1. Introduction

The International Safe Transit Association (ISTA), a non-profit association whose objective is to prevent product damage and excess packaging usage within the distribution environment. Membership of the ISTA is comprised of companies, select organizations and individuals.

The principle methods to meet the associations' objectives are:

- Testing standards
- Education and training
- Certification.

Certification of distribution packaging is accomplished through ISTA's "Transit Tested" program.

Currently ISTA has published guidelines for the design, testing and qualification of packaging solutions for insulated shipping containers (ISC's). These guidelines, Standard 0020 and ISTA 7E, provide recommendations to industry. Due to the critical nature and high value of many ISC's, especially within the pharmaceutical, diagnostic and medicinal industries, the ISTA has recognized the need for testing standards, education and training, as well as laboratory certification to address thermal conditions within the distribution environment.

2. Purpose

The purpose of this standard is to define the minimum requirements for thermal transit packaging laboratories to receive ISTA certification to perform ISTA thermal transit testing procedures and for those laboratories to be approved to designate specific packaging solutions as "certified" per applicable ISTA published standards, ISTA 7E.

3. Scope

This standard establishes the minimum criteria to be met for thermal transit packaging laboratories to become ISTA certified in the areas of laboratory processes and procedures, as well as equipment qualification.

Specific areas covered include: quality manuals, material handling; calibration, preventative maintenance, equipment qualification and re-qualification, training, document control, operating procedures, quality management system, data integrity and storage and data management files.

This standard defines the processes of:

- obtaining ISTA thermal transport laboratory certification
- maintaining certification
- re-certification
- reporting requirements
- on-site audits

4. LAB PROCESS AND PROCEDURES

This section offers guidance towards fulfilling audit requirements for ISTA certification specific to evaluating and testing thermally controlled packaging.

4.1 Lab Certification Process

The laboratory shall submit to ISTA.org an ISTA thermal transport laboratory **audit application**, **ISTA Form 0045,** for approval.

The thermal laboratory shall have at least one employee who has attained Certified Thermal Professional Level II status.

The thermal laboratory shall submit a **thermal transport laboratory certification pre-audit and audit form**, **ISTA Form 0047,** and after a successful review, an on-site laboratory audit is scheduled.

The laboratory certification period is for 2 years from completion of a successful on-site laboratory audit and "certified" status on **ISTA Form 0047.**

4.2 Lab Re-Certification Process

To maintain laboratory certification status, all labs require:

- **Annual** submission of **audit application**, **ISTA Form 0045 and membership fee to ISTA.**
    - **ISTA Form 0045 will indicate if any significant laboratory changes have occurred, such as:**
        - Major equipment acquisitions such as chambers, controllers and data acquisition systems
        - Significant facility changes such as remodeling and facilities move
        - ISTA reserves the right to determine the necessity of an on-site audit based on the scope and nature of the change(s).
            - Significant laboratory changes will require an on-site audit to verify conformance to STD 0014, irrespective of the completion date of the most recent audit.
            - An audit *application*, **ISTA Form 0045 and pre-audit *checklist*, Form 0047,** must be submitted to ISTA, within 30 days of the completion of the laboratory significant changes.
                - ISTA reserves the right to decertify any thermal package design qualification which does not comply with the requirements for laboratory re-certification.
                - Auditor review of audit form, ISTA Form 0047
                - If necessary, an on-site audit is scheduled to review the laboratory significant changes and verify conformance to STD 0014.
            - If there are no significant laboratory changes then the on-site audit period remains at the most current 2 year interval.

4.3 Quality Management System

The prospective laboratory shall have a documented Quality Management System in place for certification consideration. The provision of the table of contents and specific SOP's are required as part of the pre-audit process, **Form 0047.** ISO/IEC International Standard 17025 "General Requirements for

the Competence of Testing and Calibration Labs" may be referenced in whole for framework and in part for particular elements of the laboratory quality system.

4.4 Material Handling

A documented Material Handling process is a primary requirement of the Quality Management System. The prospective laboratory shall have a documented procedure for incoming material handling, in process control, and final disposition of test materials.

4.5 Calibration

Instruments used for measuring, monitoring and recording temperature shall be calibrated against NIST traceable standards with **stated measurement uncertainties**. A measurement result is complete only when accompanied by a quantitative statement of its uncertainty. For guidance on measurement uncertainty, reference **NIST TN 1297**, "Guidelines for Evaluating and Expressing the Uncertainty of NIST Measurement Results, **Appendix C**—Statements of Uncertainty Associated with Measurement Results".

4.6 Equipment Qualification Process: | Re-Qualification

Guidance for process validation can be found in Guidance for Industry, Process Validation: General Principles and Practices published by the U.S. Food and Drug Administration (CDER). Guidance for qualifying chamber equipment and instrumentation can be found in IEC 60068-3-5 "Environmental testing - Supporting documentation and guidance - Confirmation of temperature chambers."

For purposes of thermal transport laboratory certification, ISTA has defined the demonstration of equipment reliability and repeatability through an equipment qualification process with the inclusion of equipment calibration and preventative maintenance processes.

4.7 Training

The lab shall have in place a documented process for training individuals performing activities within the ISTA certified laboratory. Laboratory operations shall be run by ISTA Certified Thermal Professional Level II. This is important to ensure employees possess the required knowledge to perform his/her duties. This process should incorporate elements outlined in ISO 17025 "General Requirements for the Competence of Testing and Calibration Labs" ***Sec 5.2***. The training program should also address the following items, but not limited to:

- Training should be regularly conducted
- Training should be conducted by individuals with appropriate experience/qualifications
- Records of training should be maintained and periodically assessed

4.8 Document Control

All documents related to the thermal testing of insulated shipping containers (ISC's) should be prepared, reviewed, approved, and distributed according to documented procedures. These procedures should also

include provisions for retaining all appropriate laboratory control records and should incorporate the elements outlined in ISO 17025 “General Requirements for the Competence of Testing and Calibration Labs” ***Sec 4.3 and 4.13***. Control records could include a complete record of all raw data generated during testing, in addition to graphs, charts, and spectra from lab instrumentation.

4.9 Operational Requirements

All lab equipment shall be operated by authorized personnel and those with a minimum designation of **Certified Thermal Professional, Level I**. The laboratory personnel will be provided with instructions on the use and maintenance of lab equipment and computerized systems, including any necessary manuals provided by the manufacturer of the equipment. All laboratory equipment shall be operated and maintained according to documented procedures, established to govern any type of situation within the laboratory. These laboratory procedures may include, but are not limited to:

- equipment everyday use
- equipment calibration
- equipment planned maintenance or repair
- equipment transport or storage

When reporting results of qualification testing on insulated shipping containers (ISCs), the lab shall adhere to the policies established in the **ISTA STD-0020** titled “Design and Qualification of Insulated Shipping Containers (ISCs)”.

4.10 Data Integrity and Storage

The lab shall have in place a process for the storage of laboratory electronic and/or paper records. This process should address key components related to security and integrity of data and should incorporate the elements outlined in 21CFR Part 11/ ICH Q7A Sec 5.4(electronic records). If breakdowns or system failures could result in the permanent loss of data/records, the lab shall have in place a system for back-up of data/records.

4.11 Preventative Maintenance (PM) and Repair Process

Maintenance and repair of all equipment used during the testing of insulated shipping containers (ISCs) shall be carried out and logged according to documented procedures. The procedure outlining maintenance and repair should include a preventative maintenance schedule and a log of all repairs of lab equipment. Equipment not available for use due to maintenance shall be isolated to prevent use ***or*** clearly labeled or marked as being out of service. Maintenance records shall include at least the following:

- The identity of the equipment
- Manufacturer’s name, type identification, serial number or unique identification
- Any damage, malfunction, modifications, or repair done to the equipment
- Dates the modification or repair was performed, by whom the work was done, any results or reports associated with repairs or modifications performed

5. EQUIPMENT REPEATABILITY AND RELIABILITY

5.1 Qualification Requirements

Once ISTA thermal lab **initial** certification has been achieved, *subsequent* equipment qualifications (re-qualifications, new equipment, etc.) shall be executed by ISTA Certified Thermal Professionals Level II.

All equipment and systems shall be qualified prospectively.

The equipment or system qualification protocols shall be approved ***prior*** to initiation of the qualification study.

5.2 Qualification Documents

Qualification documents shall be numbered, tracked, and stored and shall be prepared, reviewed, approved, and distributed according to documented procedures.

5.3 Acceptance Criteria

Acceptance criteria shall be measurable and achievable. They shall be based on science and the process, system, or regulatory requirements pertaining to the specified laboratory equipment.

5.4 Installation Qualification (I.Q.)

Installation qualification is performed on site during the time of installation. The Installation Qualification activities document the key aspects of the installation and verify compliance with supplier's specifications on each piece of equipment when installed correctly and operates consistently according to established limits and tolerances.

The development and application of Equipment Qualification Protocols are recommended practice.

Documented and approved installation qualification activities following CDER's General Principles of Process Validation shall be performed and approved to established laboratory equipment qualification requirements. The installation qualification activities will include the following details, but not limited to:

- Location meets floor space requirements
- Power and other equipment requirements are met, and documented
- Environmental operating conditions are met and documented
- Instrument(s) checked for damage and cross-checking contents with packing slip as a checklist
- Document any computer hardware/operating system requirements, note all "as-received" calibration and certifications

5.4 Installation Qualification (I.Q.), continued

- Checking the installation of the software and its basic accessibility assuring compliance with appropriate regulations including 21 CFR Part 11, if electronic records apply.
- Installing the instrument and options per supplier's installation procedure and instructions
- Verifying all connections to peripheral units and that communication is operational
- Documenting the instrumentation controlled by the software
- Checking basic communication with the instrument
- Recording all firmware versions and serial numbers instrument with I.Q. sticker
- Recording the calibration dates for equipment used during I.Q. procedures
- All manuals, relevant outputs from the instrument, and certificates of conformity are gathered and placed in I.Q./O.Q. binder for record maintenance per documented procedures.

5.5 Operational Qualification (O.Q.)

Operational qualification is performed subsequent to successful installation, after major equipment maintenance or modification of the instrument, or can be based on a customer-specified quality schedule. The operational qualification documents that the instrument performs consistently throughout the specified operating ranges.

The development and application of Equipment Qualification Protocols are recommended practice.

O.Q. qualification is performed on the chamber as a **system**, and specified activities are used to show that the accuracy and precision of the **system (chamber)** meet required specifications outlined in the O.Q. documented procedures. The documented procedures shall include the following. If an equipment feature is either not present on the specified equipment or not utilized in the equipment's operation, then this condition must be notated with the documentation:

- Testing of configuration menus, instrument control, and data transfer
- Activate software logging
- Thermal mapping over entire operating range *reference*- IEC 60068-3-5
- Set-up of user logins and application access
- Employing automated System Check-Out feature within software and verifying its status
- Testing of all user administration settings, security settings, audit trails, and data integrity/security

5.5 Operational Qualification (O.Q.), continued:

- Instrument-specific documents verifying the analytical parameters defined within STD-0020:
- Recording the calibration dates for equipment used during O.Q. process
- All relevant outputs from the instrument are gathered and placed in I.Q./O.Q. binder

After completion of the I.Q. and O.Q., you will have a binder, including installation checklist, operational checklist, qualification data, pass/fail documentation, manuals, relevant outputs from the instrument, certificates of conformity, and qualification procedures with all appropriate approval signatures and reviews by Quality Assurance personnel or designee.

5.6 Performance Qualification (P.Q).

The objective of the Performance Qualification is to demonstrate consistently acceptable results of the instrument/equipment system(e.g. chamber) under normal operating conditions. Considerations in the documentation should include:

Actual loading of the chamber with test articles; to be run in triplicate. It is strongly recommended that maximum and minimum chamber loads be utilized in this chamber loading exercise.
Use of thermal profiles that contain the steepest temperature/time gradients. Each testing profile should be run for at least 24 hours.

The equipment manual should be used to establish PQ parameters for the events. Pre-defined temperature profiles with tolerances shall have been established and reviewed for acceptability upon completion of the PQ activities. If backup power is utilized for any of the systems, the backup power supply should be engaged at least once during each testing cycle, along with the restoration of normal house supplied power.

Abbreviated thermal mapping following a similar process as employed in the O.Q., and allowing for the presence of the test articles within the chamber. Thermal mapping activities may be included during the execution of the thermal profile, *referenc*e IEC 60068-3-5 for information on a recommended thermal mapping process.

Subsequent to initial lab certification, the performance qualification activities are to be performed by a Certified Thermal Professional Level II.

The development and application of Equipment Qualification Protocols are recommended practice.

The data collected from each run should be analyzed to the pre-defined acceptance criteria as outlined in the PQ. Any deviations to the process must be noted and investigated for corrective action. Repeats of the P.Q. due to failures to meet the acceptance criteria, must have documented justification on the corrective action prior to initiation.

5.7 Qualification Maintenance

Qualification maintenance is performed to ensure systems, equipment, or processes that have been initially qualified remain in a state of control.

Requalification is ***change-based*** testing which confirms that qualified processes, equipment, or systems maintain consistent and reliable operations or performance **following a change or modification to the process or system.**

Requalification activities shall be documented.

ANNEX 1

DEFINITIONS

Acceptance Criteria	An approved quantitative or qualitative value for a specific parameter to be tested.
Addendum	An approved document supplying additional information to an existing controlled document.
Attachment	A document supplying additional information to a controlled document prior to final approval.
Installation Qualification (IQ)	A controlled document providing evidence that the system components have been correctly installed per design specifications and/or the manufacturer's recommendations.
Operational Qualification (OQ)	A controlled document providing evidence that the system functions as intended throughout representative or specified operating ranges, and that procedures exist describing operation of the equipment and that the system is calibrated.
Performance Qualification (PQ)	A controlled document providing a sequence of tests intended to demonstrate that a system performs its intended function effectively and reproducibly while confirming the adequacy of approved procedures for a specific use.
Prospective Validation/Qualification	The validation/qualification is performed prior to the manufacture of marketable product, and the products are not sold until the equipment, system, and process meet the validation/qualification acceptance criteria.
Product	Term referring collectively to intermediate product, work in progress, final form, and final product.
Qualification	The establishment of documented evidence, which provides a high degree of assurance that equipment, system or subsystem works correctly and actually leads to the expected results.
Requalification	Requalification is change-based testing which confirms that validated/qualified processes, equipment, or systems maintain consistent and reliable operations or performance following a change or modification to the process or system.

Requirements (R)	A controlled document specifying what functions the system must perform.
Retrospective Qualification	Validation/qualification of a process for a product already in commercial distribution based upon accumulated production and testing data.
System	A group of interacting elements functioning as a complex whole.
System Qualification	Documented evidence that a system is properly installed (IQ completed) per design specification; operates per system requirements and process parameters (OQ completed); and performs effectively and reproducibly (PQ completed).
Qualification Protocol	A controlled document stating how validation/qualification testing will be conducted, including the objective, procedures to be followed, tests to be performed and acceptance criteria to meet.
Qualification Report	A controlled document stating how validation/qualification testing was performed, including the data obtained and conclusions based on test results.
Worst case	A set of conditions which pose the greatest chance of process or product failure.

CHANGE SUMMARY

Change	Justification
New	ISTA Thermal Transport Laboratory Certification

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