

# Monitoring manufacturing, production and storage environments in the pharmaceutical industry



Providing independent verification and validation of manufacturing, production and storage processes for compliance with the latest regulations and GAMP guidelines

## Measurement made easy

GAMP compliance from ABB's paperless chart recorder range

## Introduction

The conditions under which pharmaceutical products are manufactured, stored and distributed are subject to stringent standards. Satisfying these requirements is essential for companies wishing to prove that their products have been safely produced and are suitable for sale both at home and overseas.

When it comes to the use of electronic equipment in pharmaceutical production, the de facto standards are set by the International Society of Pharmaceutical Engineers' (ISPE) Good Automated Manufacturing Practice (GAMP) guidelines. Adopted by countries worldwide, these guidelines set down the main requirements that need to be considered when planning and implementing computerized systems in pharmaceutical applications. Figure 1 on the next page shows the standard drivers associated with the current GAMP guidelines.

As the world's largest market for pharmaceutical products, the US has led the way in developing its own interpretation of these guidelines, with the Food & Drug Administration's (FDA's) good practice rules setting the standard for companies worldwide.

Particularly important are the FDA's Predicate Rules, which set stringent requirements for the manufacture, processing, packing and storage of pharmaceutical products.

## The rules

The specific predicate rules relating to pharmaceutical manufacturing are:

- 21 CFR Part 210, stipulating current good manufacturing practice in the manufacture, processing, packing and storage of pharmaceutical products; and
- 21 CFR Part 211, setting current good manufacturing practice for finished products

These rules include guidance on which aspects of pharmaceutical production need to be recorded, including any process control settings, details on checking of recorded data and specific requirements relating to the collection of batch production and control records.

Where these records are collected electronically, then 21 CFR Part 11 also applies, which aims to give electronic records and signatures the same weight and trustworthiness as their paper-based counterparts. A key aspect of 21 CFR Part 11 is its focus on security, particularly relating to the prevention of data tampering and the ability to identify specific individuals and events involved in the production and/or data management processes.

## The application

The conditions under which pharmaceutical products are manufactured and stored can have a major impact on their quality. Factors such as temperature, humidity, air quality, time and production process characteristics can all have a significant impact on the final quality, and therefore the saleability, of a product or batch of products.

For the purposes of traceability, it is necessary to adhere to GAMP guidelines to accurately record every stage in the production lifecycle of a product, encompassing not just the manufacturing process but also the storage and distribution stages. In doing so, manufacturers can prove to have acted in accordance with best practice by building in quality from the outset and designing failure out of the process.

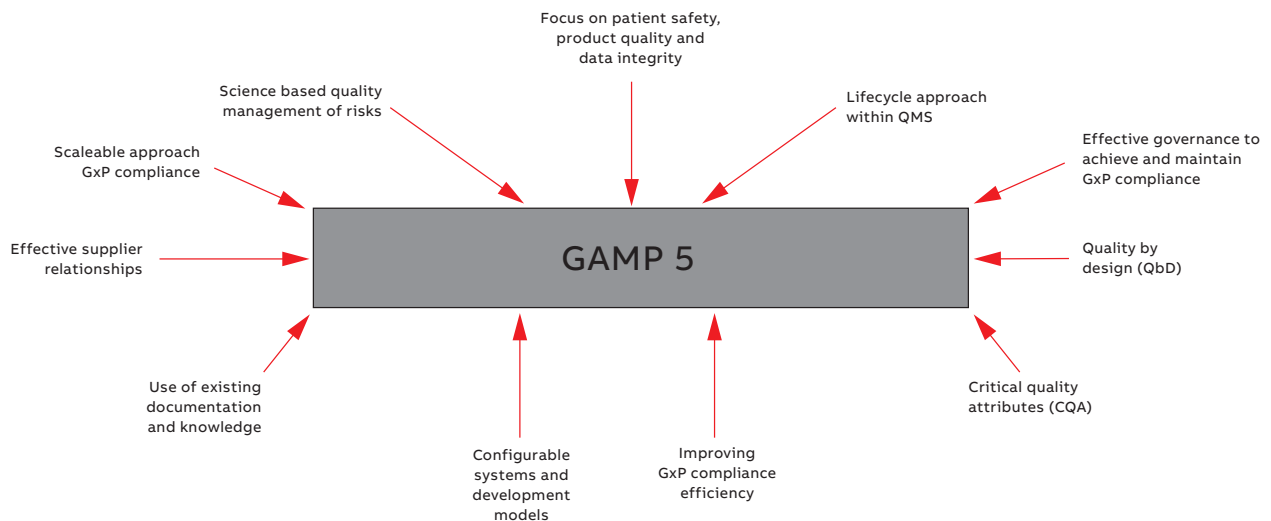


Figure 1 GAMP 5 sets the main requirements for the use of computerized systems in pharmaceutical applications.

## The challenge

### Manufacture, storage and distribution

GAMP guidelines advise that the manufacture, storage and distribution stages of pharmaceutical products are monitored to ensure that any facilities involved meet the required standards. Of the various parameters that need to be carefully controlled, temperature and humidity are perhaps the two most critical.

All parties involved in the manufacture, storage and distribution of pharmaceutical products are required to record and keep details of temperatures during these processes.

Efficient handling and processing of sensitive materials is critical to the profitable manufacture of pharmaceutical products. GAMP encourages manufacturers to use measurement techniques that allow a better understanding of the interaction between material properties, equipment design and operating conditions, in processes such as capsule forming and drying, pan coating, parenteral manufacturing, sterile filling, spray and powder drying, and tablet compression.

For many products requiring storage in cool conditions, refrigeration plant is widely used, which needs to be carefully monitored to ensure that the correct temperatures are maintained. Exactly how this is achieved varies according to the type and size of refrigerator being used and the type of product in question. High-risk products, for example, must be maintained between 2 and 8 °C (35.6 and 46.4 °F) and stored in precisely controlled refrigerators.

For operators of a storage plant, it is necessary not only to ensure that products are stored at the right temperature, but also that the refrigeration plant is capable of accurately maintaining that temperature.

Adopted by many countries worldwide, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) regulations stipulate that the performance of refrigeration plant used to store pharmaceutical products needs to be regularly checked. To achieve this, operators need to map their refrigeration equipment using one or more thermometers and /or temperature probes to ensure that temperature is uniformly maintained. The resulting temperatures need to be recorded as proof of compliance with the required standards.

The requirement to accurately map storage temperatures also extends beyond refrigeration equipment to include warehouses and controlled temperature rooms.

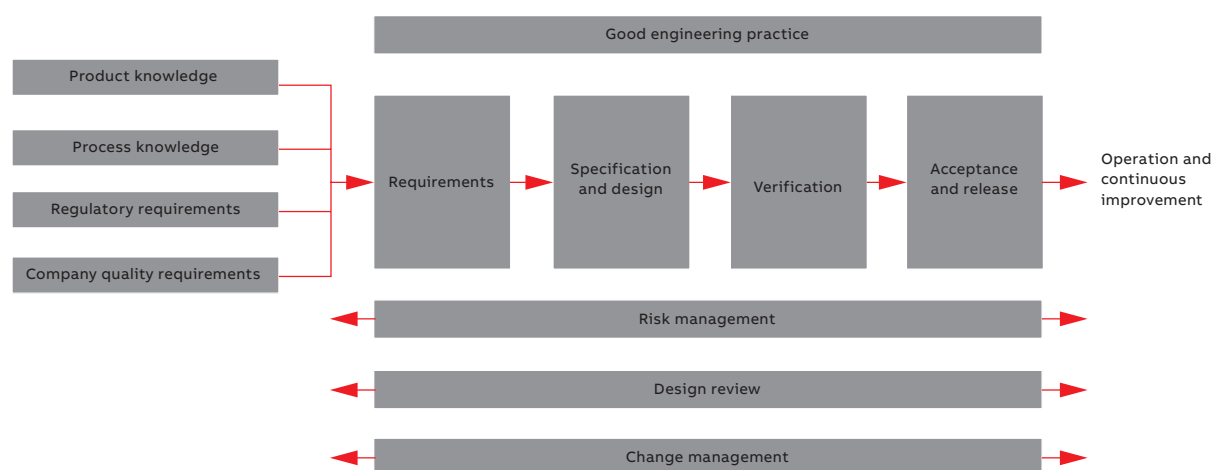


Figure 2 GAMP 5 illustrates the specification, design, and verification process.

## Security

In order for recorded data to be accepted as valid proof of compliance with the various standards relating to water purification, it is necessary to eliminate any potential for unauthorized adjustment or tampering with that data.

Whereas tampering with paper charts can be easily spotted, it is less obvious where electronic data is concerned. For this reason, any electronic data recorder must incorporate a full range of security features, including:

- data access restricted to authorized individuals only
- password protection to protect against unauthorized access
- audit trail facility to independently attribute a time and date every time a record is created, modified or deleted
- the ability to protect against unwanted loss of recorded data
- use of digital signatures to show that the device has only been used by authorized persons

It is also necessary to ensure that recorded data cannot be altered when downloaded to a PC or other device for review.

## The solution

During the manufacture of pharmaceutical products, temperature, humidity, and, in some cases, pressure measurements, should be taken to ensure the optimum process environment is achieved.

For best manufacturing practice, measurement equipment should be placed as near to the point of manufacturing as possible. The type and number of the measurement equipment will be dependent on the size of the facilities and the type of product being produced. GAMP guidelines advise that all measurements should be electronically logged in compliance with 21 CFR Part 11.

Temperature and humidity are the predominant environmental parameters that are recorded in pharmaceutical production and storage, these parameters having one of the larger effects on product quality. However, differential air pressure records are also common. This is where specific areas are required to have a positive (or negative) pressure in relation to the area outside the door. This can prevent contamination of product and/or the environment.

The temperature/humidity probes are usually wall or ceiling mounted, generally of a type that can allow full loop calibration by being placed in the manufacturer's calibration equipment. A regular calibration check and full calibration adjustment facilities for the system inputs are important to verify that the measurements made are reliable.

In the case of storage, large refrigerators (in excess of 6m<sup>3</sup>) and walk-in cold rooms used in high volume operations should be fitted with an electronic temperature recording device that measures load temperatures. With high volumes it is important that the chart, printout or direct reading should be checked daily and the examination recorded; in this instance it may be easier to install an electronic recorder, with a calibrated max/min thermometer placed inside the unit as a backup.

The system that records the data also triggers warning and active alarms should the accepted process parameters be exceeded. These often incorporate a time delay and / or a hysteresis. This only triggers the alarm once the parameter has exceeded acceptable levels by a certain amount of time, helping to prevent nuisance alarms.

The provision of Ethernet connectivity allows historical recorded data and alarm and audit trail information to be relayed automatically to a central database where archive and analysis, if required, can take place.

The use of independent recorders for environmental monitoring allows specific, independent and easily validated areas to be monitored without the requirement of validating an entire complex Environmental Monitoring System (EMS).

In large storage facilities, recording probes should be placed within the load for routine monitoring. If air distribution is not fan-assisted, the probe should be located in the part of the load at the highest risk from low temperatures.

The placement of goods within walk-in units is also critical. Any goods sensitive to temperatures greater than 8°C (46.4 °F) should not be stored next to the door and goods susceptible to temperatures below 2°C (35.6 °F) should not be placed in the airflow of the refrigeration unit.

With high risk products it is important that temperatures are recorded on a daily basis and that probe(s) are placed within the load (or within a suitable buffer) to record the load rather than the air temperature. These facilities should also be based in an external environment where the ambient temperature does not affect the temperature control within the unit.

A small but increasing number of blood and biotechnology products must be stored frozen. Storage units must be capable of maintaining the required temperature in all parts of the load, and temperatures should be monitored within the load and recorded daily.

An example of sensor and recorder placement in the manufacture and storage of pharmaceutical goods

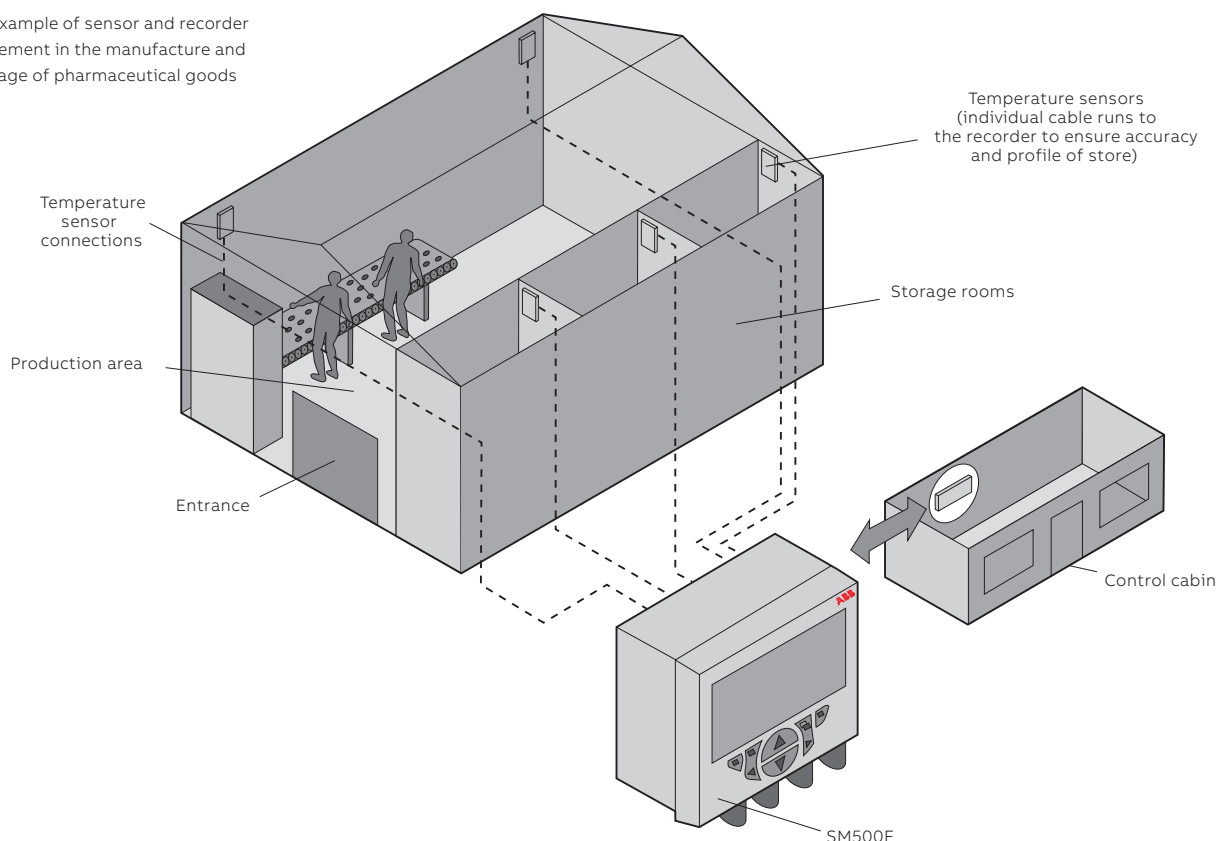


Figure 3 Monitoring manufacturing, production and storage environments in the pharmaceutical industry

## What can ABB offer?

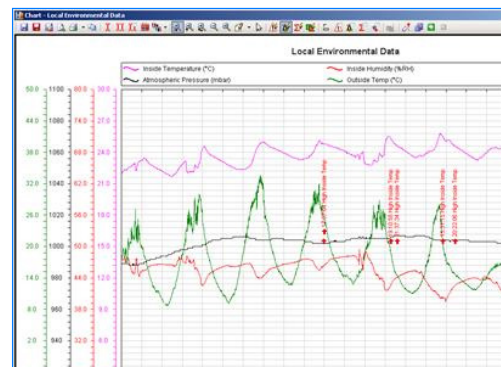
ABB offers a full range of products and expertise that can help operators comply with the requirements for water purification.

ABB offers GAMP validation templates with its SM series of videographic recorders, compliant with 21 CFR Part 11, that will follow the unit's life through delivery, calibration, production and can even extend to its end of life disposal.

ABB can offer a range of validation documentation services in accordance with the required application, such as instrument configuration sheets to help document the User Requirement Specification (URS) and aid the production of the Functional Specification (FS), as well as Installation Qualification (IQ) and Operational Qualification (OQ) documentation.



Figure 4 ABB paperless recorders and data review software



### RVG200

The RVG200 recorder takes the established operating and security benefits of the ScreenMaster range one step further. Features include touchscreen 'swipe' operation, front and rear USB ports for connecting peripheral devices (including a barcode scanner and keyboard) and Ethernet and RS485 communications. Up to 24 process signals can be connected to the RVG200's analog inputs or transferred to it via digital communications.

As with all devices in the ScreenMaster paperless recorder range, the RVG200 features extensive security measures to protect against unauthorized tampering with process data, compliant with FDA 21 CFR Part 11 requirements. Standard security features include the ability to configure and allocate multiple users with individual password and access rights.

All recorded data is also securely stored by the RVG200's 256 MB of internal flash memory that can be expanded to 2 GB if required.

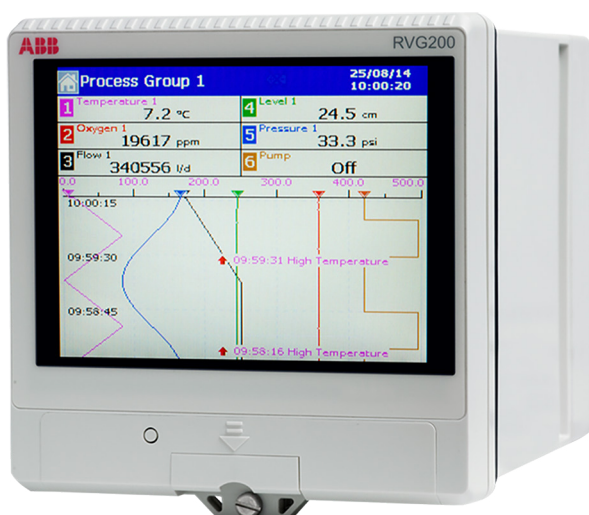


Figure 5 RVG200 paperless recorder

### DataManager Pro

ABB's DataManager Pro analysis software offers a powerful tool for reviewing recorded data. Using the software, operators can review data from multiple recorders.

Functions include the ability to compile graphical charts comparing multiple parameters, plus a dual cursor function enabling operators to review data for specific periods of time and specific recorders.

ABB's ScreenMaster series paperless recorders feature Ethernet communications, allowing users to access the recorders from any web browser. Information can be automatically retrieved and placed in DataManager Pro for further analysis.

DataManager Pro also offers a range of presentation possibilities, including the ability to annotate specific alarms and present recorded data as a combined graph accompanied by tables and statistics.

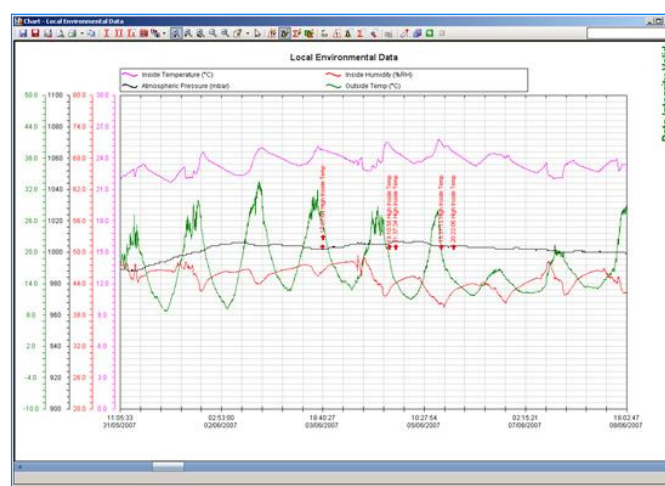


Figure 6 DataManager Pro data review software



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