to registered batch size and other situations	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5,6	

29. Variation in the batch size of the finished product

Conditions

1. The variation does not affect reproducibility and/or consistency of the product.
2. The variation relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms.
3. Any variations to the manufacturing method and/or to the in-process controls are only those necessitated by the variation 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 MCAZ guideline on validation of manufacturing processes.
5. The variation 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM or MCAZ CTD Guidelines.
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the registered 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 registered product if outside specifications (with proposed action).
3. Copy of registered 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 variation in the manufacture of the finished product**	Conditions to be fulfilled	Required Documentation
		1, 2, 3, 4	1, 2, 3, 4, 5, 6, 7, 8

30. Minor variation in the manufacture of the finished product

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 variation in the sterilization process, the variation 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM.
2. For semi-solid and liquid products in which the API is present in non-dissolved form: appropriate validation of the variation including microscopic imaging of particles to check for visible variations 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 registered product if outside specifications (with proposed action).

4. Justification for not submitting a new bioequivalence study according to the MCAZ Guideline on Bioequivalence.
5. In case of a variation to the sterilization process, validation data should be provided.
6. Copy of registered 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 registered 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 registered product if outside specification (with propose action).

1. 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

31	**Variation in the colouring system or the flavouring system currently used in the finished Product**	Conditions to be fulfilled	Required Documentation	
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	

31. Variation in the colouring system or the flavouring system currently used in the finished product

Conditions

1. No variation 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 M CAZ if outside specifications or potentially outside specification at the end of the registered shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5. Any new proposed components must comply with the appropriate section of the Guideline on Submission of application for registration of a medicine.

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 Pharmaceutical Products[21] or the NfG on Minimizing the Risk of Transmitting Anima Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products[22] 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 th M C8 FORM (if appropriate, where the end of shelf life specifications have been updated)

2. 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

3. Sample of the new product.

21 http://www .w ho.i nt/entity/bloodproducts/publ icati ons/en/W HO_TSE_2003.pd
22 (EM EA/410/01rev2; please note that rev 3 is in the consultation phase)
http://www .emea.eu.int/pdfs/human/bwp/TSE%20N FG%2041 0-rev2.pdf

[add BSE to all TSE]

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	**Variation in coating weight of tablets or variation in weight of capsule shells**	Conditions to be fulfilled	Required Documentation	
a)	Immediate release oral pharmaceutical forms	1, 3, 4	1, 4	**N**
b)	Gastro-resistant, modified or prolonged release pharmaceutical forms	1, 2, 3, 4	1, 2, 3, 4	

32. Variation in coating weight of tablets or variation in weight of capsule shells Conditions

4. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one.
5. The coating is not a critical factor for the release mechanism.
6. The finished product specification has only been updated in respect of weight and dimensions, if

applicable.

7. 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM.
2. Comparative dissolution profile data of at least two pilot scale batches of the new formulation and two production batches of the registered formulation (no significant differences regarding comparability to M CAZ Guideline on Bioequivalence).
3. Justification for not submitting a new bioequivalence study according to the current MCAZ Guideline on Bioequivalence.
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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

33	**Variation in shape or dimensions of the container or closure**	Conditions to be fulfilled	Required Documentation	
a)	Sterile pharmaceutical forms	1, 2, 3	1, 2, 3	
b)	Other Pharmaceutical forms	1, 2, 3	1, 2, 3	**N**

33. Variation in shape or dimensions of the container or closure

Conditions

1. No variation in the qualitative or quantitative composition of the container.
2. The variation does not concern a fundamental part of the packaging material, which affect the delivery, use, safety or stability of the finished product.
3. In case of an variation in the headspace or an variation 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the

M C8 FORM (including description, detailed drawing and composition of the container or closure material).

2. 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 M CAZ if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).
3. Samples of the new container/closure.

34	**Variation 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	

34. Variation in the specification of the finished product

Conditions

1. The variation is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration of the product or a major variation procedure after registration).
2. The variation should not be the result of unexpected events arising during manufacture.
3. Any variation should be within the range of registered 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 MC8 FORM.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guidelines ICH Q2A[23] and ICH Q2B[24]).
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.

35	**Variation in test procedure of the finished Product**	Conditions to be fulfilled	Required Documentation	
a)	Minor variation to a registered test procedure	1, 2, 3, 4	1	**N**
b)	Other variations to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

35. Variation in test procedure of the finished product

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.
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 M C8 FORM or MCAZ CTD Guidelines, 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 registered test and the proposed one are at least equivalent (please refer to guidelines ICH Q2A[25] and ICH Q2B[26]).

36	**Variation or addition of imprints, embossing 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	Required Documentation	
		1, 2	1, 2	**N**

[23] ~~ICH Q2A: Note for Guidance on Va~~lidation of Analytical Methods: (CPM P/IC H/381/95) [www.emea.eu.int/pdfs/human/ich/0381 95en.pdf]

[24] ICH Q2B: Note for Guidance on Validation of Analytical Procedures: (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

[25] ICH Q2A: Note for Guidance on Validation of Analytical Methods: (CPM P/IC H/381/95) [www.emea.eu.int/pdfs/human/ich/0381 95en.pdf]

[26] ICH Q2B: Note for Guidance on Validation of Analytical Procedures: (CPM P/IC H/281/95) [www.emea.eu.int/pdfs/human/ich/0281 95en.pdf]

36. Variation or addition of imprints, embossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking

Conditions

1. Finished product release and end of shelf life specifications have not been amended (except for appearance).
2. Any ink must comply with the relevant section on excipients of the Guideline on Submission of Documentation of applications for registration of medicine.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the M C8 FORM (including a detailed drawing or written description of the current and new appearance).

2. Submit a sample of the product.

37	**Variation of dimensions of tablets, capsules, suppositories or pessaries without variation in qualitative or quantitative composition and mean mass**	Conditions to be fulfilled	Required Documentation	
a)	Gastro-resistant, immediate release tablets, modified or prolonged release	1, 2	1, 2, 3, 4, 5	
b)	All pharmaceutical forms capsules, suppositories and pessaries	1, 2	1, 4	**N**

37. Variation of dimensions of tablets, capsules, suppositories or pessaries without variation in qualitative or quantitative composition and mean mass

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 amendmed (except for dimensions).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the M C8 FORM or CTD Guidelines (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 MCAZ Guideline on Bioequivalence.
3. Justification for not submitting a new bioequivalence study according to the current M CAZ-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.
6.

38	**Variation in pack size of the FPP**	Conditions to be fulfilled	Required Documentation	
a)	Variation in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1.	Variation within the range of the registered pack sizes	1, 2	1, 3, 4	**N**
2.	Variation outside the range of the registered pack sizes	1, 2	1, 2, 3,4	

3. Variation to the registered pack size	1, 2	1, 2, 3,4	
b) Variation in the fill weight/fill volume of non-parenteral multidose products	1, 2	1, 2, 3,4	

38. Variation in pack size of the FPP

Conditions

1. New pack size should be consistent with the posology and treatment duration as in the approved package insert.
2. The primary packaging material remains the same.

Documentation

1. Submit updated Appendix I, page 2 of the M C8 Form.
2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as in the approved package insert.
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).
4. Sample of the proposed pack size and packaging

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

39. Variation in Shelf life or Storage conditions of the finished product or the diluted/reconstituted product

Conditions

1. Stability studies have been done according to the registered protocol. The studies must show that the agreed relevant specifications are still met.
2. The variation 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 M C8 FORM. Replaced pages must contain results of appropriate real time stability studies conducted in accordance with the relevant stability guidelines on at least *three* production scale batches of the finished product in the registered packaging material and/or after first opening or reconstitution, as

appropriate; where applicable, results of appropriate microbiological testing should be included as well as an indication of the approved pack sizes

2. Copy of registered release and end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.
3. Copy of current medicine registration certificate

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	Documentation to be supplied	
a)	Addition or replacement	1, 2	1, 2, 3	**N**
b)	Deletion	3		

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

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the registered 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 as listed in the M C8 FORM (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.

APPENDIX I

1. Variation in the name and/or address of the applicant or principal
2. Variation in the name of the Medicine or Finished Pharmaceutical Product (FPP)
3. Variation 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
4. Variation in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP)
5. 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)
6. 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
7. 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 registered manufacturer and registered manufacturing process
8. Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient
9. Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient
10. Variation 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, variation of needle shield (different plastic used)
11. Variation or addition of imprints, embossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking
12. 12.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)

APPENDIX II

1. variationvariationvariationvariationvariationVariationVariationVariationReplacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP

2. Variation to quality control testing of the finished product
3. Variation in the manufacturing process of the API
4. Variation in batch size of API or intermediate
5. Variation in the specification of an API, a starting chemical material/ intermediate/reagent used in the manufacturing process of the API
6. Variation in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API
7. Variation in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the API
8. Variation in retest period and storage conditions for the API
9. Replacement of an excipient with a comparable excipient
10. Variation in specification of an excipient
11. Variation in test procedure for an excipient
12. Variation in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material
13. Variation to comply with a major international pharmacopoeia (BP, PhInt, JP , PhEur, USP)
14. Variation in the specifications of the immediate packaging of the finished product
15. Variation to a test procedure of the immediate packaging of the finished product
16. Variation in the qualitative and/or quantitative composition of the immediate packaging material
17. Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); excluding spacer devices for metered dose inhalers
18. Variation to in-process tests or limits applied during the manufacture of the product
19. Variation in the batch size of the finished product
20. Variation in the manufacture of the finished product
21. Variation in the colouring system or the flavouring system currently used in the finished product
22. Variation in coating weight of tablets or variation in weight of capsule shells
23. Variation in shape or dimensions of the container or closure

24. Variation in the specification of the finished product
25. Variation in test procedure of the finished product
26. Variation of dimensions of tablets, capsules, suppositories or pessaries without variation in qualitative or quantitative composition and mean mass
27. Variation in pack size of the FPP
28. Variation in Shelf life or Storage conditions of the finished product or the diluted/reconstituted product

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

APPENDIX III

Variations that make a new application necessary

Variations that make a new application necessary consist of:

Variations to the API:

Variation of the API to a different API
Inclusion of an additional API to a multi-component product
Removal of one API from a multi-component product
Variation in the dose of one or more APIs

Variations to the pharmaceutical form/dosage form

Variation from an immediate release product to a slow- or delayed-release dosage form and vice versa
Variation from a liquid to a powder for reconstitution, or vice versa

Variations in the route of administration

APPENDIX IV

Stability requirements for variations and variations to registered FPPs

This Appendix outlines the stability data which have to be generated in case of am endm ents.

The scope and design of stability studies for variations should be based on the knowledge and experience acquired on A PIs 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 to the registered medicines, the applicant has to investigate whether or not the intended variation will have an impact on the quality characteristics of A PIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Appendix document refers to the *Guideline on stability testing of medicines* .

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 M CAZ should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

Minor variations:

In cases of minor variations as listed in Appendix 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 Appendix I. The results of these studies covering the requested time period as defined in Appendix 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 variation 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 variations:

In cases of major variations the following are widely encountered examples: Variation in

the manufacturing process of the API

Variation in composition of the FPP

Variation of immediate packaging of the FPP

Variation in the manufacturing process of the API

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are amended 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 variation:

APIs known to be stable[27]	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 amended in such a way that it may impac 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 product

Variation 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, 6 months duration, long term and accelerated testing conditions on two pilot scale batches[28] are required.

For critical dosage forms (e.g. prolonged release form) or when the API is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.

Variation 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.

[27] **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 variation in the manufacturing process.

[28] 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

COMMITMENT BATCHES:

Minor variations

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

Major variations

For all major variations that require the generation of stability data on the FPP, at least the first production scale batch manufactured according to the registered 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 MCAZ 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.

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 Harmonization International

PhInt: International Pharmacopeia

JP: Japanese Pharmacopoeia

NDRA: National Drug Regulatory Authority

OoS: Out of specification (outside specification)

PhEur: Pharmacopoeia Europa (European Pharmacopoeia)

USP: United States Pharmacopoeia

WEB-LINKS

Guideline on dossier requirements for type IA and IB notifications July 2003"
http://pharmacos. eudra.org/F2/eudralex/vol-2/C/GdVarTypIAB_rev0_20030 7.pdf

Pharmaceutical Quality Information Form (MC8 FORM) ***http:/www.mcaz.co.zw/MC8.pdf***

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/documents/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAn nexes.pdf

WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-fourth report, 1996: 114-154 (WHO Technical Report Series, No.863)" and Good Clinical Practices
http://whqlibdoc.who. int/trs/WHO_TRS_863_(p99-p194).pdf

Note for Guidance on Validation of Analytical Procedures: Methodology (CPMP/ICH/281/95) *http://www. emea.eu. int/pdfs/human/ich/028195en.pdf*

Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPMP/ICH/381/95)

http://www. emea.eu. int/pdfs/human/ich/038195en.pdf

Note for Guidance on 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. emea.eu. int/pdfs/human/ich/029595en.pdf

Note for Guidance on 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. emea.eu. int/pdfs/human/ich/013995en.pdf

Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (CPMP/ICH/138/95)

http://www. emea.eu. int/pdfs/human/ich/013895en.pdf

Note for Guidance on Quality of Biotechnicological Products: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products (CPMP/ICH/294/95)

http://www. emea.eu. int/pdfs/human/ich/029495en.pdf

Note for Guidance on Biotechnological/Biological Products Subject to variations in their Manufacturing Process (CPMP/ICH/5721/03)

http://www. emea.eu. int/pdfs/human/ich/572103en.pdf

Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96)

http://www. emea.eu. int/pdfs/human/ich/036596en.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 (EM EA /410/01 rev 2)

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

Good manufacturing practices for Pharmaceutical Products: Main principle. Annex 4, WHO Technical Report Series 908, 2003 *http://whqlibdoc.who. int/trs/ WHO_TRS_908.pdf#page= 46*

Note or Guidance on Stability Testing of New Drug Substances and Products (ICH Q1A (R2), CPMP/ICH/2736/99)

http://www. emea.eu. int/pdfs/human/ich/23699en.pdf