# ⟨1118⟩ MONITORING DEVICES—TIME, TEMPERATURE, AND HUMIDITY

## INTRODUCTION

This chapter provides background information about the science and technology of temperature and humidity monitoring over time. It describes the available technologies and performance characteristics, and provides recommendations for qualifying performance. The shelf life of a drug product is a function of the temperature and humidity conditions during storage and transportation, as well as the drug product's chemical and physical properties. For this reason, the ability to monitor those conditions is important in the shipping and storage of temperature- and humidity-sensitive drug products. This chapter focuses strictly on supply chain temperature- and humidity-monitoring devices, both electronic and chemical.

The storage and distribution temperatures may be different if justified by appropriate stability studies and as indicated in the labeling. The effects of humidity are typically observed over longer time periods of exposure than are temperature effects due to the barrier to moisture ingress presented by the primary and secondary drug product packaging.

The devices described in this chapter are those most commonly used to monitor the controlled storage and established distribution of drug products following Good Distribution Practices (GDP).[1] The chapter does not address measurement of temperature at extremes, which are temperatures above those that drugs are reasonably expected to experience in the supply chain. The types of devices described are already used in the worldwide distribution of pharmaceuticals and by other similar industries that require temperature control in distribution (for example, the perishable food, blood component, and medical device industries). Devices also may be attached to individual items for the end user (for example, vaccine vials in the World Health Organization (WHO)/UNICEF global immunization program).[2] Appropriate recycling practices should be followed for all devices as required by local regulations.

## TEMPERATURE-MEASUREMENT DEVICES

### Alcohol or Mercury Thermometers

These devices are based on the change in volume of a liquid as a function of temperature. Both types of thermometers can be designed to indicate the maximum and minimum temperatures (see *General Notices, 6.80.30. Temperature Reading Devices* for more information). Historically, these types of thermometers are used in a laboratory setting or in a pharmacy, rather than during supply chain monitoring. Alcohol thermometers can have a precision as good as 0.01°, but they must be quite large to measure temperatures in ranges of more than a few degrees.

Mercury thermometers are typically used in the ranges from 0° to 50° with a precision of about 0.1°. Some local regulations apply to mercury-based thermometers, and many states and local agencies have legislated or developed collection or exchange programs for mercury-containing devices. The U.S. Environmental Protection Agency also issues regulations requiring industry to reduce mercury releases to air and water, and to properly treat and dispose of mercury wastes to avoid potential health hazards.[3] Globally, Health Care Without Harm and WHO are co-leading a Health Care Initiative Products Partnership to reduce demand for mercury-containing devices by at least 70% by 2017 and to shift production to accurate, affordable, and safer nonmercury alternatives.[4]

Both alcohol and mercury thermometers are more fragile than other temperature-measuring devices described in this chapter.

### Infrared Devices

This device is used for measuring the infrared (IR) radiant heat from the article whose temperature is being determined, and the IR reading varies as a function of the object's temperature. The advantage of this type of device is that the article may be at some distance from the IR sensor. IR devices may give inaccurate higher or lower temperature readings because of the surface characteristics of packages (e.g., black vs. white surfaces), and they also have the potential for operator error because of incorrect use of the IR reader (improper angle).

### Resistance Temperature Detectors

The resistance temperature detector (RTD) is based on the change in electrical resistance of a material as a function of temperature. The precision and accuracy of an RTD depend on the quality of the electronics used to measure the resistance. Although RTDs are among the most stable and accurate temperature sensors, their accuracy may change with the age and temperature of the device because its electronic components are affected by age and use. Although all temperature-measurement devices should be placed on an appropriate calibration program as recommended by the manufacturer or user of the device, this calibration is particularly important for RTDs.

[1] PDA Technical Report 52 (TR 52) Guidance for Good Distribution Practices (GDPs) For the Pharmaceutical Supply Chain.
[2] World Health Organization (WHO)-UNICEF Policy Statement on the Implementation of Vaccine Vial Monitors: The Role of Vaccine Vial Monitors in Improving Access to Immunization, http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.04_eng.pdf.
[3] http://www.epa.gov/mercury/.
[4] http://www.noharm.org/.

### Solid-State Devices

Solid-state devices are based on the effect of temperature on either an integrated circuit (see *Thermistors*) or a micromechanical or microelectrical system. These devices are commonly referred to as data loggers, and can attain high precision and have the advantage of producing a digital output.

### Thermistors

A thermistor is a semiconductor device whose resistance varies with temperature. Thermistors are able to detect very small changes in temperature and are accurate over a broad range of temperatures.

### Thermocouples

Thermocouples are based on the change in the junction potential of two dissimilar metals as a function of temperature. Many metal pairs can be used, and each pair provides a unique range, accuracy, and precision. Precision and accuracy depend on the quality of the electronics used to measure the voltage across both metals and the type of temperature reference used.

### Thermomechanical Devices

Thermomechanical devices are based on the change in length of a solid material as a function of temperature. An example of such a device is a mechanical spring, which expands or contracts as a function of temperature, thus opening and closing an electrical circuit or moving a chart pen. Typical examples are chart recorders used in cold rooms.

## ELECTRONIC TIME–TEMPERATURE HISTORY RECORDERS

These recorders use one of the electronic temperature-measurement technologies described above and create a record of the temperature history experienced.

### Electronic Time–Temperature Indicators

Electronic time–temperature indicators (TTIs) can be designed to alarm after a cold excursion, heat excursion, or after multiple temperature excursions and can provide a visual alarm by a colored light or LCD. The alarm(s) are generally programmable and can display conditions such as date, time, temperature, and duration of the alarm. A certificate of calibration is issued for individual units or lots. Multiple-use devices should have a calibration schedule, but single-use devices can rely on manufacturers' certificates of calibration.



### Electronic Temperature-Data Loggers

Electronic temperature-data loggers are recorders that monitor the temperature at programmable intervals and save the temperature history to a peripheral system, such as a personal computer. In addition, data loggers can record humidity using sensors described below. Electronic recorders monitor and save temperature values representative of the cumulative temperature history over a period of time and therefore have the advantage of being able to calculate the mean kinetic temperature (MKT)[5] based on the measurements. Data loggers equipped with transmitting devices (hardwired or radio transmission) can be used to monitor the temperature and humidity of a product while in transit and can download the recorded data when the data loggers arrive at a destination. Data loggers are increasingly required by worldwide ministries of health as part of a standard quality system for GDPs. Based on their communication capabilities, data loggers can be grouped into several different categories.

### Radio-Frequency Data Loggers

In addition to data loggers that require a hardwired connection to a base unit or a computer, in recent years companies have adapted wireless (radio-frequency or RF-enabled) temperature and humidity recorders. The effects of radio-frequency identification (RFID) use on biologics have been studied on a variety of blood, blood components, monoclonal antibodies, and vaccines, and have demonstrated no effect.[6] These loggers are integrated with chips capable of wireless RF communications that constitute the RFID sensor tags. The RFID chip inside the tag can be either active, which requires battery power for operation, or passive, which requires a nonzero RF field created by the RFID interrogator host unit (commonly called the reader) in the vicinity of the tag. RFID-enabled sensor tags (temperature and/or humidity) have the added capability of conveying recorded temperature history wirelessly to a host computer or database for seamless downstream processing. Multiple passive

[5] The Use of Mean Kinetic Temperature (MKT) in the Handling, Storage, and Distribution of Temperature Sensitive Molecules. R. H. Seevers, J. Hofer, P. Haber, D. A. Ulrich, R. Bishara. Pharmaceutical Outsourcing, May/June, 30–37, 2009.
[6] Effects of Radio Frequency Identification-Related Radiation on In Vitro Biologics. I. Uysal, C. Hohberger, R. S. Rasmussen, D. A. Ulrich, J. P. Emond, A. Gutierrez. PDA Journal of Pharmaceutical Science and Technology, Vol. 66(4), July/Aug, 333–345, 2012.

and active standards exist to control the communication between the tag and the host unit, including ISO-18000-6C,[7] ISO-18000-7,[8] ZigBee,[9] IEEE 802.11,[10] and many proprietary standards.

When choosing between active and passive technologies, one needs to know that active technologies typically have extended communication range and memory capabilities at the expense of a higher price. Currently, reading ranges extend to 100 m and with repeaters longer distances can be achieved. Whether the communications circuitry is passive or active, these RF loggers still are electronic temperature recorders, which means their sensor circuitry uses external power from batteries or other sources.

A completely passive wireless RFID tag with an antenna capable of functioning as a sensor has been developed. The tag uses resonant antenna structures of RFID tags that are coated with specific sensor films. The passive wireless RFID tags act like analog sensors that, when interrogated by a wireless reader, show the instantaneous temperature. The film changes the antenna's reflection characteristics based on the monitored environmental variable (such as temperature and/or humidity), which then is decoded by the reader. The sensor film can be designed to work with different variables such as temperature, humidity, and various gas and chemical vapors. Although they lack some of the memory functionality included in electronic recorders, passive wireless sensors are relatively cost effective compared to data loggers and can be considered for item-level applications.

## CHEMICAL TEMPERATURE INDICATORS

Chemical temperature indicators are relatively cost effective compared to electronic data loggers and can be considered for item-level applications There are two basic types of chemical temperature indicators: 1) a threshold indicator that responds at a specific temperature and 2) a TTI that responds to cumulative heat exposure.

### Chemical Temperature Threshold Indicators

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. Chemical temperature threshold indicators are reversible or irreversible and are suitable for high or low temperatures. Temperature threshold indicators do not include any specified time delay to 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.

**Ascending-Temperature Threshold Indicators**—Ascending-temperature threshold indicators are supplied as self-adhesive labels or cards and are normally composed of a heat-fusible compound that melts at the critical temperature. Melting of the compound gives rise to a color change or color development. Other types are provided as inks, lacquers, pellets, or crayons. Ascending-temperature threshold indicators are available from 0° to more than 200° and as many as 10 temperatures on a single unit. Some ascending-temperature threshold indicators used to monitor frozen or refrigerated temperatures require an activation step (such as a pull tab or a reservoir that is ruptured by pressure).

**Descending-Temperature Threshold Indicators**—Descending-temperature threshold indicators show a response when exposed to temperatures below a threshold. These indicators do not include a specific time delay to show a response, and the response is typically caused by the time required for solidification of a liquid at the threshold temperature. Solidification of a liquid causes a visual change in the indicator. Examples include: 1) the expansion of the liquid to crack an ampule and release a colorant, 2) contraction of the liquid to mix components to develop color, or 3) aggregation of colloidal particles to change color.

### Chemical Time–Temperature Indicators

These indicators, sometimes referred to as time–temperature integrators (TTIs), include systems in which a 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 (discussed above). The reactions generally are irreversible—once a color change, color development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state, but lower temperatures (refrigeration) will slow the color change. The accuracy and precision of these indicators depend, to some extent, on human interpretation. Some versions of chemical indicators have been prepared in a bar code format and can be read with bar code readers. Other developments include reading a chemical indicator with an imaging device such as a camera in a smart phone.

TTIs do not directly reflect the status of the drugs to which they are attached. In actual practice, the characteristics for degradation of a particular drug are known from accelerated and real-time stability studies that follow internationally accepted guidelines such as PDA TR 53[11] to guide selection of a suitable TTI.[12] The activation energy of the TTI is not required to exactly match the activation energy of the degradation of the drug being monitored, and the latter, in fact, may not be known precisely. Therefore, the TTI should be chosen to provide an early warning if the drug is exposed to an excessive heat load before the expiration date.

[7] ISO/IEC 18000-6:2010–ISO/IEC 18000-6:2010—Information technology– Radio frequency identification for item management–Part 6: Parameters for air interface communications at 860 MHz to 960 MHz.
[8] ISO/IEC 18000-7:2009—Information technology–Radio frequency identification for item management–Part 7: Parameters for active air interface communications at 433 MHz.
[9] IEEE 802.15.4—Wireless Medium Access Control (MAC) and Physical Layer (PHY) Specifications for Low-Rate Wireless Personal Area Networks (LR-WPANs), 2003.
[10] IEEE 802.11—Wireless Local Area Networks (LANs), 2007.
[11] PDA Technical Report 53 (TR 53) Guidance for Industry: Stability Testing to Support Distribution of New Drug Products, https://store.pda.org.
[12] ASTM F1416–96 (2008) Standard Guide for Selection of Time Temperature Indicators.

An important characteristic of chemical TTIs is the precision with which the end point can be determined. For TTIs that change color, a reference color normally brackets the active portion of the TTI to show the end point color, which simplifies TTI interpretation. Accuracy can vary widely with the control and quality of the manufacturing process. Some TTIs are manufactured by procedures that comply with Quality System Regulations for Medical Devices. As discussed below in *Calibration of Temperature- and Humidity-Monitoring Devices*, it is not possible to calibrate any individual single-use device because the test is, by the nature of the TTI, necessarily destructive. This is analogous to any pharmaceutical product because each dose cannot be calibrated or validated, but validated processes should be used in the manufacturing process.

The two types of TTIs are partial-history indicators and full-history indicators. Partial-history TTIs provide a time- and temperature-dependent response when the temperature exceeds a predetermined value. A partial-history indicator normally is composed of a dyed, heat-fusible compound that diffuses along a porous strip or wick when the temperature exceeds the melting point of the compound. The diffusion process of the compound down the wick is temperature dependent, and therefore the partial-history TTI provides a time and temperature response above the melting point of the compound. Migration of the compound down the wick stops when the indicator is moved to a lower temperature at which point the compound solidifies. These TTIs normally have one or more viewing windows to monitor the length the dyed compound has traveled along the wick. Some indicators are activated by removing a barrier film that separates the dyed compound from the wick or rupturing a reservoir that contains the dyed compound. Other indicators do not require activation and must be stored below the melting point of the compound before use. These partial-history TTIs can have durations (service life) anywhere from several hours to several years. Full-history TTIs provide a continuous response to temperature. They change color or physical appearance as a result of exposure to time, and the rate of change increases with temperature so they are sensitive to cumulative heat exposure. Full-history TTIs are responsive to MKT (Ref 1079) and typically are single use, irreversible, and disposable because once the color changes it will not revert to the original color.

### Chemical–Physical Time–Temperature Indicators

This type of TTI is based on a temperature-dependent diffusion or chemical reaction process. It consists of a pressure-sensitive tape device that is composed of an indicator tape and an activator tape. In one example, the indicator tape contains a dye precursor dispersed in a polymer carrier. The activator is incorporated into an adhesive on the activator tape. Laminating the activator tape over the indicator tape causes activation. A color change or readable message occurs as the activator migrates into the indicator as a function of temperature and time. Other approaches to develop color changes include the use of a pH indicator or the etching of aluminum by the activator tape.

### Chemical Polymerization–Based Time–Temperature Indicators

This type of TTI uses a solid-state polymerization process in which a color develops intensity as a function of time and temperature. The color evolution is caused by the polymerization of a colorless monomer to a highly colored polymer. These TTIs can be applied by a print process that permits direct integration into a product label or stand-alone label. Because this type of TTI does not require activation, it must be shipped from the manufacturer on dry ice or under frozen conditions and stored at temperatures according to the manufacturer's instructions, normally below –24° before use. Chemical polymerization–based TTIs can be designed to reach the end point as quickly as weeks at refrigerated temperature or as long as years at controlled room temperature.

### Chemical Enzyme–Based Time–Temperature Indicators

This type of TTI uses an enzyme-catalyzed color-generating reaction that occurs as a function of time and temperature. The color change is caused by an enzyme reacting with a substrate, accompanied by a change in pH. The enzyme and substrate are in separate solutions in adjacent compartments. Breaking the barrier between the two compartments and mixing the two solutions activates the TTI.

### Chemical-Organic Pigment–Based Time–Temperature Indicators

This type of TTI uses an organic pigment that is activated by exposure to ultraviolet light to develop a dark blue starting color. A filter is then placed over the label to protect it from deliberate or accidental reactivation. The colored pigment fades over time as a function of temperature.

## RELATIVE HUMIDITY MEASUREMENT TECHNOLOGIES

Relative humidity is the ratio of the partial pressure of water vapor in air to the vapor pressure of saturated air at a given temperature. In other words, the relative humidity is the amount of water vapor present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature. Extensive tables of relative humidity data are available. Devices for measuring relative humidity are called hygrometers. Several different technologies exist for measuring relative humidity.

### Sling Psychrometer

The simplest type of hygrometer is based on the temperature difference observed between two identical thermometers, one ordinary and one with a wet cloth wick over its bulb. The two thermometers are whirled at the end of a chain, and the evaporation of water from the wick cools (based on evaporative cooling) the wet-bulb thermometer. The temperature difference

between the wet and dry thermometers then is compared to a table specific to that psychrometer based on dry-bulb temperature, and the relative humidity is determined.

### Hair Hygrometer

This type of device is based on the fact that the length of a synthetic or human hair increases as a function of the relative humidity. This change is used to move an indicator or affect a strain gauge. A hair hygrometer can be accurate to ±3%, but it is unable to respond to rapid changes in humidity and loses accuracy at very high or very low levels of relative humidity.

### Infrared Hygrometer

This type of hygrometer determines relative humidity by comparing the absorption of two different wavelengths of IR radiation through air. One wavelength is absorbed by water vapor and the other is not. This type of hygrometer can accurately measure relative humidity in large or small volumes of air. It is sensitive to rapid changes of humidity and can be integrated with an electronic data-handling system.

### Dew Point Hygrometer

This type of device uses a chilled mirror to determine the dew point of an air sample. The dew point is the temperature at which water vapor in the air begins to condense; that is, the temperature at which the relative humidity is 100%. The relative humidity can be calculated from this measurement and an accurate measurement of the ambient temperature. The dew point hygrometer is the standard against which most commercially available instruments are calibrated.

### Capacitive Thin-Film Hygrometer

The principle of this type of hygrometer is that the dielectric of a nonconductive polymer changes in direct proportion to the relative humidity. This change is measured as a change in capacitance. This type of hygrometer is accurate to ±3%.

### Resistive Thin-Film Hygrometer

This type of hygrometer is similar to the capacitive thin-film type because it uses the effect of changing relative humidity on an electric circuit. In the resistive thin-film hygrometer the sensor is an organic polymer whose electrical resistance changes in logarithmic proportion to the relative humidity. This type of hygrometer is accurate to ±5%.

## CALIBRATION OF TEMPERATURE- AND HUMIDITY-MONITORING DEVICES

Thermometers and hygrometers that are used to provide data about the temperature and humidity exposure of a product must be suitable for their intended use. Specifically, they must be appropriately calibrated. A calibration program assures the user of the monitoring device that the device has been tested before use either by the manufacturer or the user to assess the suitability for its intended use. Calibrations should be performed with appropriate frequencies to support ongoing use. Monitors used in manufacturing, storage, and transport of drug products should be properly qualified by their users to ensure that the monitors have been received and maintained in proper working order. It is acceptable to use the calibration performed by the device's manufacturer based on the certificate of calibration and expiration date.

For temperature- and humidity-monitoring devices, measurement accuracy refers to the closeness of the value obtained with a particular device and the true value of the object or environment under measurement. In practice, this is determined by comparison with a device that has been calibrated against a standard that is obtained from or is traceable to the National Institute of Standards and Technology or a comparable national metrology organization.

Any monitor takes time to respond to a change in the temperature or humidity. Measurement responsiveness typically is defined in a device's specifications for its operating range. Different data recording intervals are appropriate for different monitoring applications and should be based on supply chain length (for example, transportation via ocean may require 30-min intervals, but 15-min intervals may be suitable for air transport). Most commonly, time accuracy is expressed as a ± percentage of total duration of the recording period. For pharmaceutical applications, a ±0.5% time accuracy is adequate.

Single-use electronic and chemical indicators should follow Good Manufacturing Practices with appropriate testing controls. Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots. For TTIs that calculate MKT, the performance of a batch can be assessed statistically by subjecting an appropriately sized sample to elevated temperature conditions for a set period of time and observing the results. Manufacturers should adopt appropriate acceptance criteria. It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or qualification.

## THE USE OF HISTORICAL TEMPERATURE DATA

Although historical geographic and seasonal trends may be used as a planning tool in selecting among the types of temperature- and humidity-monitoring devices, outside ambient temperatures are not necessarily reliable indicators of the temperatures experienced by different items in the distribution chain. For example, studies have reported important departures

from ambient temperatures on summer days for mailboxes, trucks, and warehouses.[13] Therefore, using lane-specific temperature monitoring is beneficial when manufacturers and shippers develop an ambient profile and can be a valuable consideration for a risk-based approach to maintain product quality.[14]

A drug product's quality (identity, strength, and purity) may be notably influenced by variations in temperature and humidity over the course of its shelf life, so manufacturers should appropriately monitor those environmental conditions. Pharmaceutical manufacturers perform stability testing to carefully evaluate the effects of temperature and humidity on their products. The packaging, shelf life, and storage and transportation conditions recommended for a product are chosen based on the results of these stability studies. Temperature effects can happen rapidly; therefore, temperature monitoring should be implemented on a risk-based approach taking the product stability, distribution route, mode of transportation and potential risks that may compromise the quality of the product into account. Relative humidity effects occur over a much longer time frame; humidity monitoring can be omitted when the drug product is sufficiently protected by the primary container proven by sound stability studies. Humidity monitoring is recommended when special environmental restrictions concerning the humidity are defined for the drug product.



[13] Okeke, C.C. Medwick, T., Bailey, L.C., and Grady L.T. Temperature and Humidity Conditions During Shipment in International Commerce, *PF* 25(2) Mar.–Apr. 1999.
[14] ISTA 7E Standard, http://www.ista.org.