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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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International Nonproprietary Names (INN)

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)
INN	International Nonproprietary Names
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/)
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)
WHO	World Health Organization (www.who.int)
WHO MHP	WHO Access to Medicines and Health Products Division (https://www.who.int/our-work/access-to-medicines-and-health-products)
WHO RPQ	WHO Regulation and Prequalification Department (https://www.who.int/teams/regulation-prequalification)
WHO PQT	WHO Prequalification Unit (https://extranet.who.int/pqweb)
WHO HPS	WHO Health Product Policy and Standards Department (https://www.who.int/teams/health-product-policy-and-standards)

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WORLD HEALTH ORGANIZATION

External Quality Assurance Assessment Scheme

Phase 10

Marius Brits (Marius.Brits@nwu.ac.za)[1], Steve Estevão Cordeiro (estevaos@who.int)[2]

[1] North-West University, Faculty of Health Sciences, School of Pharmacy, Potchefstroom, South Africa

[2] Norms and Standards for Pharmaceuticals, Health Products Policy and Standards Department, World Health Organization, Geneva, Switzerland

INTRODUCTION

Pharmaceutical Quality Control Laboratories (PQCLs) demonstrate, monitor and improve the quality of their analytical services by participating in appropriate proficiency testing schemes. Participation in these proficiency testing schemes is an internationally recognised requirement.[1&2] The value of proficiency testing lies therein that it covers the overall performance of a laboratory in that it evaluates the process from sample reception, storage thereof, the experimental work in the laboratory, processing of data, interpretation of results and the conclusions to the reporting sheets. Failure at any of these stages thus reflects on the competence of the PQCL.

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. The EQAAS is organized by WHO with the assistance of the European Directorate for the Quality of Medicines and HealthCare (EDQM) since 2000.

The EQAAS serves to also 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 1232 studies involving 36 different tests were carried out to date.

DESCRIPTION OF EQAAS PHASE 10

During EQAAS Phase 10, laboratories were provided with the opportunity to evaluate their performance with regards to three procedures using zinc sulfate tablets and zinc salts (acetate and sulfate) as common test samples as depicted in Figure 1.

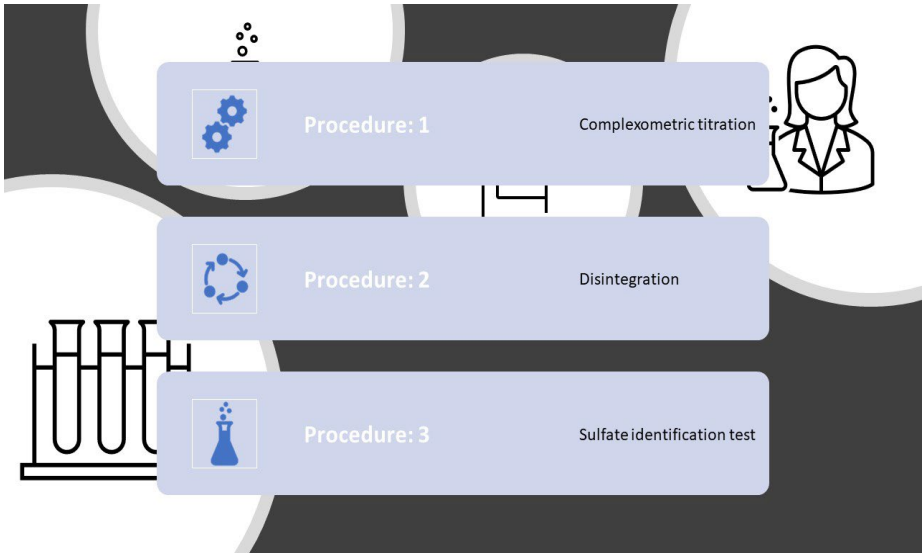

Figure 1: Schematic presentation of analytical procedure bouquet incorporated into EQAAS Phase 10.

- **Procedure 1:** The aim of this procedure was to assess the performance of the laboratories with regards to the determination of the zinc content by complexometric titration. Laboratories were requested to determine (in triplicate) the percentage content of zinc in the tablets, according to the monograph on Paediatric zinc sulfate tablets and general method 2.5 Complexometric titrations of *The International Pharmacopoeia* published by WHO.
- **Procedure 2:** the aim of this procedure was to assess the performance of the laboratories with regards to disintegration testing. Laboratories were requested to confirm whether or not the tablets disintegrated within 60 seconds, according to general method 5.3, Disintegration test for tablets and capsules (Test A) of the *International Pharmacopoeia* published by WHO; and

- **Procedure 3:** the aim of this procedure was to assess the performance of the laboratories with regards to the sulfates identification test. The laboratories received two (2) vials labelled zinc sample A and zinc sample B and were asked to confirm whether or not the samples were positive for the sulfates identification test (reactions A and B) of the *International Pharmacopoeia* published by WHO[3].

STATISTICAL METHODS

Procedure 1: Zinc Assay

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, reported or expected precision of techniques and according to fitness for purpose.

Assigned value for procedure 1

The assigned value used in this study is the consensus value obtained when calculating the Huber's robust mean which is equal to 99.89%. The assay value determined during the feasibility studies was 99.77%.

Target standard deviation for procedure 1

The target value for the standard deviation (TSD) for procedure 1 was set at 1%. EDQM indicated that the uncertainty of the assigned value (0.17%) was found to be negligible compared with 0.3 x TSD, and could thus be ignored in the interpretation of the performance scores.

Scoring for procedure 1

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 laboratory according to:

$$z - score = \frac{\bar{x} - \hat{x}}{TSD}$$

Where $\bar{x}$ is the unrounded mean value calculated by EDQM based on the reported results of the individual laboratory,
$\hat{x}$ is the assigned value,
TSD is the target value for the standard deviation.

As a first step, a check for high standard deviations (Cochran's test) and for outlying means (Grubbs' test) was carried out. An outlier is a value that is so unlikely in the light of the overall distribution of results, that it would have an unreasonable impact on the calculation of certain statistics (e.g. the overall mean and the overall standard deviation). These tests do not necessarily detect values that are obviously unacceptable to a trained eye. Standard deviations or relative standard deviations printed on a black background are only to indicate that these values are high compared to the (R)SDs found in other laboratories, but they do not necessarily imply that they are unacceptable.

The purpose of (R)SDs is to provide participants with comparative material so that they can interpret their own data in the light of the performances of other laboratories and draw their own conclusions. It is also important to be aware that the SD for precision is not the same as the SD for accuracy (TSD) on which the z-scores are based.

Procedure 2: Disintegration test

Since only disintegration within a specified time (Yes/No) was requested to be reported from the participants, no consensus value or z–score was determined and no statistical evaluation of the data *sensu stricto* was carried out by EDQM. The paediatric zinc tablets were tested in the feasibility study and were found to be compliant with the disintegration test, meaning all six units disintegrated within 60 seconds.

Procedure 3: Sulfate identification test

Since only positive or negative identification of sulfates in the samples was requested to be reported from the participants (Yes/No), no consensus value or z–score was determined and no statistical evaluation of the data *sensu stricto* was carried out by EDQM.