VAISALA / APPLICATION NOTE

Matching Environmental Monitoring & Mapping to FDA/ICH Guidance for Better Stability Studies

Mitigating Risk in Stability Applications

Stability testing and monitoring is a critical step in drug research, development and manufacturing. It impacts how pharmaceuticals are produced, packaged, labeled and sold. Creating the exact environmental conditions in a stability test is a complex process, but necessary to comply with standards defined by regulatory bodies like ICH and the FDA, as well as to ensure the safety and efficacy of pharmaceutical products.

Guidance on stability monitoring for medicinal and pharmaceutical products is addressed by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use). The final guidance has been adopted across Europe, Japan and the United States. Additionally, the FDA states in 21 CFR part 203 that manufacturers, authorized distributors of drugs and their representatives shall store and handle all drug samples under "conditions that will maintain their stability, integrity and effectiveness," ensuring that the drug samples are free of contamination, deterioration and adulteration.

However, if the data compiled during a stability study is inaccurate or incomplete, the credibility of the study is at risk and creates the potential for devastating liabilities and loss. Background knowledge of the basic attributes of sensors, their calibration details and the recording and reporting capabilities is helpful when deciding on a system for performing accurate, gap-free stability studies.

Sensor Accuracy: Crucial in Stability Testing

A data logger can record temperature and humidity within a defined operating range, but there are other parameters that must be taken into account lest the data obtained comprise only evidence of conditions within that range. A truer picture is gained for the test environment by considering the uniformity of conditions and calibration uncertainty of the measurement device used.

To establish uniformity, it is necessary to perform a mapping study. To manage calibration uncertainty for the devices used to map the stability chamber, the device manufacturer should have factored temperature non-uniformity into their calibration process. For instance, before calibrating humidity sensors that will be used in a stability mapping application, the manufacturer performs a high-accuracy temperature calibration on every data logger. Each logger's measured temperature is then able to *compensate* for chamber non-uniformity during RH calibration — greatly reducing this source of error.

Temperature and Humidity Sensors

Temperature is an easier parameter to accurately measure because temperature calibration is a straightforward process. Most standard temperature sensors provide accuracy to ±0.10°C. Obtaining accurate humidity measurement is more complex because if your procedure requires that you cycle temperature and humidity, the humidity sensor has to be temperature-compensated for that range.

Unless the humidity sensor is of superb quality and properly calibrated, it will quickly degrade to the point where data obtained is inaccurate and essentially useless. Most humidity sensors are highly unstable, losing accuracy from the exposure to moisture that is part of any rigorous stability testing process. This is why humidity sensors must be regularly calibrated for the environment in which they will be used; to reduce the "drift" in accuracy that occurs with each stability study.

Calibration intervals will vary based on the type of sensor and the conditions of operation (range of temperature and humidity, atmospheric contaminants, etc.). Stability applications require humidity sensors that are calibrated over a wide range of calibration points, and with all factors on accuracy taken into account.

Immunizing Stability Studies from Data Gaps

Ideally, data loggers that are used for monitoring stability test environments are flexible and stable enough for validation as well. The purpose of performing regular validation of stability chambers is to ensure that acceptance criteria are met throughout the chamber, i.e.: temperature and humidity are evenly distributed. While the exact number of sensors will vary with the size of the chambers, most validation technicians use at least ten sensors, for example, one sensor at each of the chamber's corners and at the center, or 3 sensors on each shelf. Traditionally, temperature mappings were conducted with thermocouples; however, this sensor has been mostly outmoded by more stable and accurate thermistor-equipped data loggers, which can often contain humidity sensors as well. The simplest option for mapping stability chambers is to use wireless sensors.

A major issue in any validation process is the risk of "data gaps" in critical test procedures. This occurs when the data collection systems stop taking readings due some sort of infrastructure failure. The result is periods of time where no temperature or humidity data are recorded.

Regardless of the system or method used (both chart recorders and centralized systems share this vulnerability), the potential for data gaps exists.

In the case of chart recorders, possible causes of gaps in data include:

- Chart paper or ink runs out
- Power outage or disruption
- Undetected damage to the recorder mechanisms

With centralized data recording systems, data gap causes include:

- Power outages
- Network failures
- Wire cuts
- Equipment relocation
- System viruses
- Computer crashes
- Component malfunctions
- Operator errors

Minding the Gaps for Regulations' Sake

To eliminate the risk of data gaps, most stability monitoring applications use data loggers that include an automatic back-up to function as "redundant" data collectors. Each device collects data independently, with its own memory and power source. Used as a primary, or a secondary data collection system, the loggers fill in any gaps that may occur as a result of recording failures.

For regulatory reference in stability monitoring and validation, the FDA, CDER, CBER and the ICH have published "Guidance for Industry: Q1A (R2) Stability Testing of New Drug Substances and Products," which seeks to define what stability data is sufficient within the three regions of the European Union (EU), Japan, and the United States. Under the General Principles of this guidance, the purpose of stability testing is stated as the need to produce evidence on how the quality of a drug substance or product is affected for a given amount of time and under the influence of a number of environmental factors, including temperature, humidity and light.

Stability testing should also help define a retest period, as well as recommended storage conditions for the determined life cycle of the drug. Another source of guidance on stability testing is the World Health Organization, which has published "Stability testing of active pharmaceutical ingredients and finished pharmaceutical products Annex 2" as part of their Technical Report Series. Both guidances contain key principles of designing and executing stability testing protocols.

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