

Temperature and humidity monitoring systems for transport operations

Technical supplement to
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*Annex 9: Model guidance for the storage and transport of time and
temperature-sensitive pharmaceutical products*

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ECSP/ECBS version

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Contents

Acknowledgments	1
Contents	2
Abbreviations	3
Glossary	4
1. Introduction	8
1.1 Requirements.....	8
1.2 Objectives.....	9
1.3 Target readership.....	9
2. Guidance	10
2.1 Associated materials and equipment.....	10
2.2 Temperature and humidity monitoring devices	10
2.2.1 <i>Device types</i>	11
2.2.2 <i>Data collection, storage and retrieval</i>	15
References	16
Revision history	17

Abbreviations

CI	Chemical Indicator
ETI	Electronic Temperature Integrator
EDLM	Electronic Data Logging Monitor
IATA	International Air Transport Association
NIST	National Institute of Standards and Technology (USA)
PDA	Parenteral Drug Association
TTI	Time-Temperature Integrator
TTSP	Time- and Temperature-Sensitive Pharmaceutical Product
URS	User Requirements Specification

Glossary

3PL: Third party logistics provider: a firm that provides service to its customers of outsourced (or "third party") logistics services for part, or all of their supply chain management functions.

4PL: Fourth party logistics provider: a general contractor who manages other 3PLs, truckers, forwarders, custom house agents, and others, essentially taking responsibility for a complete logistics process for the customer.

Ancillary packaging components: Packaging elements used to protect the TTSP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices.

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. *Threshold type* chemical indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature. *Progressive type* chemical indicators register multiple events in a cumulative way. As long as the device remains below the threshold temperature no changes occur. However, whenever the threshold temperature is exceeded the reaction is activated and the indicator starts to change. Further temperature violations increase the change process. The indicator for this type of device usually takes the form of a progressive colour change along a paper strip.

Critical Control Point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to an acceptable or critical level. In the context of distribution and handling of time and temperature-sensitive healthcare products, critical control points are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk.

Electronic Data Integrator (EDI): A hybrid electronic instrument intelligently programmed like an Electronic Temperature Indicator (ETI) with the report/data producing capabilities of an Electronic Data Logging Monitor (EDLM) that combines the features and functions of a Go/No-go device with the record retention and data tracking of an EDLM. It uses pre-programmed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel.

Electronic Data Logging Monitor (EDLM): A small portable device that measures and stores temperature at a pre-determined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Electronic Temperature Indicator (ETI): A compact, portable device that measures, temperature over time by means of a built-in sensor. They come in a wide range of forms,

features, configurations, cost and levels of performance. Their composition consists of four basic components: a thermistor sensor, a microprocessor, a memory chip, and power source (lithium battery).

Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door-opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution*.

Humidity (Relative Humidity): The partial pressure of water vapour in air to the vapour pressure of saturated air at a given temperature. In other words, the relative humidity is the amount of water vapour present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature.

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution*.

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.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included¹.

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. The refrigeration unit requires an external electrical power supply when located at a land based site, on a container ship or on a quay. During road transport electrical power is typically supplied by a diesel generator.

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailers whose isolated thermostatically controlled cargo compartment is maintained at a temperature

¹ Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.*

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.

Service Level Agreement (SLA): A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes².

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature stabilizing medium.

Storage temperature: The temperature range listed on the TTSP label, and within the regulatory filings, for long-term storage.

Temperature excursion: An event in which a TTSP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water packs, phase change materials, dry ice, rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants.

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 pre-defined limits.

Temperature-modified: Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

Thermistor: An electrical resistor whose resistance is greatly reduced by heating, used for measurement and control.

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

Time-Temperature Integrators (TTI's): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see Chemical Indicators). The reactions are irreversible – once a colour change,

² Definition from IATA. 2013/2014 Perishable Cargo Regulations (ePCR) & Temperature Control Regulations (eTCR)

colour development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change colour, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative changes in temperature, such as heat, at a rate dependent on the Arrhenius Equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The colour development can be customized based on the known stability of the product, and in much the same way that most biologics and pharmaceuticals degrade when exposed to heat - faster at higher temperatures, and slower at lower temperatures.

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

User Requirement Specification (URS): The attributes assigned by the user in advance of a qualification test to establish minimum performance limits. Sometimes referred to as a *Functional Requirements Document*.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria.³

³ PDA Technical Report No. 39: *Guidance for Temperature Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment*, 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in Section 6.5 and Section 9 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*⁴.

The strength, efficacy, and potency of a drug can be profoundly degraded by changes in temperature. Some products may also be affected by exposure to adverse humidity levels⁵. It is not always possible completely to prevent degradation during transport, but damage can be minimized through good handling and storage practices, by qualifying the mode and route of transport, and by using qualified packaging.

For quality assurance purposes, stakeholders in the supply chain should be able to supply documentary evidence that the pharmaceutical product has not exceeded the acceptable limits of time, temperature and humidity exposure, as determined by the manufacturer's stability data for the product. This evidence is supplied by recording devices and technologies that provide a history of exposure to temperatures and/or humidity during transport and external distribution. It is important to bear in mind that humidity can only be *measured* during transport; it cannot generally be *controlled*.

Effective temperature and humidity monitoring is an important component of Good Distribution Practice (GDP) and can only be achieved if close attention is paid to the relevant Critical Control Points.

The following Technical Supplements are also relevant:

- *Qualification of temperature-controlled road vehicles.*
- *Qualification of shipping containers.*
- *Transport route profiling qualification.*
- *Temperature-controlled transport operations.*
- *Temperature and humidity monitoring systems for fixed storage areas*

1.1 Requirements

Generally speaking, the shipper is responsible for ensuring product temperature compliance during transport. Shippers should operate under the terms of a formal Service Level Agreement (SLA) with their carrier(s) or logistics service provider(s) i.e. freight-forwarder, 3PL, 4PL or integrator. If shipping operations are carried out in-house, they should be controlled by a comprehensive set of Standard Operating Procedures (SOPs).

SLAs and SOPs must clearly specify the types of temperature and humidity monitoring device that are to be used, when and where they are to be employed, and how the data they generate should be collected, reported and stored.

⁴ <http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf>

⁵ Note that it is generally considered that humidity exposure data has a minimal effect on drug products that are in their original manufacturer's packaging and further enclosed in an active or passive shipping container. However, there may be some products for which this is an important consideration. Card packaging and primary container labels can also be degraded by high levels of humidity.

1.2 Objectives

The objective of the Technical Supplement is to provide:

- A technical description of the device technologies used to record temperature and humidity exposure during the transport life-cycle of a drug product.
- A description of the documentary evidence that should be supplied to regulatory authorities and other interested parties so that quality assurance and regulatory compliance can be demonstrated and maintained.

1.3 Target readership

This supplement is intended for all those responsible for the transport of TTSPPs from one fixed storage point to another in the supply chain. The target readership also includes those responsible for providing evidence of temperature and humidity exposure during this process. Monitoring temperatures in fixed storage locations is covered by the companion Technical Supplement: *Temperature and humidity monitoring systems for fixed storage areas*.

Staff responsible for transport operations need to have a good knowledge of the various types of temperature and humidity monitoring device used in the transport environment, together with their strengths, weaknesses and appropriate uses. They must also be capable of operating, reading and interpreting data from these devices and must be familiar with, and follow, good documentation practice.

2. Guidance

Temperature control during air, ocean or ground transport can be maintained using either active or passive shipping systems. These systems are fully described in the companion Technical Supplement: *Temperature-controlled transport operations*; this supplement covers product packing, distribution and product off-loading for the following system types:

- Refrigerated and temperature-controlled vehicles;
- Passive shipping systems;
- Active shipping systems for air transport, and;
- Active shipping systems for ocean transport.

The guidance below focuses on the selection and use of suitable temperature monitoring devices for different legs (or stages) of the transport operation.

2.1 Associated materials and equipment

The key physical components of a quality-assured temperature-controlled transport system are the active and passive packaging systems in which products are placed during transport and the monitoring devices used to record temperature and humidity exposure within these packaging systems. The specific characteristics of the operational environments where these monitoring devices are used are described in the companion Technical Supplement: *Temperature-controlled transport operations*.

2.2 Temperature and humidity monitoring devices

The main reason for choosing a temperature or humidity-monitoring device is to determine whether or not the quality of a pharmaceutical product has potentially been compromised as a result of exposure to harmful or unwanted conditions. The type of technology and the device selected should be based on a user requirement specification (URS).

Depending on the purpose defined in the URS, the selected device may serve as:

- A device for determining acceptance or rejection of a shipment;
- A post-use analytical tool for determining weakness in the transport system, for carrying out a trend analysis, or for collecting performance data.

The level of detail provided by the available range of devices varies widely and is dependent on the specific application and the technology used. This is a field in which there is rapid technological development.

All monitoring systems must meet regulatory expectations and requirements and must provide the evidence needed to demonstrate that the TTSP has not been exposed to adverse temperatures during storage or transport. When specified to do so, the system must also be able to provide the temperature records needed for documentation purposes.

Single-use devices should be supplied with a manufacturer's calibration certificate and the certificate should cover the entire temperature range over which the device is designed to be used. These devices cannot be re-calibrated. Multiple use devices should be calibrated against a certified, traceable reference standard once a year, unless otherwise justified.

Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used.

Whenever devices are selected it is essential to consider the needs of the specific application, including ease of use and ease of integration across the supply chain. Some devices require additional software or hardware, such as a docking station; this may not be acceptable in certain use-cases. Whatever device or system is chosen, it should be accurate, stable, reliable and validated.

2.2.1 Device types

The glossary gives a full definition of each of the temperature monitoring devices listed below. Some of the more sophisticated electronic devices include humidity data collection. However, it is generally considered that humidity exposure data has minimal adverse effect on pharmaceutical products when they are in hermetically sealed primary packaging and further enclosed in an active or passive shipping container.

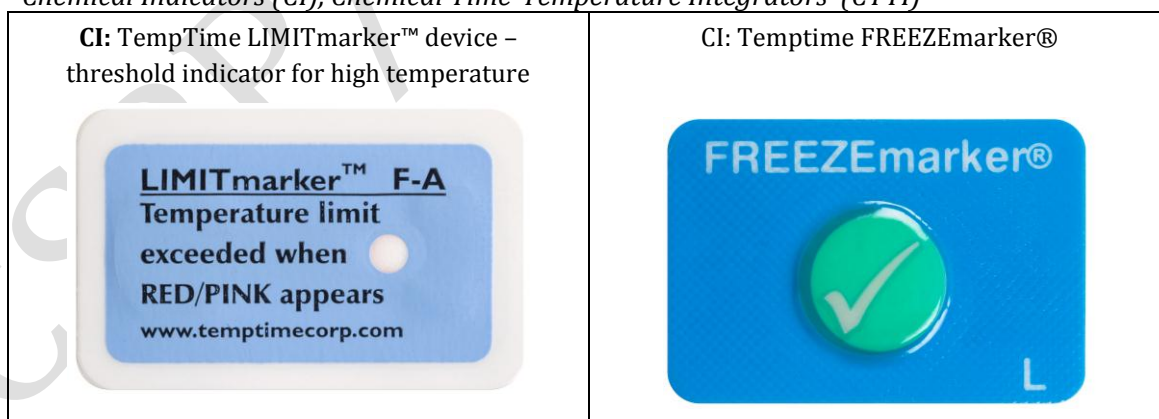
Figure 1 shows examples of the following commonly used device types and Table 1 itemizes their features, benefits, limitations and proposed applications:

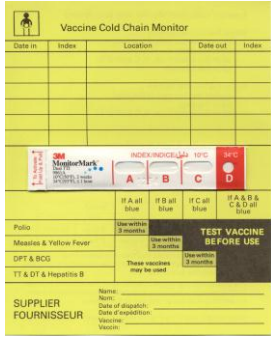

- Chemical Indicators (CI) both threshold and progressive types and Chemical Time-Temperature Integrators (CTTI).
- Electronic Temperature Indicator (ETI).
- Electronic Data Logging Monitors (EDLM).
- Electronic Data Integrators (EDI).
- Electronic temperature monitoring and event logger systems for refrigerated vehicles (TMEL).

The accuracy and level of performance of these devices varies between manufacturers and they should therefore be carefully selected to meet the specific URS.

Figure 1 – Examples of device types

Chemical Indicators (CI), Chemical Time-Temperature Integrators (CTTI)





<p>CI: Cold Chain Monitor Card (progressive and threshold types in one card)</p> 	<p>CTTI: Vaccine Vial Monitor</p> 
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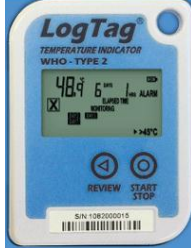

Electronic Temperature Indicators (ETI)

<p>Sensitech FreezeAlert™</p> 	<p>Berlinger Q-tag® Quad</p> 	<p>LogTag TICT-iSO°Tag®</p> 
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Electronic Data Logging Monitors (EDLM)

<p>Libero data logger</p> 	<p>LogTag® TRIX-8 Temperature Recorder</p> 
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Electronic Data Integrators (EDI)

<p>Berlinger Q-Tag® CLm Doc</p> 	<p>LogTag® TIC20</p> 	<p>VaxAlert™ Temperature Indicator</p> 
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Electronic temperature monitoring and event logger systems (TMEL)

Transcan Sentinel with thermal printer



Table 1 – Performance characteristics of monitoring devices

		Portable						Fixed
		CI		CTTI	ETI	EDLM	EDI	TMEL
		TCI	PCI					
Features and benefits	Provides go / no-go information at a glance	✓			✓			
	Responds when a temperature threshold has been exceeded	✓	✓		✓			
	Responds to a single event	✓			✓			
	Irreversible change	✓	✓	✓	✓			
	Responds to a temperature equivalent integrated over time			✓				
	Responds as a result of a single and cumulative events		✓	✓				
	Response occurs as a result of cumulative exposure		✓	✓				
	Visual indication: color change, color development, diffusion, graphical indication	✓	✓	✓	✓			
	No additional equipment needed to read results	✓	✓	✓	✓	1	1	1
	Accuracy of ±0.5 °C				✓	✓	✓	✓
	Multiple temperature alarm threshold capabilities				✓	✓	✓	✓
	Multiple time alarm threshold capabilities				✓	✓	✓	✓
	Alarm parameters programmable by manufacturer only	✓	✓	✓	✓			
	Alarm parameters programmable by manufacturer or user					✓	✓	✓
	Can be used as an analytical tool			✓		✓	✓	✓
	Capable of producing graphs, numerical data and summary reports				2	✓	✓	✓
	Single use devices are calibrated by manufacturer prior to use				✓		✓	
Devices are individually serialized for traceability	✓ ³	✓ ³	✓ ³	✓	✓	✓	✓	
User activation required		✓		✓	✓	✓	✓	
User deactivation required					✓	✓	✓	
Limitations	Accidental activation may occur if not properly stored/transported prior to use	✓ ⁴						
	Monitoring upper and lower limits at the same time requires use of two indicators	✓	✓	✓				
	Interpretation of color change may be affected by human factors		✓	✓				
	Not an analytical tool	✓	✓		✓			
	Standard time and temperature limits (some customization available for high volume applications)	✓		✓	✓		✓	
	Single use device	✓	✓	✓	✓			
	No time-specific traceability	✓	✓	✓	✓			
	Requires regular calibration					✓	✓ ⁵	✓
	Temperature accuracy varies over operating range				✓	✓	✓	✓
	Recording frequency and recording time tied to size of device memory					✓	✓	✓
	Additional proprietary hardware, software application or licensing may be required for downloading data				2	✓	✓	
	12-36 month battery life			✓ ⁶	✓	✓	✓	
Requires professional installation							✓	
Usage	Point-to-point distribution	✓	✓		✓	✓	✓	✓
	Entire life-cycle of drug			✓				

Key: CI: Chemical Indicator; TCI: Treshold Chemical Indicator; PCI: Progressive Chemical Indicator; CTTI: Chemical Time Temperature Integrators; ETI: Electronic Temperature Indicator; EDLM: Electronic Data Logging Monitor; EDI: Electronic Data Integrator; TMEL: Electronic temperature monitoring and event logger system.

¹ Some versions of these devices have LCD screens where results can be read. However, for download, additional equipment may be needed.

² Some versions of these devices are downloadable and produce both graphs and detailed data sheets

³ These devices are serialized by lot, not individually

⁴ If devices are incorrectly packed during shipment from the supplier, the START button on some electronic devices may inadvertently trigger activation. This is uncommon.

⁵ Applies only to multiple use devices

⁶ Some devices have 5 year battery life

2.2.2 Data collection, storage and retrieval

Different devices generate different types and amounts of information. Devices, such as EDLMs, that record time and temperature data that can be downloaded must be used to produce this information in accordance with the relevant regulatory requirements for documented data storage.

In most instance downloaded time and temperature data should be retained for at least three years in a non-volatile format that enables the data to be retrieved. Suitable formats include printed hard copies or a non-volatile and retrievable electronic medium such as a computer hard drive, tape drive, flash drive or DVD. Storage in a secure web-based data repository may also be acceptable.

Go/ No go data of the type supplied by CIs, CTTIs and ETIs should be recorded on the appropriate product arrival report and this information should be used to make decisions on whether to accept the TTSPPP consignment into active storage at the receiving store, or whether to quarantine it until an investigation has taken place and a final disposition has been made.

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Revision history

Date	Change summary	Reason for change	Approved