ETHIOPIAN FOOD AND DRUG AUTHORITY

A Guidance document for Time and temperature sensitive pharmaceutical product (TTSPP) transport and Storage

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Signature

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Abbreviations

TTSPPs	Time and Temperature-Sensitive Pharmaceutical Products
SOP	Standard Operating Procedure
FDA	Food and Drug Administration
CGMP	Current Good Manufacturing Practices
EFDA	Ethiopia Food and Drug Administration
WHO	World Health Organization
GDP	Good Distribution Practices
GSP	Good Storage Practices
IATA	International Air Transport Association

Definition

Active systems: Externally powered or on-board powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks).

Ambient temperature: The uncontrolled prevailing temperature(s) within a specific environment or series of environments, such as a supply chain.

Cold Chain: Equipment and practices used to ensure a constant temperature for a product that is not thermostable (such as vaccines, serums, tests, etc.), from the time it is manufactured until the time it is used. It also includes all the temperature monitoring equipment and routines.

Good Distribution Practices (GDP): That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process.

Good Storage Practices (GSP) That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Operational qualification (OQ): Documented verification under controlled conditions that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word validation is sometimes extended to incorporate the concept of qualification.

Refrigerated container or reefer: A thermally insulated shipping container or intermodal freight container, equipped with an integrated refrigeration unit, used for the transport of TTSPPs, by road, rail or ocean freight.

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailers whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than the external ambient conditions. The environment inside the cargo compartment may be temperature-controlled or temperature-modified.

Refrigeration equipment: The term 'refrigeration' or 'refrigeration equipment' means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.

Temperature excursion: An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribe for storage and/or transport by the product manufacturer, based on stability data.

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature sensitive pharmaceutical product (TTSPP): Any pharmaceutical or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Transport temperature profile: Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport

1. Introduction

1.1. Purpose of the guidance document

This document provides guidance to EFDA to set general requirements for cold chain for assessing cold chain management. This supplement guideline set out the principal requirements for the safe storage and transportation of time- and temperature-sensitive pharmaceutical products (TTSPPs). Cold chain logistics for TTSPP is concerned about the storage and the transportation of them in a safe environment from the manufacturer to the person who will use it. This is extremely vital as it is known that TTSPP lose its medical benefits over time, especially if exposed to sun light and heat.

1.2. The importance of the cold chain to the pharmaceutical products

To preserve drug safety, quality and efficacy, proper storage and transportation conditions must be maintained throughout the drug supply chain. This ranges from the point of manufacture to the delivery of products to the final distribution point, normally the person who dispenses or provides medicine to the patient.

Medicines requiring controlled-temperature storage conditions must be distributed in a manner that ensures their quality will not be adversely affected. The importance of keeping temperature-sensitive pharmaceuticals within their prescribed ranges throughout their journey (including storage at their destination) cannot be overstated. The issue of temperature excursions is crucial to logistic industries since many of products require temperature-controlled storage and distribution to maintain their efficacy and other properties. In terms of quantity, cold chain logistics accounted for more than 26% of the pharmaceutical industry in 2019. This share is likely to increase.

In recent years, there is growing demand for temperature-controlled products with the

1.3. The challenge of transporting temperature sensitive pharmaceuticals

Pharmaceuticals sensitive to high temperatures can become less effective, and in some cases even toxic, while those sensitive to low temperatures usually lose their therapeutic properties if frozen. Either way, not transporting or storing pharmaceuticals within their prescribed temperature range can have a serious effect on the health of individuals, in some cases it can even be life-threatening.

To preserve the efficacy of products, pharmaceutical companies ship a significant proportion of their cargo as either chilled or frozen.

Cold chain management is making great strides in temperature sensors, data loggers, telematics and cloud computing solutions, all of which enable track and trace and real-time remote temperature monitoring—safety and quality aspects that are crucial to the pharmaceutical industry.

2. Standards and regulations for TTSPPs

Maintaining a safe supply chain is essential, which presents significant challenges to the logistics industry. Consequently, the supply chain is highly regulated. The aim of compliance is to maintain the quality and the integrity of medicinal products. Considering it FDA sets outs its standards for the manufacture, storage and distribution of pharmaceutical products in the Current Good Manufacturing Practices (cGMP). FDA Guidance on Stability for the industry notes that adverse shipping and/or environmental conditions may affect the product quality. Deficiencies in Good Distribution Practices with specific focus on temperature control and monitoring during shipment have been cited by the FDA. The (WHO) working document QAS/04.068 states: where special storage conditions (e.g. temperature and relative humidity) are required during transit, these should be provided, checked, monitored and recorded. The overall objective of these guideline is to: “ensure the quality and integrity of pharmaceutical products during all aspects of the distribution process. The USP standards are cited in Good Storage and Shipping Practices. USP describes procedures to maintain proper storage environments for individual articles and ensure the pharmaceutical preparations integrity until

it reaches the user. The supply chain parties should maintain a quality system setting out responsibilities, processes and QRM principles in relation to their activities (Risks associated with distribution routes include exposure to temperature). EU has published the Good Distribution Practice of Medicinal Products for Human Use (GDP) and EFDA has published Good Storage and Distribution Practices guideline for pharmaceutical products.

Further, refrigerated and temperature-controlled transport services are often supplied by a third-party service provider specializing in such transport. The regulators are not the only organizations introducing regulations and standards for cold chain logistics. The International Air Transport Association (IATA) sets out its standards for transporting pharmaceutical products by air in its comprehensive Temperature Control Regulations (TCR). It also requires a Time and Temperature Sensitive Label to be affixed to all shipments booked as time and temperature sensitive cargo. And, since 2013, airlines and ground-handling agents must use IATA's Standard Acceptance Checklist for time and temperature sensitive shipments to ensure that essential control activities are carried out.

In recent years, partly as a result of the huge increase in pharmaceuticals that are sensitive to temperature change, there has been a clear shift towards standardizing global transportation and storage regulations for healthcare-related products. The regulatory bodies are on the way to create, enforce, and ensure compliance with rules and regulations for temperature sensitive product transportation and storage. considering the current situation, a technical supplement to the available guideline of EFDA published in September ,2015 for highly specialized supply chain is crucial.

2.1. Cold Chain logistics or Chill Chain logistics

There are two main ways to preserve temperature in the ranges that the temperature sensitive products require:

— Keeping the temperature sensitive products in a container able to continuously produce cold by itself (i.e. an electric fridge).This method is called active cold chain, as the container "actively" produces the cold required. Such devices are commonly referred as refrigeration units. It includes: refrigerators, freezers, cold rooms and air conditioners. It is mostly used for storage.

— Keeping the temperature sensitive products in a container together with a cold material able to emanate cold for a certain period of time (i.e. a box loaded with ice).This method is called passive cold chain, as the container is passive, and only retains cold from the stored item itself. Such devices are commonly referred as isothermal boxes or insulated shipping containers or passive containers. Pre-cooled packs (normally with frozen water, carbon dioxide or gel) are put into an insulated box packed together It includes cold boxes, vaccine carriers and insulated boxes. It is mostly use for transport. They can only maintain a temperature range for a set period of time before they expire, making them an effective option for short journeys.

3. Assessment of Cold Chain and Its Management

Cold chain encompasses the infrastructure, the equipment, the people and the management processes and its implementation. It consists of a series of storage and transport. links, all designed to keep temperature sensitive products within an acceptable range until it reaches the user. The following are universal conditions that can be used during any cold chain assessment.

3.1. Assessing the Management Processes

Assess the availability of a cold chain management policy or standard operating procedures. It should be available and applied. Cold chain management policy or standard operating procedures should include clear information on:

— Validation and qualification policy (Transport validation and equipment qualification)
— Actions if the temperature recordings are outside the +2°C to +8°C range or any other specified range.
— Change control mechanism (example transport change, storage facility changes and storage condition change).
— Deviation control mechanism or system (Example mechanical failure)
— Compliant handling system or mechanism
— Investigation report against temperature excursions and duration should be notified immediately to the responsible person or manufacturer in a timely fashion.

- The appropriate corrective actions that should be taken to avoid the recurrence of temperature excursions, if any. Modify the storage and transportation conditions on the basis of Quality Risk Management programme.
- Quality Risk Analysis in case of risk to quality, temperature excursions, OOS and regulatory risks.
- Review period for policy and standard procedures.
- Should indicate a self-audit tool and program to check the cold chain is on target for excellence
- Product recall/traceability program should be carried out in case of product failure
- What to do if the facility has a cold chain failure
- Emergency plans and equipment for use in the event of refrigerator failure and/or power outage

3.2. Assessing Infrastructure

The infrastructure should enable the cold chain to function effectively. This includes the adequateness of the store building (the location and the construction standard) and the basic utilities, particularly the power supply feeding the active cold chain.

All the infrastructures should be of a satisfactory standard and correctly maintained through planned preventive maintenance. Emergency repairs should be exceptional and conducted in a timely manner. If relying in an emergency generator, it should be also well serviced and operational.

The facility and its structures, such as ceilings, walls, floors, windows, vents, drains, and overheads (e.g., pipes, air vents, and lights) designed and constructed of materials to be adequately cleaned and maintained in good repair, to protect product from cross-contamination.

3.3. Assessing Cold Chain Equipment

The assessment of the cold chain equipment should include both active and passive cold chain devices as well as other cold chain material such as coolant packs and temperature monitoring equipment.

For the existing cold chain equipment, assess:

- Load - The TTSPPs should be correctly arranged inside the refrigerators or cold chain, letting enough space for the cool air to flow. Each device containing TTSPPs should be equipped with (at least) one thermometer or data logger. Temperature monitoring sheets should be attached to the device and records up to date.
- Temperature performance - All TTSPPs should be stored within recommended temperature ranges. Continuous temperature records should be available and demonstrate that TTSPPs have been stored correctly.
- Condition and robustness - Assess if the equipment broke or malfunctioned in the near past and how often this happened. Also, if repairs were performed, indicate the type of repair.
- Consider if the malfunctioning resulted in the inability to use the equipment.
- The age and past handling of the equipment could be a vulnerability factor: assess its first "use date" and past history. Be aware that refrigerators have a life duration of about 10 years.

3.4. Assessing the shipment conditions or transportation study encompasses:

Temperature-monitoring and record-keeping are required to make sure that TTSPPs are maintained under appropriate conditions. The data gathered from temperature monitoring devices must be recorded and analyzed on a regular basis to demonstrate that TTSPPs are being stored and transported at the correct temperatures. Analyzing that data should consider the environmental conditions: temperature (day–night and seasonal temperature extremes) and geographical and natural hazards.

3.5. Assessing Human Resources

The assessment of the human resources involved in the cold chain management should include the responsibilities, the correct staffing and the knowledge and capacities.

The assessment will consider:

- The responsibilities and tasks should be clearly specified for each person with a role to play in the cold chain management (verifying the availability and accessibility to job descriptions)
- Responsibilities related to cold chain management should be described for all management levels and for every step of the chain: from the personnel monitoring temperatures to decision makers.
- All the pertinent personnel should be trained in the management of the cold chain, logistics, and waste management to protect the integrity of the cold chain. Records of assistance to briefing or training sessions could demonstrate these.
- In addition, the personnel should have access to the guidance policy, manuals and/or the standard operational procedures.

4. Requirements for Cold Chain Management

4.1. Qualifications

Installation of cold chain equipment must be done in the adequate room. The room must be accessible for reception and delivery, large enough, in good building conditions (roof, ceilings, floors, electrical services, etc.).

Cold chain is not only about refrigeration equipment, it includes: storage space for diluents, packaging materials, cold boxes and icepacks should be also considered. A proper planning of the storage room and all needed pre-operation must be completed before installing any active cold chain equipment.

Manuals shall be provided by the manufacturer with each equipment with clear descriptions on procedures for installation, operation, diagnostic and maintenance.

Operational qualification is carried out under laboratory-controlled conditions and the OQ protocol must clearly define the acceptance criteria for the shipping system(s) to be qualified.

The final stage of qualification – is the performance qualification; this stage is mandatory in all cases (shipping containers and refrigerated vehicles), except where every shipment on every route is monitored. PQ is conducted as a field test in the real operating environment. protocol must be developed to document the process and define the acceptance criteria. Based on performance qualification protocol and acceptance criteria, the performance qualification should be affected.

Reusable shipping container systems, with and without interchangeable parts, should periodically be re-qualified to ensure that the thermal performance has not been adversely affected as a result of age, change in chemical properties, physical damage, off-gassing, evaporation of temperature stabilizers, or other potential performance loss.

Vehicles should be qualified vehicles equipped with active temperature-control systems which are used to transport TTSPPs. In addition, Transport route profiling qualification should be done as part of all other qualifications.

— Considerations in qualification of refrigerators and freezers include:

- Temperature mapping to assess temperature distribution using empty and full loads.
- Door open challenges to assess how long the door can be kept open without exceeding temperature limits or recovery time after door opening.

- Power loss challenges to assess how long temperature ranges can be held during a power failure.
- Alarm challenges to verify set-points and functionality.
- Sufficient duration in studies to capture compressor and defrost cycles
- Ambient load challenges or cool down verification to assess the time it takes to achieve set temperatures after being loaded with higher temperature goods representing typical loads

Maintenance, Calibration and Alarm equipment verification

— The warehouse should implement a maintenance program for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers: Improperly maintained or outdated refrigeration equipment contribute to the weakness of the existing cold chain.

— Cold chain maintenance should be planned from the moment of installation by defining a regular schedule of basic tasks to be implemented by on-site workers.

— There should be a designated person or service provider responsible for the servicing of the power sources and cooling equipment.

— Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

— Carry out regular planned preventive maintenance on all temperature controlling equipment. Keep records to demonstrate compliance with the programme.

— Implement procedure to ensure that emergency maintenance is carried out within a time period that does not place temperature-sensitive products at risk of damage

  - Ensure that there is a contingency plan to move products stored in nonfunctioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner
  - Maintain records to demonstrate compliance

— Implement documented procedure, requirements and plan a schedule to ensure replacement of cold chain equipment’s

5. Calibration of temperature control and monitoring devices

- The warehouse should calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified in the quality policy.
- Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used.
- Single-use devices (disposable devices) that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated. Example Paper-based temperature monitoring device which change color irreversibly and at a constant rate.
- The warehouse should check functionality of temperature and humidity alarms at least once every six months at the designated set points and should have appropriate procedures and maintain records to demonstrate compliance.

6. Temperature monitoring systems and devices

In order to maintain temperature sensitive products quality, provide air temperature monitoring systems and devices for vehicles used to transport and equipment used to store TTSPPs. Temperature monitoring devices and routines are used during every storage and during every transportation stage, until the product is administered to the recipient.

Temperature monitoring devices are used to keep track of the temperature to which the TTSPPs are exposed. Based on the data from these devices, important decisions may be made.

6.1. Devices for Cold Rooms and Freezer Rooms

For Cold Rooms and Freezer Rooms, monitoring devices integrate different functions like temperature and event loggers and alarm systems. They are fed by several sensors allowing the temperature monitoring in several room locations simultaneously. These systems are commonly configurable to suit user requirements by adjusting parameters such as logging interval or measurement unit. Any device which requires frequent reading should be placed in an accessible location within the refrigerator unit and where they are unlikely to be damaged. Also consider the warmest and coolest places of the refrigerator model when placing the alert

6.2. Devices for Refrigerators and Freezers

The temperature in refrigerators and freezers is commonly monitored by the use of (analogic) thermometers and (digital) data loggers. Data loggers are battery operated devices which measure and store data for a period of time. The time limit is the device memory. Some data logger models display the data instantly on an LCD screen while some other require data to be downloaded by USB or cable to a computer for later analysis.

7. Operating Temperature Range for cold chain

It is important to consider, as part of the environment criteria, the ambient operating temperature range where the refrigerator or freezer performs. This information should be provided by the manufacturer. Though a standard is a range between +5°C and +43°C, some models have a maximum ambient operating temperature of +32°C.

Chemical Indicators - Also called markers or phase-change indicators. They are the most accessible and easy to use, they are based in a chemical impregnated onto a paperboard that changes its appearance under certain temperature. There are two types of chemical indicators: Example a vaccine vial monitor or VVM6, is a circular indicator, printed directly on the vaccine vial label or affixed to the top of the vial or ampoule. The inner square of the VVM is made of heat-sensitive material that is initially light in color and becomes darker when exposed to heat over time. By comparing the color of the square to the reference ring, health workers can determine the extent to which the vaccine has been exposed to heat.

8. Transportation practices and temperature monitoring during transportation

- The warehouse shall have practices for the inspections of incoming trucks and are inspections (e.g., cleanliness, temperature) documented, and available for review.
- Temperature-sensitive products must be transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labeling and supported by stability data.
- Temperature excursions outside of their respective labeled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exists demonstrating that product quality is not affected. Procedures shall be in place to address similar situations.

- The transportation process and containers should be designed to prevent damage and maintain the integrity and quality of the drug products. For example, transport conditions for ampoules should limit their exposure to physical stress to avoid the development of hairline cracks.
- Written procedures for the shipping of drug products should be established. Such procedures should consider the nature of the drug products, local conditions, modes of transport and any seasonal variations experienced, as well as describe any special handling precautions.
- Procedures should be qualified to ensure that appropriate conditions are maintained under probable extremes of ambient temperature and should also account for possible unforeseen delays which may occur in shipping/transportation
- Refrigerated vehicles/transportation containers should be mapped and monitored if they provide the primary means for environmental control.
- Temperature and humidity monitoring devices, such as data loggers, should be calibrated at predetermined intervals.
- Single use monitoring devices should be qualified (for example, verification of performance for indicator strips or freeze indicator units).
- Transportation practices by carriers, including any storage and/or transportation activities performed by sub-contractors, should be verified by reviewing documentation. A record of the review should be kept, and any discrepancies should have a follow up.
- Loading activities (loading and unloading) should be done in a manner that preserves the quality of the drugs.
- Shipments temporary stored at port of entry should be preserved in a secure to under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs, in order to avoid risk damage during temporary storage.
- Vehicles and equipment used to distribute, store, or handle drugs should be suitable for their use and appropriately protective of the products to prevent exposure to conditions that could affect their stability and packaging integrity, as well as prevent contamination of any kind.

- Special storage conditions (temperature, humidity, others) required for the cold chain, should be provided, checked, monitored and recorded within vehicles.
- Temperature mapping of vehicles should support uniformity of the temperature across the vehicle. Recorded temperature monitoring data should be available for review.
- stability data should exist to address the planned excursion and evaluates the worst case in terms of frequency and severity of excursions potentially encountered throughout the distribution chain. This information is also useful in assessing the effects of unplanned excursions.

9. Warehousing and storage

- The warehouse should keep the site free of accumulated dust, dirt, waste and debris.
- Pests should be kept under control within the site area.
- Waste should be collected in designated closed containers and arranged for safe disposal at frequent intervals.
- The warehouse should provide suitable fire detection and fire-fighting equipment, including fire hydrants where possible, in all temperature-sensitive products storage areas
- Equipment should be regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations or procedures
- The warehouse should ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage the products and measures should be taken to minimize pest activity in these areas.
- Deliveries should be examined at receipt in order to check that containers are not damaged, and that the consignment corresponds to the order.
- The warehouse must maintain records and inventories that show receipt and distribution TTSPPs.
- The supply chain records must include the source of the drugs, the address of the location that the drugs were shipped from, the identity and quantity, and the dates of receipt etc. Records must be kept and easily identifiable.

— The warehouse should provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department.

— Materials within quarantine areas must be clearly identified with their status: - With temperature control, for items returned for re-stocking - With temperature control, for items recalled for testing - Without temperature control, for items awaiting disposal.

— Written procedure(s) shall be in place to ensure the appropriate management of products in quarantine status

— In the case of complaint, the compliant shall be forwarded to manufacturer and the complaint sample and control sample (retained by manufacturer) may be simultaneously analyzed by using the validated analytical method. The analysis may consider loss of assay as well as increase in impurity in sample impacted due to temperature excursion or else.

10. Storage conditions control & monitoring in storage

— The warehouse should provide thermostatic temperature control systems for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store temperature-sensitive products.

— Temperature monitoring systems and devices should comply with the following minimum requirements:

- Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapor pressure thermometers.
- Monitoring sensors calibrated
- Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume
- Monitoring sensors positioned to be minimally affected by transient events such as door opening
- Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays

Temperature-controlled rooms, cold rooms and freezer rooms should:

— Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position
— Provide documentation for each monitoring sensor position which can be stored and accessed
— The sensors should continue to operate independently in the event of a power failure

11. Refrigerators and freezers used to store drugs should:

- Be well maintained
- Be equipped with alarms
- Be free from excessive frost buildup
- Allow for adequate air distribution and orderly storage within the chamber
- Storage practices and loading configurations should not lead to the obstruction of air distribution
- Have sensors for continuous monitoring and alarms located at the points representing the temperature worst case scenarios
- Be calibrated as required by the calibration program
- Be equipped with a backup power source or have alternate storage available in the event of a power failure: Alternatively, the warehouse can use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour. The least preferred option is a thermometer or maximum/minimum thermometer. Documentation should be provided for each appliance which can be stored and accessed.
- Where possible, and where necessary, ensure that all temperature controlling equipment for TTSPP storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply system (example Stand-by generators and/or UPS or Voltage stabilizer) are amendatory in cold chain.

- Be of commercial grade and not be of household type unless they incorporate the above controls. The use of household type refrigerators and freezers is discouraged.

— When specified on the label, controls for other storage conditions such as humidity, light, etc., should be in place. Storage areas should be designed or adapted to ensure good storage conditions. Adherence to these conditions should be checked, monitored and recorded.

— More specifically, for temperature-sensitive products which are adversely affected by high relative humidity and are not sufficiently protected by their packaging such products are typically labeled “store in a dry place” or carry similar wording and require a humidity-controlled environment which should be provided by the warehouse.

— Logbook for record of power failures should be available and recorded immediately during power failures

— The warehouse should provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store temperature-sensitive products which require a humidity-controlled environment, complying with the following minimum requirements:

  - Sensors accurate to ± 5% RH
  - Sensors calibrated
  - Sensors located to monitor worst-case humidity levels within the qualified storage volume
  - Sensors positioned to be minimally affected by transient events such as door opening
  - Humidity records should be provided with a minimum recording frequency of six times per hour for each sensor position.
  - Documentation should be available for each sensor position which can be stored and accessed
  - Sensors continue to operate independently in the event of a power failure

— The warehouse should provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store temperature-sensitive products.

— The warehouse should provide humidity alarm systems for temperature-controlled rooms used to store temperature-sensitive products that require a humidity-controlled environment.

12. Warehouse cleaning and decontamination program

— The warehouse should implement a cleaning and decontamination program for all temperature-controlled rooms:

- Floor areas are fully accessible for cleaning
- Goods are not stored directly on the floor
- Storage is not permitted for any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like
- No accumulation of dust, dirt and waste, including packaging waste
- Precautions are taken against spillage or breakage, and cross-contamination
- No accumulation of frost and ice, particularly ice contaminated by spillages
- Waste is collected in designated closed containers and arrange for safe disposal at frequent intervals
- Cleaning compounds and sanitizing agents shall be appropriate (anti-microbial, food grade approved) for non-product contact surfaces.

13. Personnel training

- Training has always been a large part of cold chain management or for handling cold chain pharmaceutical products
- All personnel must be adequately trained in the use of the equipment in the cold chain.
- The cold store or cold chain installer must provide a user training course.
- All personnel involved in the distribution activities should be competent on the basis of appropriate training in the requirements of cold chain and the handling of temperature sensitive products.
- Personnel training on cold chain requirements should be based on written standard operating procedures (SOPs).
- Personnel should receive initial and continuing training relevant to their tasks, in accordance with a written training program including but not limited to applicable pharmaceutical legislation and regulations, SOPs and safety issues.
- Trainings should be assessed as applicable to evaluate the effectiveness of the actions taken.
- Appropriate training records should be maintained, including details of subjects covered and participants trained.

14. Documentation & SOPs

- There should be a cold chain management policy or standard operating procedures. It should be available and applied.
- There should be documented evidence about equipment used, format for monitoring, and reporting processes.
- Warehouse should maintain transportation records of inbound and outbound shipments, including monitoring records where applicable, for a period of one year after expiry date of the product.
- Records of investigations and actions taken in the event of excursions outside predetermined temperature conditions, as per labeled storage conditions are kept for a minimum of one year after the expiration date of the product.

— Documents, and in particular instructions and procedures relating to any activity within the cold chain that could have an impact on the quality of pharmaceutical products, should be designed, completed, reviewed and distributed with care. They must be available at all times in the warehouse and reviewed regularly.

— The SOPs should cover:

- Methods for pharmaceutical products requiring specific warehousing conditions.
- Shipment preparation (including a description of the shipping configuration of the protective package used and taking into consideration the requirements for labeling, sealing and warning for the shipping / warehousing)
- Use of equipment and instruments related to the cold chain (refrigerator, cold room, controllers, etc.).
- Calibration of monitoring instruments dedicated to cold chain equipment.
- Validation or qualification of shipping carrier
- Corrective and preventive actions in case of unfavorable events during transportation under cold chain.
- Verification of the pharmaceutical product condition and labels in the receiving area as per the requirements (required verifications to ensure that containers have not been opened).
- Management of specific warehousing practice.
- Conduct of transportation study or qualification of transport system
- Defining, maintaining and ensuring temperature specifications during shipment
- Labeling policy and others that include cleaning, alarm management, qualification of thermal equipment, etc.
- Recall activities

— For temperature excursion management,

- Actions to be taken in the event of temperature excursions outside the labeled storage conditions.
- Investigation during temperature excursions outside the labeled storage conditions.

- Disposition of the stock in question must be evidence-based (for example, stability data and technical justification).

— Quality Risk Management procedure should be in place to identified and evaluation shall be made to estimate the severity, occurrence and detectability.

— Quality Risk Management report (monitoring to mitigate and identify risks) should be for both transportation and storage activities.

— The responsibilities and tasks (Job descriptions) should be clearly specified for each person with a role to play in the cold chain management

— All records associated with the product Management program shall be maintained for a specified number of years (at least 1 year).

— A document control system or procedure shall be in place to protect physical and electronic documents against loss and unauthorized access.

15. References

1. Food and Drug Administration, Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products. 2003
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7. US Pharmaceopaedia: Chapter<1079>: « Good Storage & Shipping Practices »; Updates: « Good Storage and Transportation Practices for Drug Products » (2010).

Annex

Annex 1: Cold chain assessment checklist

Name of Organization /Facility						
Address:						
Assessment date:						
Assessment team (name and signature):			_____ _____ _____			
				Yes	No	Remark
1.	Management (Mgmt.) Commitment	1.1.	Is there a TTSPP management policies and procedures and that are up to date?			
		1.2.	Is a product quality policy communicated to all levels of the organization and is there documentation for it?			
		1.3.	Is there a self-audit tool to audit the cold chain is on target for acceptance?			
		1.4.	Is there a procedure what to do if the facility has faced a cold chain failure? Or Emergency plans for product failure?			
		1.5.	Is there recall/traceability program or procedure in the case of product failure?			

2.	Facility Infrastructure	2.1.	Is the facility and its structures, such as ceilings, walls, floors, windows, vents, and drains, (e.g., pipes, air vents, and lights) designed and constructed of materials to be adequately cleaned and maintained in good repair, to protect product from cross-contamination?			
3.	Qualifications	3.1.	Is performance qualification is done for cold chain equipment, shipping containers and refrigerated vehicles?			
		3.2.	Is there transport route profiling qualification done?			
		3.3.	Is there any plan or procedure for requalification of reusable shipping container systems?			
4.	Calibration	4.1.	Are the cold chain devices calibrated periodically like temperature monitoring devices? or is there a procedure to test device for accuracy annually or biannually as per quality policy?			
		4.2.	Are there calibration records for temperature monitoring and/or measuring equipment?			
5.	Maintenance and Repair	5.1.	Availability of planned preventive routine maintenance to equipment and building?			
		5.2.	Is there an itemized vehicle and equipment replacement plan?			
		5.3.	Existence of emergency repair procedure to cold chain equipment?			

6.	Transportation practices	6.1.	Is TTSPP transported in a temperature monitored shipping containers and refrigerated vehicles?			
7.	Temperature monitoring during storage and transportation	7.1.	Is the ambient temperature along a transport route is recorded?			
		7.2.	Is the ambient operating temperature range provided for manufacturer for refrigerator or freezer or other equipment performs recoded and maintained accordingly?			
8.	Warehousing and storage	8.1.	Does the warehouse have practices for the inspections of incoming trucks and are inspections (e.g., cleanliness, temperature) documented, and available for review?			
		8.2.	Is graph/logbook/chart for temperature recording readily available and implemented?			
		8.3.	Is there Standby power supply or other means to avoid power interruption			
		8.4.	Is there procedure for what to do during a power failure?			
		8.5.	Is the good warehousing practices procedure in place?			
		8.6.	Are freeze indicators correctly used and/or are freeze indicators are used in all deliveries?			
		8.7.	Do the temperature control devices have an alarm system; is it in working condition?			
		8.8.	Is there a Pest Control Program and Procedures in the warehouse?			

9.	Warehouse cleaning and decontamination program	9.1.	Is there a cleaning schedule & record?			
		9.2.	Are cleaning compounds and sanitizing agents appropriate (anti-microbial, food grade approved) for non-product contact surfaces?			
10.	Personnel	10.1.	Is there a written standard operating procedure (SOPs) for Personnel training on cold chain?			
		10.2.	Is there a personnel training manual?			
		10.3.	Designated staff receiving the stock understand and follow the receiving procedures and systems.			
		10.4.	Have designated staff received training and/or an annual update on TTSPP management for cold chain?			
		10.5.	Designated staff have the proper warehouse operating forms.?			
		10.6.	Is personnel know regulatory standards and guidelines for TTSPP?			
		10.7.	Does the designated staff take corrective action when the temperature is out of range?			
		10.8.	Does the designated staff know who to call if the refrigerator / refrigerated cool room temperature is out of range or all deviations outside the limit? Is it stated in any procedure?			

		10.9.	Does the designated staff record the temperature level of the freezer / refrigerator cold room in the temperature log, at least twice a day or as per their procedure?			
11.	Documentation, records & SOPs	11.1.	Are records available for each and every cold room and freezer room?			
		11.2.	Are instructions and checklist, format available?			
		11.3.	Is there system to document Data logger records? Like computer system.			
		11.4.	Are performance qualification protocol and report available for each cold chain?			
		11.5.	Is there transport route profiling qualification protocol and report?			
		11.6.	Have the responses to all deviations outside the limit range been documented and recommended actions taken?			
		11.7.	Are all records associated with the product Management program maintained for a specified period (At least one year)?			
		11.8.	Is there a Quality Risk Management procedure for supply chain and report?			
		11.9.	Is there a standard practice for performance testing of shipping containers?			
		11.10	Is there a procedure for change control (transport change ,storage facility change and storage condition change)?			

		11.11	Is there a stability data that address the planned excursion and evaluates the worst case in terms of frequency and severity of excursions potentially encountered throughout the distribution chain?			
		11.12	Are there acceptance criteria for storage and transportation from manufacture to cold chain or between any sites?			
		11.13	Does a document control system protect physical and electronic documents against loss and unauthorized access?			