Update on new guidelines, DEG/EG contamination, and the use of new technologies

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WHO TRS 1044, 2022, 56TH ECSPP Report

1. **Annex 1**: Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations
2. **Annex 2:** WHO GMP for sterile pharmaceutical products
3. **Annex 3:** IAEA/WHO Guideline on GMP for Investigational Radiopharmaceutical products
4. **Annex 4:** WHO Guidelines on technology transfer in pharmaceutical manufacturing
5. **Annex 5:** WHO GMP for medicinal gases
6. **Annex 6:** WHO Good Practices for R&D facilities of pharmaceutical products

TRS 1044, Annex-6: Good practices for R&D facilities of pharmaceutical products

Annex 6

WHO good practices for research and development facilities of pharmaceutical products

Background

In view of the need for the development of health products, including research and development for the treatment of COVID-19 therapies, the World Health Organization (WHO) Prequalification Team – Inspection Services (PQT/INS) raised the urgency for the development of life cycle-appropriate good practices text to address the manufacturing of developmental batches, pilot batches and the sequential stability data that are submitted in product applications (dossiers) for marketing authorization and the prequalification of medical products.

There is currently no other specific WHO guideline that addresses this matter. The data collected from these batches influence the following aspects of the product:

- stability
- process validation
- analytical method development and validation.

Fig. 1
Application of this guideline

[a] The principles described in this guideline are applied, based on risk management principles, in an increased manner from early research to development to registration batches.

WHO TRS 1052, 2023, 57TH ECSPP Report

1. **Annex 1:** Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations
2. **Annex 2:** WHO good manufacturing practices for excipients used in pharmaceutical products
3. **Annex 3:** IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations
4. **Annex 4:** WHO good practices for pharmaceutical quality control Laboratories (GPPQCL)
5. **Annex 5:** WHO/UNFPA female condom generic specification
6. **Annex 6:** WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms
7. **Annex 7:** WHO guideline on Biopharmaceutics Classification System-based biowaivers.

TRS 1052, Annex-2: WHO GMP for excipients used in pharmaceutical products

- This document provides information on GMP that should be implemented to assist manufacturers to produce and control excipients used in pharmaceutical products that will meet their intended specifications, in a consistent manner.
- It is the responsibility of the finished product manufacturer and of the applicant to ensure that the finished product is manufactured using excipients of a suitable grade conforming to its intended use.
- Excipients should be of appropriate quality, as they could affect the safety, quality, and efficacy of finished pharmaceutical products.

TRS 1052, Annex-2: WHO GMP for excipients used in pharmaceutical products

The revised WHO GMP for excipients added the following contents to provide clear requirements such as:

- **Introduction and scope**
- **Quality management (QRM and MR)**
- **Complaints, recalls, returns**
- **Self-inspection, quality audits, and supplier audits/approval**
- **Personnel**
- **Sanitization and hygiene**
- **Premises, equipment and utilities**
- **Materials**
- **Production (rework and reprocessing)**
- **Qualification and validation**
- **Quality control**
- **Life cycle and continuous improvement principles**
- **Storage and distribution**

Annex 2

WHO good manufacturing practices for excipients used in pharmaceutical products

Background

The WHO guideline *Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients* was published in the WHO Technical Report Series No. 885, Annex 5, 1999.

As excipients are sometimes used in large quantities in pharmaceutical dosage forms, and may contain impurities, they can affect the quality of a finished pharmaceutical product.

The manufacturer of the finished pharmaceutical product is normally dependent on the excipient manufacturer to supply excipients meeting the required specification. An appropriately established and implemented quality management system evaluating and controlling risks in the production and quality control of such excipients is therefore required.

Excipient manufacturers should be required to apply the appropriate principles of good manufacturing practices (GMPs) in producing pharmaceutical excipients. Reports of pharmaceutical products that contain contaminated excipients, or excipients with impurities leading to the death of patients,

TRS 1052, Annex-2: WHO GMP for excipients used in pharmaceutical products

Appendices

Note: The following appendices to the *WHO good manufacturing practices for excipients used in pharmaceutical products* will be developed and included:

Appendix 1. Points to consider document focusing on a risk management-based approach for excipients with possible impurities.

Appendix 2. List of high-risk excipients (for example, considering contamination with diethylene glycol, ethylene glycol, nitrosamines).

Test for DEG and EG in International Pharmacopoeia

Working document QAS/23.922/rev4
17 July 2024

World Health Organization

TESTS FOR DIETHYLENE GLYCOL AND ETHYLENE GLYCOL IN LIQUID PREPARATIONS FOR ORAL USE

Chapter for inclusion in *The International Pharmacopoeia*

(17 July 2024)

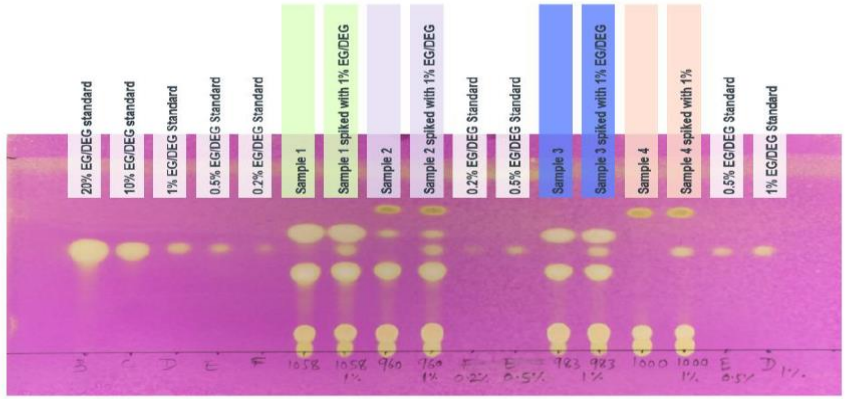

Image 4. Typical chromatograms obtained with EG/DEG reference solutions and samples (without DEG/EG and spiked with 1% DEG/EG).

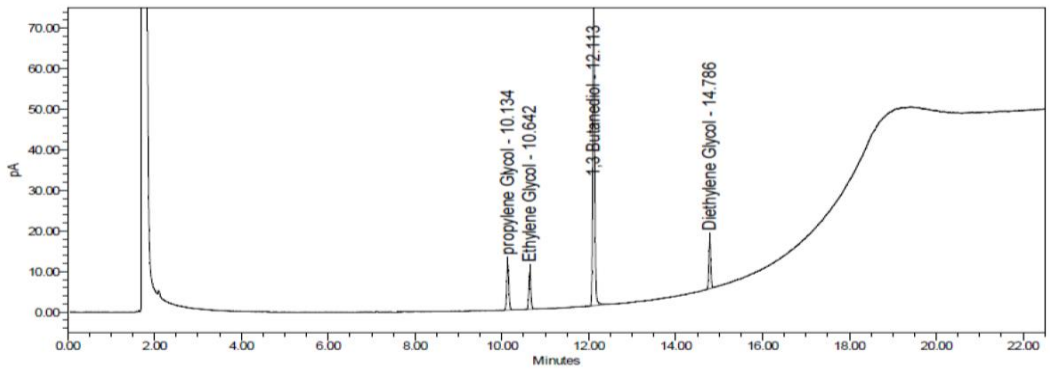

Image 5. Typical chromatogram obtained with solution (G).

High-level overview of the changes in the WHO GPPQCL (2010 Versus 2024), TRS 1052, Annex 4

Section	2010 Version Details	2024 Version Details	Impact of Changes
Organization and Management System	Organization and management, Quality management system, Control of documentation, Records, Data-processing equipment, Personnel, Premises, Equipment, instruments, and other devices, Contracts.	Structural and general requirements, Quality management system, Control of documentation, Change control, Control of records, Control of data, Corrective and preventive actions, Internal audits, Complaints, Management review, Improvement.	**Expanded with more detailed** data integrity, change control, reagents, and management practices. **Reorganization:** personnel, premises, equipment, instruments, and other devices moved to **"Resources" section.**
Planning and Strategic Management	Not present	Externally provided services and supplies, Review of tenders and contracts, Performance management, Quality risk management, Crisis management, Communication management.	**New section enhances strategic management and planning capabilities.**
Resources	Personnel, Premises, Equipment, instruments, and other devices, Reagents, Reference substances and reference materials.	Personnel, Premises, Equipment, instruments, and other devices, **Reagents and materials**, Reference substances and reference materials.	Detailed information in the respective sections.
Technical Activities	Incoming samples, analytical worksheet, calibration, verification of performance and qualification of equipment, instruments and other devices, validation of analytical procedures, Testing, Evaluation of test results, certificate of analysis, Retained samples, traceability.	**Sampling,** Incoming samples, Selection, validation, and verification of analytical procedures, Technical records, Testing, Evaluation of test results, **Measurement uncertainty**, Validity of test results, **Out-of-specification results,** Reporting of results, **Nonconforming work**, Retained samples.	Detailed sub-sections on measurement uncertainty, OOS and validity improve technical precision.
Safety Rules	General rules	General rules	Include more detailed or updated safety protocols.
Appendices	Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory.	Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory, **Recommendations for the target uncertainty and the maximum permissible uncertainty for normal analytical practice, Examples of the uncertainty estimation for compliance with normal analytical practice.**	**New appendices provide additional guidance on uncertainty and examples of compliance.**

Potential impact of revised WHO TRS 1052, Annex-4, GPPQCL

Laboratory operations will not be severely hindered in general. However, adapting the QMS to meet the new requirements will be necessary, and a change control plan will need to be established. Also:

- Risk management plans **to be updated.**
- Measurement uncertainty provisions **to be put in place.**
- Performance management, communication management, and crisis management, **if not already in place, should be addressed.**
- Procedures for handling nonconforming work **to be established or updated** to ensure proper documentation and corrective actions.

Current thinking

Continuous manufacturing: QAS/24.957_WHO Points to consider in continuous manufacturing of pharmaceutical products

- ✓ Introduction (background and scope)
- ✓ Glossary
- ✓ Challenges in continuous manufacturing
- ✓ Good Practices considerations
- ✓ Risk management
- ✓ Control strategy
- ✓ Process dynamics
- ✓ Computerized systems
- ✓ Validation and verification
- ✓ Stability testing

Current thinking

Points-to-consider/Reflection paper on Artificial Intelligence in Pharmaceutical Manufacturing
Guideline on the design of QCL
WHO good manufacturing practices for pharmaceutical products: Main principles
WHO guidelines for sampling of pharmaceutical products and related materials (Annex 4, TRS 929, 2005)
WHO good practices for pharmaceutical microbiology laboratories (Annex 2, WHO Technical Report Series 961, 2011)
WHO guidelines for preparing a laboratory information file, Annex 13, WHO Technical Report Series 961, 2011


Thank You