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World Health Organization

WHO Drug Information

WHO Drug Information provides an overview of topics relating to medicines development, regulation, quality and safety. The journal also publishes and reports on guidance documents and includes lists of International Nonproprietary Names for Pharmaceutical Substances (INN), ATC/DDD classification and monographs for The International Pharmacopoeia. It presents and describes WHO policies and activities while reflecting on technical and pharmaceutical topics of international and regional interest.

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Abbreviations and websites

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency (www.ema.europa.eu)
EU	European Union
FDA	U.S. Food and Drug Administration (www.fda.gov)
Health Canada	Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA	Health Products Regulatory Authority, Ireland (www.hpra.ie)
HSA	Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP	International Generic Drug Regulators Programme (https://www.igdrp.com)
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe	New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int	*The International Pharmacopoeia* (http://apps.who.int/phint/)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic	Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA	Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S.	United States of America
WHO	World Health Organization (www.who.int)
WHO MHP	WHO Access to Medicines and Health Products Division (www.who.int/medicines/en/)
WHO RPQ	WHO Regulation and Prequalification Department
WHO PQT	WHO Prequalification Unit (https://www.who.int/topics/prequalification/en/)
WHO HPS	WHO Health Product Policy and Standards Department

Note: The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and websites referenced

WHO
External Quality Assurance Assessment Scheme
Phase 9

INTRODUCTION

The participation of Pharmaceutical Quality Control Laboratories (PQCLs) in appropriate proficiency testing schemes is an internationally recognised requirement[1&2] as this enables the PQCL to demonstrate, monitor and improve the quality of the analytical services provided. Proficiency testing covers the overall performance of a laboratory, evaluating the process from the reception and storage of samples, the experimental work in the laboratory, the interpretation and the transcription of the data and the conclusions to the reporting sheets. Failure at any of these stages also reflects on the competence of the respective laboratory.

In support of PQCLs, the World Health Organization (WHO) offers proficiency testing through its External Quality Assurance Assessment Scheme (EQAAS) which offers a platform for PQCLs to measure their performance through a confidential system of blind testing. Since 2000, the EQAAS is organized by WHO with the assistance of the European Directorate for the Quality of Medicines and HealthCare (EDQM).

This proficiency testing scheme also serves to demonstrate the reliability of laboratory analytical results by objective means; thereby fostering the establishment of mutual confidence/recognition within collaborating networks, promoting work sharing based on reliance, especially in countries with limited or no quality control testing capabilities.

The EQAAS is facilitated in accordance with the International Organization for Standardization and International Electrotechnical Commission (ISO/IEC) standards for proficiency testing (i.e. ISO/IEC 17043:2010). This Scheme has entered its tenth phase period in 2020. Laboratories across WHO's six regions have participated in the past comparative external assessment studies and more than 1 100 studies involving 33 different tests were carried out.

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DESCRIPTION OF EQAAS PHASE 9

During EQAAS Phase 9, laboratories were provided with the opportunity to evaluate their performance with regards to three procedures using mebendazole chewable tablets as a common test sample (as depicted in Figure 1).

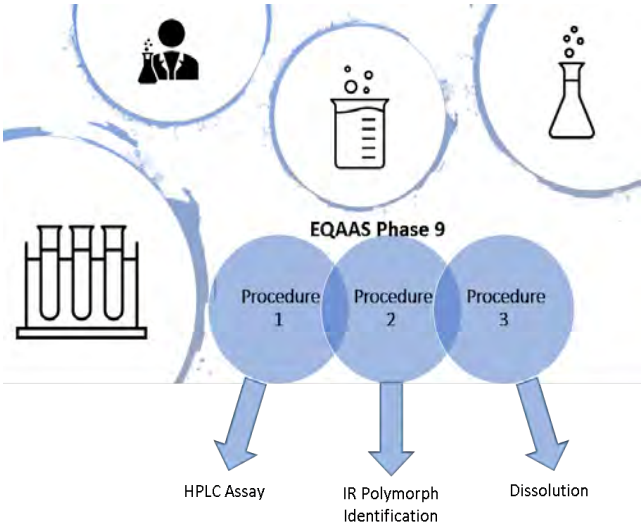

Figure 1: Schematic presentation of analytical procedure bouquet incorporated into EQAAS Phase 9.

- **Procedure 1:** the aim of this procedure was to assess the performance of the laboratory with regards to the determination of the assay by liquid chromatography. Laboratories were requested to determine (in triplicate) the percentage content of mebendazole in mebendazole chewable tables using the liquid chromatography method from the monograph on mebendazole chewable tablets of *The International Pharmacopoeia.*
- **Procedure 2:** the aim of this procedure was to assess the performance of the laboratories with regards to the identification by Infrared Absorption Spectrophotometry. Laboratories were requested to confirm the polymorphic form of mebendazole present in mebendazole chewable tablets through infrared absorption spectrophotometry; and
- **Procedure 3:** the aim of this procedure was to assess the performance of laboratories with regard to the performance of a dissolution test. Laboratories were requested to carry out the dissolution test and to determine the percentage of mebendazole released at 60 minutes from mebendazole chewable tablets, according to the monograph of *The International Pharmacopoeia* published by WHO.

STATISTICAL METHODS

For procedures 1 and 3, the following approaches applied: Different approaches may be adopted to assign the content of the analyte in the samples. The methods commonly applied in the WHO EQAAS operated in accordance with the Proficiency Testing Scheme developed by the EDQM are the use of a theoretical value or the addition of a known quantity of the analyte to the sample ("true" value) confirmed in the feasibility study or the use of a consensus value based on the results from the participants. To determine the consensus value, robust statistics are generally applied (e.g. the median value, mean interquartile range, Huber's robust mean) to avoid the influence of "outliers" on the overall mean.

The target standard deviation is set based on experience, or on the reported or expected precision of techniques, and according to fitness for purpose.

Assigned value

The assigned values used in this study are the consensus values obtained when calculating the Huber's robust mean. Table 1 provides a summary of the consensus values and the values obtained during the feasibility studies.

Table 1: Summary of consensus values and feasibility study values for procedures 1 and 3

	Consensus Value	Feasibility Value
Procedure 1: Mebendazole Assay	99.25%	99.2%
Procedure 3: Mebendazole Dissolution	69.0%	72.8%

Target standard deviation

The target values for the standard deviation (TSD) for procedures 1 and 3 are summarized in Table 2.

Table 2: The target values for the standard deviation (TSD) for procedures 1 and 3

	Target value for TSD
Procedure 1: Mebendazole Assay	0.8%
Procedure 3: Mebendazole Dissolution	3.5%

The target value for the TSD for the assay values took into account the variability between the mean results, calculated at the EDQM on the basis of the individual values reported by the participants.

The uncertainty of the assigned value was found to be negligible compared with the defined TSD and can be ignored in the interpretation of the performance scores.

Scoring

The z-score gives a bias estimate of the result. Absolute z-scores less than 2 are acceptable. A zone of doubtful performance exists for absolute z-scores between 2 and 3. Those do not necessarily have to be unacceptable since there is some uncertainty how close the consensus value is to the true value. An absolute z-score of 3 or more can be interpreted as an unacceptable performance.
Corrective actions should also be triggered when z-scores are frequently in the doubtful zone. For the purposes of this exercise, the calculation of a z-score has then been made for each