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Prequalification Team Inspection Services
WHO PUBLIC INSPECTION REPORT
WHOPIR

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site (Inspected site)	International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) 68, Shaheed Tajuddin Ahmed Sarani Mohakhali, Dhaka 1212 Bangladesh
Corporate address of Organization	N/A
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**WHO application no: DI013** Zinc sulfate acceptability study in children with acute diarrhea: A prospective, open-label, interventional study
Sponsor & Applicant	The ACME Laboratories Ltd. Bangladesh
Inspection details	
Dates of inspection	26 – 28 July 2021 9am – 12pm (Geneva time)
Type of inspection	Initial – Real-Time Remote Assessment
Introduction	
Brief summary of the activities	icddr,b is an international health research institute based in Dhaka, Bangladesh with focus on diarrheal disease, working closely with the Government of Bangladesh, many NGO practitioners in Bangladesh to devise, test and evaluate interventions. The hospital's doctors and nurses are deployed by the WHO to assist during cholera outbreaks in other countries. Clinical services in malnutrition, as well as advice and training in humanitarian

	emergency response situations may also be provided by the organization.
General information about the company and site	icddr,b was established in Dhaka in 1960s as the South-East Asia Treaty Organization (SEATO) Cholera Research Laboratory (CRL). The hospital was initially treating patients with diarrheal disease. In 1978, the CRL received fresh impetus and a new name; i.e. the International Centre for Diarrheal Disease Research, Bangladesh. In recent years, the hospital has been known simply as icddr,b. icddr,b is now performing studies on multiple infectious diseases, other threats to public health, and methods of healthcare delivery. This hospital provides free of cost treatment for approximately 20 000 patients per year, 60% of whom are children. After admission to the hospital, patients might be treated at Emergency ward, General ward or ICU, depending on their health condition.
History	The site was not previously audited/inspected.
Brief report of inspection activities undertaken	The inspection included one clinical study with the intention to evaluate the acceptability of Zinc Sulphate Dispersible Tablets in children with acute diarrhea. The following scope and study-related activities were reviewed: The company's history, clinical study performance, monitoring of study, informed consent process, ethics committee approvals and correspondence, archiving procedure, IMP accountability, dispensation and storage, equipment calibration, employee training, and a tour of the facility. A review of the clinical study data was conducted, along with comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Not applicable

Abbreviations		
	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BE	bioequivalence

BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSR	clinical study report
DQ	design qualification
ECG	electrocardiogram
ERC	ethics review committee
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
LC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
icddr,b	international centre for diarrhoeal disease research, Bangladesh
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OPD	outpatient department
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system

	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	RRC	research review committee
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

Part 2	**Summary of the findings and comments (where applicable)**

General section

1. **Organization and management**

A video- and a PowerPoint presentation were provided explaining the activities of the organization and management of the clinical trial in detail.

A collaboration agreement was signed between the ACME Laboratories Ltd. and icddr, b. None of the clinical related activities was outsourced to any third party. In the agreement, the ACME Laboratories was mentioned as "1st party", committed to collaborate with icddr,b mentioned as "Collaborator". Roles and responsibilities of both parties were defined in the agreement. 1st Party and Collaborator jointly owned the proprietary rights to the data, results, inventions and other findings resulting from and specific to the work performed pursuant to the agreement. The joint ownership included the right to make further use of the study data and results.

The Principal investigator was responsible for adequate and safe medical care of the subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures were maintained.

An organogram was submitted. The organization was led by a Board of Trustees and divided in 7 divisions, in addition to the Administration section. The operation was respectively supervised by the Executive Director and the Deputy Executive Director.

The participating investigators were ensured not to have any conflict of interest with the sponsor or manufacturer of product by indicating it on the protocol RRC application.

The general site's working hours were established from 8:30 am to 5 pm on weekdays. Overtime would apply during conducting of studies.

The deficiencies related to the Management and organization were adequately addressed in the respective CAPA plan.

2. Quality management

In 2009, the Laboratory Sciences and Services Division (LSSD) of icddr,b designed a Quality Management System (QMS) in line with the requirements of ISO 15189 & ISO 15190 standards and Good Clinical Laboratory Practices. Although the above mentioned standards were applicable to medical laboratories, the QMS evolved and applied to all icddr,b divisions and departments including the Nutrition and Clinical Services Division which was responsible for this study. The Quality Manual was under revision at the time of inspection and was not presented. Quality Assurance functions including documentation control system, training programmes, audits and CAPAs were described in the SOPs.

The Nutrition and Clinical Services Division had developed SOPs focusing on the conduct of clinical studies. Several of these SOPs were provided for review before and during the inspection.

A Quality Assurance Office was established and was responsible for overseeing QMS activities including but not limited to documentation review, approval and withdrawal, audit plan, CAPA implementation and monitoring. No internal audits were conducted focusing on this trial.

The deficiencies related to QMS were adequately addressed in the respective CAPA plan.

3. Archive facilities

Subject files and other supporting data were kept for a 10-year period as per the requirements and the agreement with the ACME Laboratories. It was possible to identify each trial subject by name against subject identification codes, treatment assignment, and the CRFs.

The study documents were stored in sealed cupboard or boxes, in a secure designated location, with limited access. The facility was accessed by key. The key was stored under auspices of the study Co-investigator. The key to the archiving facility could also be collected by the authorized personnel under the supervision of pharmacists by recording the collection of the key in the respective logbook.

All files were labelled with study information. SOP for Archival of study documents, was available and reviewed. The archive processes were tested through the successful recall of study documentation and supporting records during the conduct of the inspection.

A pest control was regularly carried out and the facility was protected from fire through a central firefighting system.

The deficiencies related to the Archive facility were adequately addressed in the respective CAPA plan.

4. Premises

During the Real-time remote assessment, a virtual tour of facility was conducted and led by the study physician.

The site consisted of following units:

- Emergency area, including registration desk where the patient was admitted.
- Outpatient Department (OPD)
- General Department
- Intensive Care Unit (ICU)
- Pharmacy
- 2nd pharmacy, with designated area for storage of expired study drugs
- Archiving facility

The premises were equipped with smoke detectors and fire extinguishers to ensure safety for subjects and personnel. Adequate safety measures were also taken to limit the spread of COVID-19 virus.

The following equipment were used in the study:

- Scales
- Length / Height machine (Infantometer)
- MUAC tape
- Computers (hardware & software systems) for data entry and analysis
- Printer

Pharmacy

Pharmacy temperature and humidity condition were monitored by three different Data Loggers model. The respective calibration certificates were available.

The deficiencies related to the Premises and qualification of equipment were adequately addressed in the respective CAPA plan.

5. Personnel

A sufficient number of medical staff with the appropriate qualifications, training and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies were available.

A training documentation log for Protocol training session on Zinc Sulfate acceptability study was provided. A training was provided on 26 Aug 2019 by the PI with 9 participants, including study physicians and health workers. The updates on Zinc Sulfate acceptability study, such as rate of recruitment and the respective challenges were provided between 3 & 13 Nov and 10, 18 & 24 Dec 2019, as recorded on the training logs. The sponsors' representatives were also present at these meetings.

Records of training and assessment of knowledge of GCP, and other relevant area were maintained for the investigators. The investigators' GCP certificates and CVs were available and reviewed. It was certified that the PI and one of the co-investigators had completed the NIH web-based training course on "Protecting Human Research Participants".

The deficiencies related to the Personnel were adequately addressed in the respective CAPA plan.

Clinical section

6. Clinical phase

The study protocol was amended twice, and the latest amendment was used during the study conduct.

The objectives of the study included:

Primary objectives:

- Acceptability of the zinc product in the management of childhood diarrhea was assessed by observing:
    - Incidence of vomiting or regurgitation among enrolled children receiving the improvised zinc formulation.
    - The adherence: The number of days (out of the total 10 days) the child took the protocol-prescribed dose of the medicine. The treatment was considered to have

good acceptability if at least 80 % of the prescribed treatment was taken by at least 70 % of the children over the duration of 10 days, as per WHO guidelines.

Secondary objectives

- To assess the palatability of a new formulation of Zinc Sulfate.

The following endpoints were defined in the protocol:

Adherence
Adherence was the primary endpoint for the study. It was evaluated in terms of the dose given and the number of days the child took the medicine and preparation (dispersion) of the tablets.

Palatability
Palatability was measured based on a caregiver's documentation in "diary Card" of his/her child's behavior when the medicine was administered. The caregivers were asked about their perception of the taste of the zinc tablet given to their child as compared to other medicines.

An additional investigation was planned to be done on the measurement of serum zinc in 20 paired sub blood samples, taken prior to the administration of IMP as pre-test and on the 11th day after the enrolment and having completed the dosage schedule of 10 tablets in 10 days as post-test. Since this investigation was irrelevant to the primary and secondary study objectives, the process and respective results were not included in the scope of this inspection.

The first patient was recruited & enrolled on 9 Sep 2019 and the enrolment of the last patient with study ID no. 325 was completed on 28 Mar 2019. The confidentiality agreement was signed by PI and the study agreement was available in the ISF and signed by the parties.

The PI had accepted in written the responsibility for the scientific conduct of the project and to provide the required progress reports. An agreement to abide by the approved protocol and to obtain approval of the ERC (Ethics Research Committee) for any changes in the protocol was signed.

Subject screening and enrolment logs were provided as an Excel sheet with information about screening ID, screening date, name and hospital ID, study ID etc. It was verified

that an ICF was provided for all the screened volunteers, regardless the outcome of the screening procedure, through review of randomly selected study specific ICFs.

The clinical trial was carried out under conditions which ensured safety for the subjects. The site was appropriate to the stage of development of the product and the potential risks involved.

The trial site had facilities, including laboratory, equipment and adequate medical and clerical staff to support the trial and to deal with reasonably foreseeable emergencies. The investigator had sufficient time to conduct and complete the trial.

The PI had provided information to the staff involved in the trial and the relevant local hospital management, i.e. RRC was notified in compliance with the applicable regulation.

Investigator Brochure (IB) was provided and released by icddr, b. The documentation was signed and dated by PI.

The deficiencies related to the Clinical phase were adequately addressed in the respective CAPA plan.

7. Clinical/Pathology lab

Not applicable.

8. Ethics

The study was approved by the ERC (Ethics Review Committee) organized by icddr,b; Board of Trustee. List of EC members, their qualification and a list of documentation submitted to the ERC and the respective approvals were available.

A list consisting of Chairperson, Co-chairperson and other members of the Committee during July 2019 was provided. The independency of the Ethic committee members was verified since none of the members were involved in the study. The selection of members took place based on a guideline prepared by the Hospital's Research administration. The members were selected for a period of 6 month to one year to review the proposed clinical trials within a reasonable time in the respective term.

Insurance certificate was not applicable. Principle of compensation was defined in the study ICF to ascertain that the treatment at icddr,b hospital was free for all patients. If the child had a study related injury s/he would receive standard care at the Dhaka Hospital of the icddr,b.

INORMED CONSENT FORMS

Information for study participants (parents) were provided in Bangla language which was easily understood by the study subjects' caregivers. Options were considered in the ICF to advise the parents whether their children would be selected for the additional investigation on level of zinc in the blood, by taking blood samples.

The applicable ICF was provided and reviewed.

The defficiencies related to the Ethics Review Committee and ICF were adequately addressed in the respective CAPA plan.

9. Monitoring

The trial site had procedures in place, i.e. to facilitate, plan and respond to sponsor monitoring visits. The logbook for registration of such visits was available.

The proof of the first and last visit by the sponsor was provided. No pre and post study visits were registered in the relevant logbook and no reports were made available. Inspectors were told that the sponsor and icddr,b had collaborated in the past in another Zinc Sulphate acceptability study and relevant exchange of communication was presented during the inspection. A post-study visit was not conducted because of COVID-19 restrictions.

According to the respective logbook, six monitoring visits were conducted. Visit reports were made available. CAPA implementation was followed up at the next visit. Most of the monitoring visits were conducted by the ACME personnel, working at the regulatory affairs and the international business departments. Their qualifications were not available at the trial site.

The deficiency related to the Monitoring visits was adequately addressed in the respective CAPA plan.

10. Investigators

Refer to section 5; Personnel

11. Receiving, storage and handling of investigational drug products

According to the contract, the ACME laboratories Ltd was responsible for the supply and transport of the IMP to icddr, b. Shipping documentation indicated the sponsor was responsible for providing the Diary Cards and dataloggers during transport and storage at the trial site. A certificate of analysis was made available.

The IMP was stored in a display case in the pharmacy along with other medications. The carton box containing the IMP was labelled. A logbook for dispensing packs of Zinc Sulphate to study physicians was presented. After initial dispensing from the pharmacy, the medication was kept in a locker under supervision of the study staff. Similarly, a logbook for dispensing tablets to caregivers was available.

Unused IMPs were returned in accordance with the protocol to the pharmacy. The unused and expired study medication was separately stored in Pharmacy II in a carton box labelled with study information. The reconciliation documentation was reviewed.

Children were provided their first dose of zinc when they would be considered settled, i.e. not dehydrated, no vomiting during the last 30 minutes, and taking ORS as instructed. At the OPD (Outpatient Department) trained research staff would observe each child for 60 minutes following ingestion of zinc and record regurgitation and/or vomiting event if any.

The deficiencies related to the handling of IMP were adequately addressed in the respective CAPA plan.

12. Case report forms

The site had a paper based medical documentation. The source data was compared with the Clinical Study Report data listings and the data entered in the CRFs.

Source data verification included all source data for randomly selected study subjects both for the screening / enrolment visit and follow up (if applicable) / end of study visit.

The deficiencies related to Case Report Forms were adequately addressed in the respective CAPA plan.

13. Volunteers, recruitment methods

Following admission to the Hospital and registration in Sheba internal database, patients were treated at the Emergency ward, General ward or Intensive Care Unit, based on the severity of disease. Children with less severe illness were treated at outpatient department, which was the patient enrolment area, where the screening of patient took place. Children without some dehydration were enrolled after obtaining the caregivers' informed consent. Dehydration status was assessed in accordance with the modified WHO guideline (Alam et al., 2003).

All children within the defined age group were screened for study eligibility criteria by the study physician. Parents / attending care givers of those fulfilling the eligibility, in application of the inclusion and the exclusion criteria, were invited to provide their consent for enrolment of their children in the study.

Upon signing a written informed consent, after providing information about the study and its interventions, possible benefits and risks, and voluntary nature of participation along with the right to withdraw children at any time after the initial consent without providing any reason, children were enrolled by the study physician.

Inclusion of study subjects took place based on the inclusion and exclusion criteria for subject selection and screening procedures were described in the clinical trial protocol. The screening procedures were performed in the Outpatient department of icddr,b. Randomly selected screening forms were reviewed to verify the process.

Eligible study subjects were given their first dose of zinc together with the ORS as instructed. Each child was observed at the OPD by the trained research staff for 60 minutes following ingestion of zinc to record regurgitation and/or vomiting event if any on the "Enrolment form". In addition to the study data, patients' socio-demographic information was captured on the form.

The children were sent home with the caregivers who received verbal instructions regarding home administration of ORS for ongoing loss through diarrhoea stool, and the dosage of zinc product, and study procedure requirements. The children should be followed up by their parents / caregiver at home. The taste evaluation and acceptability status of the study medication were documented in the provided "Diary Card" which was collected with any remaining tablets at the follow up visit to the OPD on 11th day. If no tablet was left, the empty blister should be returned to the hospital. A follow up questionnaire was completed as a part of the CRF with information about usage of study medication, diarrhoea condition, observed adverse events and usage of any concomitant medication.

The deficiencies related to the Volunteers and recruitment method were adequately addressed in the respective CAPA plan.

14. Safety, adverse events, adverse event reporting

The method by which adverse events would be monitored was stated in the study protocol.

The study subjects' care providers were instructed to monitor the occurrence of adverse events. The incidence of adverse events was documented and recorded during the follow-up visit in the CRF form. The most expected adverse event was vomiting which was recorded by the number of occurrences in the CRF.

The deficiency related to the Adverse event reporting was adequately addressed in the respective CAPA plan.

15. Data processing and documentation

The study data were either captured on paper based CRFs or in study specific logbooks, depending on the source data. The essential documentation was kept in the ISF and was provided upon the Inspectors' request. Questionnaires were reviewed and marked for omissions, inconsistencies or mistakes that were addressed contemporaneously.

Data were copied on the hard disks of two computers as soon as data verification was completed.

SPSS software system was used for the statistical part of the study in accordance with the applicable protocol version. The respective license was provided and maintained by the IT-department. Data entry was performed by the study physician, verified by the co-investigator and approved by the PI.

The deficiency related to the Data processing and documentation was adequately addressed in the respective CAPA plan.

16. Study report

Clinical Study Report (CSR) was authorized by the PI. The statistical data were available in the CSR appendix B which were used for the analysis of the study results.

The CSR was used by the inspectors for the Source Data Verification.

The deficiency related to the Study report was addressed in the respective CAPA plan.

Part 3	Conclusion

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the study was considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at ***International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)***, located at ***68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212 ; Bangladesh***.

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR, were addressed by ***International Centre for Diarrhoeal Disease Research, Bangladesh*** to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of guidelines referenced in the inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP
   https://www.who.int/tdr/publications/documents/gclp-web.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP Annex 3
   https://apps.who.int/iris/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1

4. Guideline for good clinical practice E6(R2). EMA/CHMP/ICH/135/1995
   Short name: ICH GCP E6
   https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

5. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
Short name: WHO TRS 1010, Annex 9
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

6. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009.
Short name: OECD GLP
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

7. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
Short name: WHO Ethics Committee Guidance
https://www.who.int/ethics/publications/9789241502948/en/

8. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***
https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf;jsessionid=B7F180F317E8BE2DB4289C7BF9A561FF?sequence=1

9. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf?ua=1

10. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
Short name: Glove use information leaflet
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

12. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability
Republication of Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, WHO Technical Report Series, No. 992, Annex 7 with a new Appendix 2
WHO Technical Report Series, No. 1003, 2017, Annex 6
Short name: WHO multisource guidance
https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf

13. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

14. Model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products. WHO Technical Report Series, No.961, 2011, Annex 9.
Short name: WHO TRS No. 961, Annex 9
https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1

15. Ethical principles for medical research involving human subjects, 52nd WMA General assembly, Edinburgh Scotland, October 2000.
Short name: Declaration of Helsinki
https://www.who.int/bulletin/archives/79(4)373.pdf

16. Good manufacturing practices: guidelines on validation, WHO Technical Report Series, No. 1019, 2019
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1