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Automated climate monitoring in a validated environment

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Abstract

Both pharmaceutical and medical technology products directly influence the health and well-being of patients and users. Efficacy, identity and purity are therefore the most important quality attributes applied to these products. In order to guarantee the required quality, the monitoring of the climate parameters of temperature (°C) and relative humidity (%RH) in particular assume a key role in production and storage. There are also detailed requirements for this in directives and standards. Nevertheless, these very parameters are often recorded and documented using manual or semi-automated methods which are inadequate or prone to errors. In this respect, all the criteria support the use of automated monitoring systems which record, analyze and continuously document measurement data autonomously, in particular where there are critical and sensitive environments and processes. Systems of this kind also have alarm functions to enable a fast response in the event of a violation of limit values. There are special requirements for computer-based systems of this kind in a validated environment which ensure that the recorded data are just as reliable and have the same level of integrity as manually recorded and signed data sets. This for instance includes a detailed authorization concept along with electronic signatures. In order to be able to meet the requirements of a really wide range of measuring tasks, automated systems have to reconcile the issues of reliability and flexibility.

Keywords

- Temperature monitoring
- Climate monitoring
- Monitoring
- Measurement data
- Data loggers
- CFR

References

“Testo Saveris temperature monitoring system is a great tool which is helping us to monitor the storage conditions (temperatures, humidity) of our may important pharmaceutical samples. It is one simple to use but powerful system that monitors all our freezers, refrigerators, storage rooms and stability chambers which are in different physical sites.”
Ying Chen
Research Scientist at Wilmington Pharma Tech

“It is important to keep our devices at the right temperature and humidity. The Saveris 2 data loggers work well for our needs and I can access the readings even when I am working from home due to the corona virus pandemic.”
Sue Thomas
Quality and Regulatory Manager at Pajunk Medical Systems

Objectives of climate monitoring

Pharmaceutical and medical technology products come into direct contact with people or animals. This means they directly influence the health and well-being of patients and users.

Efficacy, identity and purity are therefore the most important quality attributes applied to these products.
The raw materials and substances involved, but also the end products, are very sensitive to the wrong climatic conditions, such as temperature and humidity. Incorrect conditions may mean the stability and therefore the efficacy of drugs are significantly affected.

This is primarily due to proteins, which are found in many pharmaceuticals. They are extremely sensitive to changing environmental influences, but in particular to temperature fluctuations. However, it is not only the drugs per se, or their ingredients, that are at risk when stored outside the permissible temperature range, their storage containers or packaging are also affected. Sub-zero temperatures or major fluctuations in temperature can cause hairline cracks in vials and glass containers or dissolve out glass fragments. This can lead to contaminations and even to a loss of sterility.

When storage conditions are too humid, this can also negatively influence the quality of drugs, making them useless for any further application: damp packaging or blurred and illegible labelling occur, as well as mould on and in boxes.

For these reasons, constant monitoring and documentation of the prevailing climate parameters in the relevant areas are indispensable and they are controlled by a really wide range of regulations and legal requirements. These for instance include the specifications of the World Health Organization (WHO) regarding Good Storage Practice (GSP), the requirements of the United States Pharmacopia (USP) and Active Pharmaceutical Ingredients (AMWHV), along with the FDA guidelines on Good Manufacturing Practice (GMP) and the US requirements regarding Current Good Manufacturing Practice (cGMP) from 21 CFR Part 211.

This means that sophisticated climate monitoring is an enormously important component of the whole product development and distribution process – starting in the research laboratory, via production (see Fig. 1) and storage, through to the final transport of the goods.

Cleanrooms are also very sensitive in this connection. Here, quality assurance also has to involve permanent monitoring and documentation of the differential pressure, air flow velocity and quantity of particles in the air, in addition to the temperature and relative humidity parameters which have already been mentioned.

The risk of financial losses is another very important reason for permanent monitoring of the right environmental conditions, though it is somewhat supporting to the quality attributes. Disruptions to production caused by the wrong conditions or negatively affected operating procedures may entail high costs either directly or further downstream.
It is not possible to exclude all risks through monitoring, but they can be reduced to a manageable and safe level.

Figure 1: Pharmaceutical environment
(source for all images: Testo SE & Co. KGaA).

Current measuring technologies

There are different ways to measure important climate parameters. Measuring values can thus be recorded using mechanical, analog or digital methods. This process can be carried out manually or in a semi-automated or fully-automated way. The technology which is used in each individual case very much depends on the sector and the directives in force.

In some sectors, electronic measurement methods are mandated by law, which for example excludes the use of analog liquid thermometers right from the start.

The use of electronic measuring instruments makes sense for a number of reasons: Analog measuring instruments already have a high potential for errors, simply because the measuring values have to be read out from an analog display, which does not have the high resolution of an electronic instrument. In this respect, the question of how accurately individual employees are able to read out the display also arises. There is already the potential here of allowing unacceptable ranges of fluctuation in terms of the measuring value. Measurement methods of this kind cannot of course be used for extremely critical processes and areas of application which involve measuring the temperature to the tenth of a degree – particularly as documentation which is carried out manually also has an enormous potential for errors and tampering.

With semi-automated methods, such as electronic handheld measuring instruments or data loggers, measurement is carried out digitally and automatically. However, manual steps are still necessary to analyze the data. For example, with data loggers an employee has to read out the values on each individual measuring instrument and transfer them to a database, which involves a very labor and time consuming process, depending on the number of measuring points.

When we look back at all the measurement methods described, the reflection is the same: the values read out only really show whether all the parameters have complied with the limit values in the last cycle. However, if the temperature has for instance been exceeded, it is still necessary to check what effect this excess temperature had on the product or process. There is no possibility of actively intervening and promptly reacting to incorrect parameters. Only automated systems are in a position to do this.

Automated climate monitoring

What can measurement systems which provide automated climate monitoring offer? The answer is already contained in the question: they monitor.

All the options described so far measure and document measurement data, but they do not monitor them. In addition to recording and documenting measuring values, monitoring also involves providing alarms in cases which may be dangerous for the in-house products and processes. This means that modern monitoring systems offer a really wide variety of alarm options, from simply providing an alarm when there is a violation of limit values, through to synchronized cascading of several alarm recipients. This is intended to ensure that an alarm notification is delivered to the required recipients, even at critical times of the day. The alarm notification itself can be provided either via acoustic or visual signals, but also by sending messages via text message or emails. In addition, these kinds of systems not only monitor the measuring points which have been set up, but also their own status as part of the process. This means they can detect problems autonomously within their own systems, including for example connection problems, low battery statuses or an inadequate mobile phone network. All the conditions that jeopardize the reliable operation of the system can be detected, reported and thus immediately rectified.

What does an automated system offer in addition to this? As well as providing alarms, these kinds of modern systems have 2 very important advantages which make the entire measurement reliable and save resources. This involves the automatic transmission and documentation of the measuring values. In this respect, transmission of the measuring values from the measuring point to the database is possible both via Wi-Fi, and a wired connection. Many systems combine these possibilities, which means the technology has a high level of flexibility and readiness for use. This process involving

the automated transmission and analysis of measuring values prevents all errors which may occur due to the human factor in manual readouts and the interpretation of values. Furthermore, any tampering with the values is virtually ruled out. This is ensured by automatic documentation and reporting which is set up individually. This means that reports are generated from the raw data and even directly dispatched, without there being any contribution from a user.

The validated environment

A validation is required everywhere where documented proof has to be provided that a process or system meets previously specified requirements in a reproducible way. For the pharmaceutical sector in particular, this means that a measurement system is tested within the operational environment and together with all the influences that have an effect on the system and has to comply with all the prescribed directives and laws in the process. Special mention of the 21 CFR Part 11 and GxP directives is needed here. In this respect, GAMP 5 (Good Automated Manufacturing Practice) is the accepted guideline for the validation of computer-based systems in GxP-regulated areas. It describes the validation process, but is not binding. Automated measurement systems necessarily involve so-called computer-based systems, which means they have to be validated according to these specifications. In this respect, a computer-based system not only includes the actual system itself, but also to the same degree the environment in which the system is used. In addition to the hardware and software, the personnel and their processes and equipment, along with the neighbouring systems, form part of the validation (see Fig. 2).

Special mention is needed here of the 21 CFR Part 11 directive from the US statute book which was referred to previously. This deals with the handling of electronically stored data sets and the necessary security measures related to this. This involves an electronic record being seen as equivalent to a record with a handwritten signature in terms of integrity and trust. A manual activity which has been replaced by a computer-based system must not therefore be impaired with regard to quality and control.

All data sets which are created, modified, maintained, archived and transmitted, and thus may also be the subject of a GxP inspection, come under this directive.
The systems used must already be equipped with the necessary requirements by the manufacturer, so as to be able to achieve this high level of reliability. This involves ensuring through detailed user management that employees and their authorizations can be individually configured. There is therefore a guarantee that individual system contents are only used by authorized employees. Furthermore, control is crucial: systems must have the possibility of noting every movement within a system and assigning it to an employee. This may for example involve login/logout, setting limit values or the acknowledgement of alarms. To achieve this, there is the so-called audit trail, along with electronic signatures. Every action is unambiguously assigned to one person by these mechanisms.

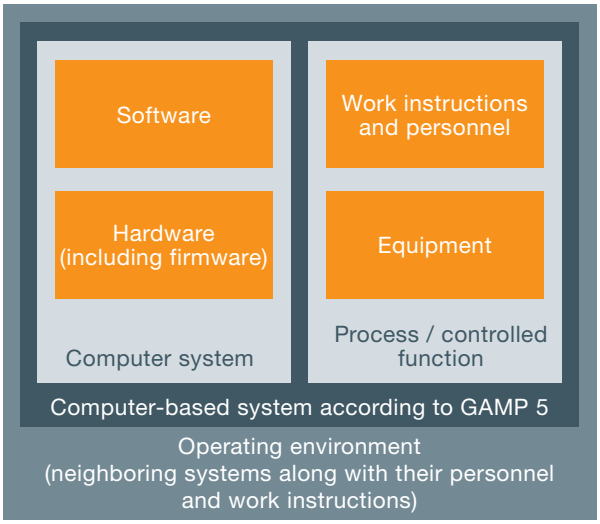

Figure 2: Computer-based system according to GAMP 5.

The possibility of combining flexibility and reliability

In regulated sectors, it is justifiable to ask the question as to whether the high reliability requirements allow a system which is individually tailored to every customer requirement. Closer consideration of both terms, flexibility and reliability, is needed to answer this question. What do they involve and can they be combined with one another?

When is a monitoring system flexible? Firstly, it has to offer the technological capabilities to enable the recording of individual measuring points. It must therefore have functions

allowing it to deal with long distances and architectural challenges. Secondly, a wide selection of sensors is an advantage, enabling the user both to reach difficult measuring points and to achieve the required levels of accuracy. If a system is installed, it must have the ability to grow with the customer's tasks, as well as to adapt to the conditions that prevail with the customer in each individual case and to be extended in line with these.

Users must also be mentioned when it comes to flexibility. The system should be intuitive to operate, so that a variety of different users can handle it reliably. The maxim that employees' work should be made easier and not more difficult applies here.
In contrast to flexibility, the 3 key words of availability, integrity and data protection are at the heart of the topic of reliability. Availability means that continuous and dependable measurement data documentation is ensured, along with a reliable process flow. The system must be completely available at all times and reliably raise the alarm in the event of process discrepancies. Insofar as system functions are jeopardized or have failed, the system should also detect this and trigger an alarm independently. The term integrity is understood to mean that the measuring values which are recorded, transmitted and documented are both complete and correct in terms of content. Because users themselves have little opportunity to detect whether a measuring value is correct or not.

Last but not least, data protection should also be mentioned (see Fig. 3). Mechanisms have to be implemented here which prevent the viewing or modification of data by third parties.

Figure 3: Product reliability and data security.

Difficult implementation

As described, a very large number of functions and methods have to be implemented in a system to enable all the requirements to be met. But, how exactly can a system offer both reliability and flexibility?

When it comes to flexibility, it is exclusively a matter of system design: virtually every conceivable measuring point within a company network can be reached through a combination of radio and wired (e.g. Ethernet) components. The system can then also be very precisely adjusted for the actual measuring task (indoor climate monitoring, refrigerator monitoring, etc.) via a wide range of probes. The system can also be used by any operator thanks to an intuitive user interface.

Reliability requires many functions in terms of hardware and software in order to ensure smooth operation. As far as hardware is concerned, multiple data storage and continued operation in the event of a power failure thanks to batteries and rechargeable batteries should be mentioned here. As far as software is concerned, there is a high level of reliability both in the event of violations of limit values and of system problems. Users achieve valuable protection with specific reference to data tampering via integrated radio and network protocols. Finally, a distinctive reporting system, which automatically transfers measuring values into logs and sends them, ensures permanent data storage outside the actual system.

All the functions and system contents described with regard to flexibility and reliability can be combined. In addition, they are needed in order to offer users a system which is individually tailored to their needs and in which they can have complete trust.

Testo - High Tech from Germany

Testo is a world leader in the design, development, and manufacture of innovative products and services for environmental and industrial measurement. For more than 60 years, leading companies in the life sciences industries have relied on Testo to help protect their products.

Testo's first product was a simple electronic thermometer. Today, the product line has expanded to include a large variety of critical measuring instruments, such as data loggers, air velocity meters, humidity and dew point meters, sound, pressure, and light meters.

With over 2,700 employees in 33 offices worldwide, Testo understands local requirements and culture. Testo currently has hundreds of thousands of data loggers in the market, storing over 17 billion data sets.

More information at testo.com

Figure 4: Testo headquarters in Titisee-Neustadt/Germany

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