



GUIDELINES ON THE SUBMISSION OF APPLICATIONS FOR
REGISTRATION IN COMMON TECHNICAL DOCUMENT (CTD)
FORMAT

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1.0 APPLICATION

This guideline applies to all pharmaceutical manufacturers, applicants and regulatory assessors involved in the preparation, submission, evaluation and review of applications for registration of medicines.

2.0 PREAMBLE

This guideline is issued by the Medicines Control Authority of Zimbabwe (MCAZ) to provide the current regulatory framework for the submission of medicine registration applications in the Common Technical Document (CTD) format.

It replaces the MCAZ Guideline on Submission of Documentation for Registration of a Multisource (Generic) Finished Pharmaceutical Product: Quality Part in the Common Technical Document Format, approved in August 2012 and implemented in March 2013. The replaced guideline established the CTD format as the only accepted format for submission of applications for registration of finished pharmaceutical products from March 2013.

3.0 PURPOSE

The purpose of this document is to formalize MCAZ's adoption and implementation of submission requirements for Applications for Registration in Common Technical Document Format: Quality (WHO TRS 986 Annex 6 and ICH M4Q). It informs applicants and assessors of the standards to be applied during product registration.

4.0 ADOPTION STATEMENT

MCAZ formally adopts Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part: Annex 6, WHO Technical Report Series, 986, 2014 and the Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality, Quality Overall Summary of Module 2, Module 3: Quality ICH Harmonised Tripartite Guideline (ICH M4Q).

The source guidelines are accessible at:

1. <https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs986-annex6.pdf>
2. https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf

5.0 RATIONALE FOR ADOPTION

To ensure that the MCAZ standards are aligned with international standards and state-of-the-art scientific practices. Adopting international standards such as WHO and ICH reduces duplication of studies, promotes information exchange among the regulators, including reliance, more efficient assessment, aligns the region with global standards, and ultimately increases the availability of medicines to the public. ICH M4Q applies broadly to new chemical entities, biotechnology-derived products, and generics, thereby covering the full spectrum of medicinal products relevant to MCAZ, while WHO TRS 986 Annex 6 provides specific guidance and further clarification for multisource (generic) pharmaceutical products. The intended benefits of adopting the WHO TRS 986 Annex 6 and ICH M4Q are in line with the MCAZ agenda. derived products, and generics, thereby covering the full spectrum of medicinal products relevant to -derived products, and generics, thereby covering the full spectrum of medicinal products relevant to

6.0 SCOPE

This guideline outlines the requirements for the preparation and submission of dossiers in the Common Technical Document (CTD) format, specifically addressing the structure and presentation of the quality section of a product dossier. It provides detailed specifications on the format and content of applications for the registration of drug substances and their corresponding drug products of synthetic, semi-synthetic, or biotechnological origin. The document reflects the current position of the MCAZ regarding quality-related expectations for product dossiers.

7.0 VALIDITY

This document is valid from the effective date of adoption. It will be reviewed when required, but not later than 3 years from the effective date. In case of revision or updates to the source guideline(s), the latest version(s) automatically applies, unless a specific transition period is specified by MCAZ.

8.0 ANNOTATIONS/NOTES

The following guidelines provide detailed supplementary information on regulatory requirements specific to the MCAZ.

3.2.S DRUG SUBSTANCE/ ACTIVE PHARMACEUTICAL INGREDIENT (NAME, MANUFACTURER)

Active Pharmaceutical Ingredient (API) Information Submission Options

In alignment with international practices and considering the framework outlined in WHO Technical Report Series (TRS) No. 986, Annex 6, MCAZ requires that full (complete) information (**open part and restricted part**) on all active pharmaceutical ingredients (APIs) be available to support product dossiers. For reliance purpose, the applicants may select from the following recognized review pathways for API information, if applicable:

- i. **Submission of a Confirmation of API Prequalification document (CPQ); or**
- ii. **Submission of a Certificate of Suitability (CEP).**

Option 3: Confirmation of API Prequalification document (CPQ).

The following information is added for the applicant to include in the dossier, with data summarized in the QOS:

- i. 3.2.S.2.1 Manufacturer(s)- All sites involved in the manufacture of the substance covered by the CPQ after the introduction of the starting material(s), including quality control and in process testing sites, should be listed in this section.
- ii. 3.2.S.5 Reference standards or materials – The information on reference standards should include API reference standards and impurity standards.

Option 4: Certificate of Suitability of the European Pharmacopoeia (CEP)

The following information is added for the applicant to include in the dossier, with data summarized in the QOS:

- i. 3.2.S.2.1 Manufacturer(s)- All sites involved in the manufacture of the substance covered by the CEP after the introduction of the starting material(s), including quality control and in process testing sites, should be listed in this section.
- ii. 3.2.S.5 Reference standards or materials –The information on reference standards should include API reference standards and impurity standards.

3.2.S.1.3 General Properties (name, manufacturer)

The interpretation in the calculation of the dose solubility volume of “largest dosage strength” means the largest single therapeutic dose in line with the determination of high or low solubility according to BCS classification.

Reference: WHO TRS 1019, Annex 4.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)***Recovery solvents:***

At the time of submission, if applicable where there is use of recovered of solvents, the applicant should justify the proposed ratio of recovered to fresh solvents on the basis of quality data for three API batches or downstream intermediates, manufactured with all recovered solvents at the proposed maximum ratio of recovered solvents to fresh solvents. In Section 3.2.S. the specifications for the recovered solvents should include control of residue on evaporation/non-volatile matter and the corresponding certificates of analysis of recovered solvents used to manufacture the profiled API batches and/or the downstream intermediate batches should be provided demonstrating compliance to and suitability of the proposed specifications.

Unless the specifications of the recovered solvent used in the manufacturing process final step or purification are more stringent than the specification of the fresh solvent, the use of recovered solvents in the final step or purification is not recommended.

Particle size reduction:

If the process is atypical (other than jet milling), the type of equipment used, and process parameters should be described.

3.2.S.3.2 Impurities (name, manufacturer)

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) for antibiotics are outlined in the EMA Guideline on setting specifications for related impurities in antibiotics.

For establishing limits for highly toxic impurities (genotoxic and carcinogens) used in the process or formed as a by-product, the applicant should use available guidance's such as the ICH M7, EMA Nitrosamine impurities in human medicines and WHO TRS 1060, Annex 2: WHO good practice considerations for the prevention and control of nitrosamines in pharmaceutical products. Other equivalent guidelines may also be considered.

With regards to control of potential contamination of the API with benzene or other class I solvents, applicants are expected to include testing as a routine parameter in API specifications. Where omission or skip testing is proposed, a clear scientific justification must be provided upfront, and specific criteria should be selected in line with the requirements of the relevant guidelines and risk-management principles.

3.2.S.7.1 Stability Summary and Conclusion (name, dosage form)

Regarding the requirement for stability data for the drug substance, MCAZ requires that 12 months' long-term and 6 months' accelerated stability data be made available at the time of submission in the new registration application to facilitate allocation of retest period or shelf-life.

**3.2.P. DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP)
(NAME, DOSAGE FORM****3.2.P.2 Pharmaceutical Development (name, dosage form)*****3.2.P.2.2.1 Formulation Development (name, dosage form)******In vitro dissolution or drug release:***

Applicants should describe the development of the dissolution method, including understanding the properties of the drug substance and drug product, evaluating sink conditions, and optimizing the dissolution conditions. Adoption of pharmacopoeia methods or methods described in the OGD are considered acceptable; however, applicants must justify the appropriateness of these methods for their formulation including discriminatory nature. In addition to the data required for formulation development (as prescribed in the guidelines), applicants are expected to provide the actual experimental data supporting the selected dissolution method.

In addition to the requirements specified in Appendix 1 of the WHO TRS 986 annex 6, the in vitro dissolution profiles for the biobatch in the standard buffer media at pH 1.2, 4.5, and 6.8, should be conducted using either the paddle apparatus at 50 rpm or the basket apparatus at 100 rpm.

3.2.P.3.5 Process validation and/or evaluation (name, dosage form)

In addition to submission of process validation protocol, the applicant should provide results of process validation studies in a form of comprehensive process validation reports for all product strengths and orientations, in line with the requirements of the guideline.

Process validation protocols for prospective production scale batch sizes would be considered upon evidence of satisfactory validation of three pilot scale batches of the product.

Process validation report should be derived from minimum of three consecutive batches, including the biobatch (representative biobatch). It is the responsibility of the applicant to justify consecutive manufacture of batches submitted under manufacturing process validation by providing the batch numbering SOP.

For common blends, validation of relevant critical steps should be demonstrated using a minimum of three identified consecutive lots/batches of the blend.

At the time of submission, the process validation report should include results of multi point comparative dissolution profiles of validation batches against the batch(es) used in the clinical, bioavailability or biowaiver studies in routine QC medium. Results should be provided for individual units and average results, including % RSD and demonstrated calculation of similarity factors, where applicable.

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form) and 3.2.P.4.2 Analytical procedures

At the time of submission, specifications and analytical procedures for all excipients, irrespective of the standard claimed, should be included in the Product Dossier.

For excipients with a potential risk of contamination with diethylene glycol (DEG) or ethylene glycol (EG), applicants should control such excipient(s) in line with the relevant international guidance documents. These include:

- i. *EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Glycerol and other excipients at high-risk of DEG/EG contamination.*
- ii. *USFDA Guidance on Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol.*
- iii. *The Officially recognized Pharmacopoeia for testing DEG/EG.*

3.2.P Control of Drug Product/ Finished Pharmaceutical Product (name, dosage form)

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

For establishing limits for highly toxic impurities (genotoxic and carcinogens) used in the process or formed as a by-product, the applicant should use available guidance's such as the ICH M7, EMA Nitrosamine impurities in human medicines and WHO TRS 1060, Annex 2: WHO good practice considerations for the prevention and control of nitrosamines in pharmaceutical products. Other equivalent guidelines may also be considered.

3.2.P8.1 Stability Summary and Conclusion (name, dosage form)

Stability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in Zimbabwe. Zimbabwe falls into climatic zone IV (studies in climatic zone IVa and IVb are both acceptable. (Refer to WHO Technical Report Series, No. 953, Annex 2, Appendix 1 for information on climatic zones).

Regarding the requirement for stability data for all product types, MCAZ requires that at least 12 months' long-term and 6 months' accelerated stability data is made available at the time of submission in the new registration application to facilitate allocation of shelf-life.

At the time of submission, accelerated and long-term stability data older than five years should be supplemented with recent long-term stability data (covering at least 12 months and not older than five years) from a minimum of three batches, generated under the annual stability program in accordance with the established protocol.

9.0 ADDITIONAL QUALITY REQUIREMENTS FOR SPECIFIC PRODUCT CATEGORIES

Additional quality requirements for other categories of products, such as biologicals and vaccines, are outlined in specific MCAZ guidelines. Applicants should consult those guidelines in conjunction with the requirements specified in this guideline.

10.0 DOCUMENTATION

The Applicant should ensure that the Product Dossier (PD) is accompanied by the current versions of both the QOS and QIS (MS Word format) fully populated by the Applicant.

Applicants are advised to consult the MCAZ guideline on submission of applications for registration for further details on information required to accompany the PD.

11.0 DISCLAIMER

All guidelines adopted/adapted by MCAZ from international organizations such as WHO, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) must be read in conjunction with the current, applicable MCAZ guidelines.

MCAZ reserves the right to request additional information in keeping with the knowledge current at the time of evaluation. It is not intended as an exclusive approach as alternative approaches may be used but should be scientifically and technically justified.

12.0 ADDITIONAL REFERENCES TO THE QUALITY GUIDELINES.

In addition to the main guidelines, the following topic-specific guidelines are considered fully adopted. Applicants are advised to consult the respective Questions and Answers for further clarity

1. ICH Q1A(R2) Stability Testing of New Drug Substances and Products
<https://www.ich.org/page/quality-guidelines>
2. ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products
<https://www.ich.org/page/quality-guidelines>
3. ICH Q1C Stability Testing for New Dosage Forms Annex to the ICH Harmonised Tripartite Guideline on Stability Testing for New Drugs and Products
<https://www.ich.org/page/quality-guidelines>
4. ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
<https://www.ich.org/page/quality-guidelines>
5. ICH Q1E Evaluation for Stability Data
<https://www.ich.org/page/quality-guidelines>
6. ICH Q1 Stability Testing of Drug Substances and Drug Products
<https://www.ich.org/page/quality-guidelines>
7. TRS 953 - Annex 2, Appendix 1: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products: Stability conditions for WHO Member States by Region
<https://www.who.int/publications/m/item/trs953-annex2-appendix1>
8. ICH Q14 Analytical Method Development
<https://www.ich.org/page/quality-guidelines>
9. ICH Q2(R2) Validation of Analytical Procedures
<https://www.ich.org/page/quality-guidelines>
10. ICH Q3A(R2) Impurities in New Drug Substances
<https://www.ich.org/page/quality-guidelines>
11. ICH Q3B(R2) Impurities in New Drug Products
<https://www.ich.org/page/quality-guidelines>
12. ICH Q3C(R9) Impurities: Guideline for Residual Solvents
<https://www.ich.org/page/quality-guidelines>
13. ICH Q3D(R2) Guideline for Elemental Impurities

- <https://www.ich.org/page/quality-guidelines>
14. ICH Q3E Guideline for Extractables and Leachables (Draft)
<https://www.ich.org/page/quality-guidelines>
 15. EMA Guideline on setting specifications for related impurities in antibiotics
<https://www.ema.europa.eu/en/setting-specifications-related-impurities-antibiotics-scientific-guideline>
 16. ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline
<https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential-carcinogenic-risk-scientific-guideline>
 17. ICH Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
<https://www.ich.org/page/quality-guidelines>
 18. ICH Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
<https://www.ich.org/page/quality-guidelines>
 19. ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
<https://www.ich.org/page/quality-guidelines>
 20. ICH Q5D Derivation and Characterisation of Cell Substrates Used for the Production of Biotechnological/Biological Products
<https://www.ich.org/page/quality-guidelines>
 21. ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
<https://www.ich.org/page/quality-guidelines>
 22. ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
<https://www.ich.org/page/quality-guidelines>
 23. ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
<https://www.ich.org/page/quality-guidelines>
 24. EMA Guideline on setting specifications for related impurities in antibiotics
https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-guideline-setting-specifications-related-impurities-antibiotics_en.pdf
 25. EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action
<https://www.ema.europa.eu/en/dissolution-specification-generic-oral-immediate-release-products-scientific-guideline>
 26. ICH Q7 Good Manufacturing Practice
<https://www.ich.org/page/quality-guidelines>

27. TRS 986 - Annex 2: WHO good manufacturing practices for pharmaceutical products: Main principles Annex 2, WHO Technical Report Series 986, 2014
<https://www.who.int/publications/m/item/trs986-annex2>
28. TRS 970 - Annex 3: Pharmaceutical development of multisource (generic) finished pharmaceutical products: points to consider
[https://www.who.int/publications/m/item/pharmaceutical-development-of-multisource-\(generic\)](https://www.who.int/publications/m/item/pharmaceutical-development-of-multisource-(generic))
29. ICH Q11 Development and Manufacture of Drug Substances
<https://www.ich.org/page/quality-guidelines>

13.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Reason for Change and Amendments
0	April 2026	Reason for Change: To add the preamble Details of change Added Section 2.0 Preamble This guideline is issued by the Medicines Control Authority of Zimbabwe (MCAZ) to provide the current regulatory framework for the submission of medicine registration applications in the Common Technical Document (CTD) format. It replaces the MCAZ Guideline on Submission of Documentation for Registration of a Multisource (Generic) Finished Pharmaceutical Product: Quality Part in the Common Technical Document Format, approved in August 2012 and implemented in March 2013. The replaced guideline established the CTD format as the only accepted format for submission of applications for registration of finished pharmaceutical products from March 2013.