Application Description AD/RandC/008-EN

Freeze drying in the pharmaceutical industry

- Provides independent verification and validation monitoring of the freeze drying process
- Enables compliance with the latest regulations and GAMP guidelines
- Eliminates unauthorized adjustment of recorded data

Introduction

The conditions under which pharmaceutical products are freeze dried 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 freeze drying, 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 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

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Freeze drying is a technique used by pharmaceutical manufacturers to derive dry product from aqueous solutions. Originally developed during the 1940s, the technique produces a dry product which can be readily reconstituted to its original form by adding water when required. As such it is as an ideal way of prolonging the life of pharmaceutical products, particularly where this may involve long periods of storage and transit prior to use.

The freeze drying process itself entails first freezing the aqueous form of the product on shelves in a vacuum chamber, after which the chamber is evacuated. At the next stage, the Primary drying process, the product is slowly warmed up over a number of hours to boil off the liquid, with any moisture being evacuated throughout the process through a cold condenser.

This is then followed by a Secondary drying process, during which the temperature in the chamber is raised to help remove any residual water.

As a final check that the product is dry, a pressure rise test is carried out, with any more than a fractional rise in pressure indicating that there is still some residual liquid present.

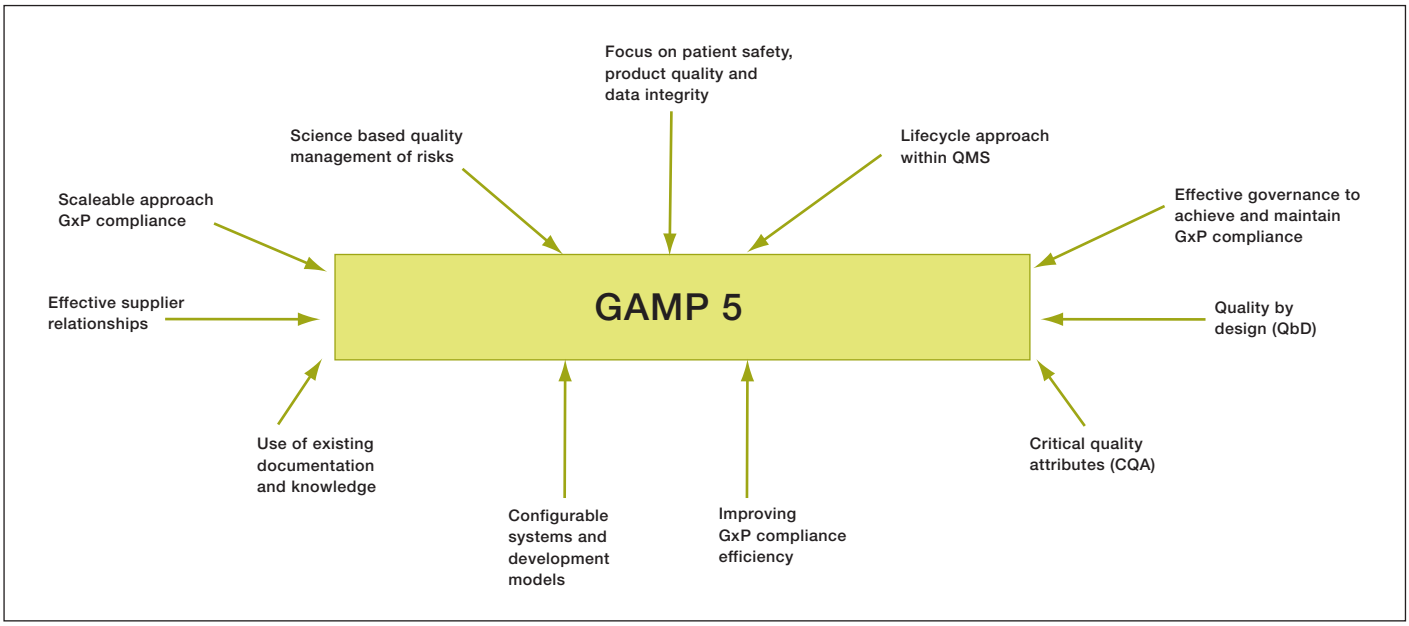


Figure 1. GAMP 5 sets the main requirements for the use of computerized systems in pharmaceutical applications.

The challenge

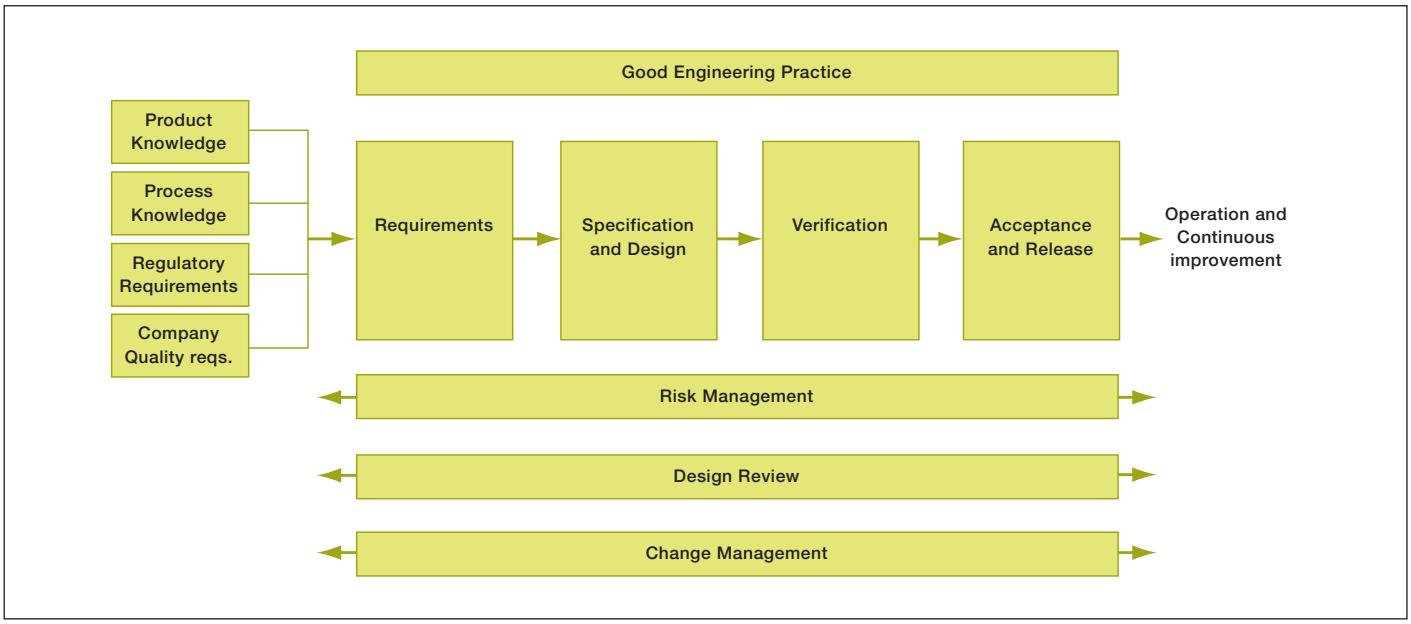


Figure 2. GAMP 5 illustrates the specification, design, and verification process.

The challenge

The high financial value of pharmaceutical products makes it essential that correct procedures are followed. For this reason, it is critical that the various stages in the freeze drying process are precisely controlled and independently monitored in accordance with GAMP guidelines.

There are two key challenges during the process that make close control particularly important.

The first, during the initial freezing stage, is the need to ensure that the product is completely frozen before the chamber is evacuated. To achieve this, a long stabilization period is needed, during which the operator may need to manually check and confirm that the process is ready to proceed to the next stage. It is also imperative to ensure that the freezing process itself is properly carried out, as the product can easily be spoiled if not frozen at the correct rate.

The second challenge is during the Secondary phase, where it is important to make sure that the water does not boil off too quickly, which could otherwise ruin the product. This requires careful control of the temperature.

Given the potential for error, it is essential to have a control system that can both maintain the required conditions for freezing and heating and also respond quickly to address any potential variations in process conditions.

Furthermore, in order to satisfy Good Automated Manufacturing Practice (GAMP) and other guidance requirements for documentation of the process, the system should also incorporate reliable data recording equipment. This equipment should be able to provide independent verification and be capable of collecting data on the entire process as well as incorporating a high level of security to protect against tampering or alteration of data.

The solution

The solution

Any control system used for a freeze drying application should ideally be capable of automatically adjusting the process to maintain the ideal conditions. Traditionally, open loop control systems have been used, with the freezing and heating temperatures and the chamber pressure being controlled according to a specific profile. However, this approach has several drawbacks, including the inability to cope with temperature variations outside of the set profile. With no way of accelerating the process if conditions change, the overall freeze drying period is also prolonged.

For optimum control of the freeze drying process, a closed loop control system should instead be used. Data from the pressure and temperature sensors is fed back to the controller where it is compared against a reference value. The controller takes the difference between the output and the reference value and uses it to change the inputs to the system to help compensate for the difference. The result is a more dynamic and precise control of the freeze drying process, with the ability to address any unexpected fluctuations in process conditions.

The control functions of a freeze dryer are normally performed using an integrated control system from the manufacturer. However, it is usual that key parameters are independently recorded against time, including humidity, temperature and pressure (or vacuum).

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

It is important to perform a regular calibration check and to be able to perform full calibration adjustment for the system inputs as it is important to verify that the measurements made are reliable.

To satisfy FDA requirements, all data from the freeze drying process should be recorded. Where data recorders are used, the requirements of the International Society of Pharmaceutical Engineers (ISPE)'s Good Automated Manufacturing Practice (GAMP) will also apply, including the stipulation that any recording equipment has to be validated for use in pharmaceutical processes. A recorder with Ethernet connectivity allows historical recorded data and alarm and audit trail information to be retrieved automatically to a central database where archive and analysis, if required, can take place.

Any electronic recording equipment also has to be compliant with the FDA's 21 CFR Part 11 rule. 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 use of independent recorders for monitoring the freeze dryer allows specific, independent and easily validated processes to be monitored without the requirement of validating an entire complex Distributed Control System (DCS). It shows exactly what has happened and alarms, in real-time.

What can ABB offer?

What can ABB offer?

ABB offers a full range of products and expertise that can help operators make sure that they comply with the requirements for freeze drying.

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.

SM500F

The world's first field-mountable videographic data recorder, the SM500F can be part of a fully compliant 21CFR11 system - the FDA's (Food and Drug Administration) regulations concerning electronic process data collection. Process data is displayed clearly to the local operator through a variety of display formats, including chart, bargraph and digital indicator displays.

The SM500F offers up to seven analogue inputs, enabling multiple sensors to be connected. This is accompanied by 12 recording channels that can each record process and communications inputs, math block results, digital signals and other values, providing additional detail and functionality.

The SM500F comes with a choice of Ethernet or RS485 communications. The Ethernet allows link enabled historical data to be remotely downloaded to a PC for subsequent analysis via ABB's DataManager software. It also allows a web browser view and connection to a SCADA or PLC system using the Modbus TCP protocol. The RS485 option gives Modbus RTU in either three or five wire configurations. These protocols give the ideal opportunity for integration of third party equipment into the display and recording systems by OEMs.

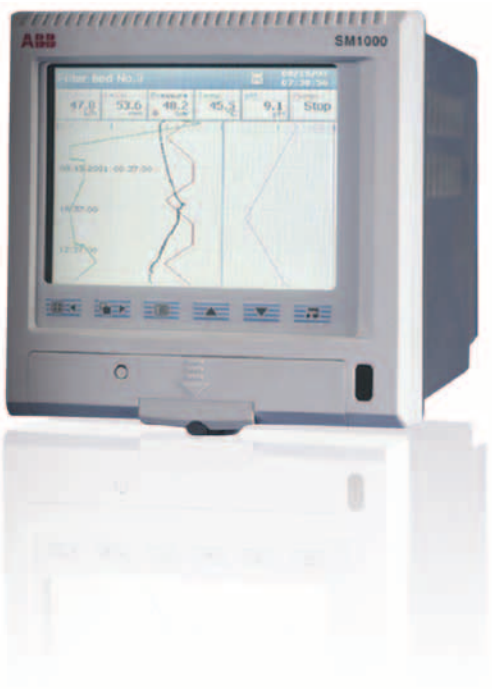
The SM500F can send email notifications whenever an alarm occurs to ensure that any potential problems are promptly addressed. Users can also choose to receive email status reports at any time.

The SM500F now also provides users with greater functionality for batch recording processes. When a new batch is initiated on the control system, the SM500F will automatically start to record the batch, including any associated batch information. This eliminates the need for the operator to duplicate the data entry process on both the recorder and the PLC, saving time and reducing the chance of any potential errors.

What can ABB offer?

SM1000/2000

Now with multi-batch added functionality the SM1000 and SM2000 range of videographic recorders are a state-of-the-art solution to recording and data storage. They provide 12 recording channels and up to 12 universal analog inputs which can be viewed in a variety of display formats: chart, bargraph, digital indicator and process summary. Historical logs are provided for recording alarms, operator and system events and totalizer values.



SM3000

The SM3000 Multipoint Videographic Recorder features state-of-the-art data storage and security technologies. It enables up to 36 universal analogue inputs, communicated inputs or math results to be recorded and displayed in a variety of operator views. Its 8Mb onboard flash memory can store 2.8 million samples of data. There is also the option of Compact Flash removable memory cards, providing extensive data storage capabilities.

DataManager Pro

ABB's new 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 videographic recorders feature Ethernet communications, allowing users to access the recorders from any web browser. Information can be automatically retrieved and placed in DataManagerPro 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.

For advice on how ABB can help you independently monitor your freeze drying process email:
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ref 'Pharmaceutical freeze drying.'

Notes

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