



White paper: The 10 golden rules of GMP

The Good Manufacturing Practice (GMP) regulations that govern pharmaceutical and medical device manufacturing can seem overwhelming.

Use these '10 golden rules' to drive your day-to-day operations, keeping them in mind whenever you make decisions that have GMP implications.

This white paper is an ideal refresher for the experienced GMP professional or great training material for the newbie

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What are the 10 golden rules?

The 10 golden rules of GMP discussed in this Whitepaper are:

- Golden Rule#1 Get the facility design right from the start
- Golden Rule#2 Validate processes
- Golden Rule#3 Write good procedures and follow them
- Golden Rule#4 Identify who does what
- Golden Rule#5 Keep good records
- Golden Rule#6 Train and develop staff
- Golden Rule#7 Practice good hygiene
- Golden Rule#8 Maintain facilities and equipment
- Golden Rule#9 Build quality into the whole product lifecycle
- Golden Rule#10 Perform regular audits

Golden Rule #1

Get the facility design right from the start

Every pharmaceutical and medical device manufacturer should aim to operate their business following the principles of Good Manufacturing Practice (GMP) and it's much easier to be GMP compliant if the design and construction of the facilities and equipment are right from the start.

Facility layout

The production area should be laid out to suit the sequence of operations. The aim should be to reduce the chances of cross-contamination and to avoid mix-ups and errors. For example, final products should not pass through or near areas that contain intermediate products or raw materials.

A logical and well-planned layout will improve productivity and:

- remove unnecessary traffic in the production area which could result in a hazardous environment
- segregate materials, products, and their components to minimise confusion and potential for mix-ups and errors.

Example

A company, through poor planning, failed to keep the product manufacturing process linear. As the product moved through the factory, it was zig-zagged from one area to another. This meant that the near-final product was exposed to an early-stage product which increased the potential for contamination.

Before making any changes, the company should have stepped back and reviewed the layout as a whole.

Environment

It's important to control the air, water, lighting, ventilation, temperature, and humidity within a facility to ensure that it does not impact the quality of the product. Facilities should be designed to reduce the risk of contamination from the environment.

You should ensure that:

- lighting, temperature, humidity, and ventilation are appropriate
- interior surfaces (walls, floors, and ceilings) are smooth, free from cracks and do not shed particulate matter
- interior surfaces are easy to clean
- pipework, light fittings, and ventilation points are easy to clean
- drains are sized adequately and have trapped gullies.

Equipment

Equipment should be designed, located, and maintained to suit its intended use.

You should ensure that equipment is:

- easy to repair and maintain

- designed and installed in an area where it can be easily cleaned
- suitable for its intended use
- not reactive, additive, or absorptive
- calibrated at defined intervals (as necessary)
- clearly labelled.

Golden Rule #2

Validate processes

It's one thing to design and construct a state-of-the-art facility, but how do you ensure that it is operated in a controlled and consistent manner? To prove that equipment and processes consistently do what they are supposed to do, testing and documentation are required.

Consistent performance is the key to maintaining the safety and effectiveness of every product and enhances a company's reputation for quality and reliability.

Validation

By definition, validation is: *"A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting pre-determined acceptance criteria."* [PE 009-14 Guide to Good Manufacturing Practice for Medicinal Products].

All validation activities should be well planned and clearly defined, and take the life cycle of the facilities, equipment, utilities, process, and product into consideration. A Validation Master Plan (or VMP) should be prepared and should include:

- the company validation policy
- validation roles and responsibilities
- a summary of the facilities, equipment, systems, processes on site and their status
- guidance on developing validation acceptance criteria
- the company validation (and re-validation) strategy.

Validation usually involves:

- Installation Qualification, or IQ, which is testing to verify that the equipment, facilities, utilities, or systems are installed correctly
- Operational Qualification, or OQ, which is testing to verify that the equipment, facilities, utilities, or systems operate correctly
- Performance Qualification, or PQ, which is testing to verify that a product can be consistently produced to specification.

A protocol describing each test and the acceptance criteria should be prepared, and once the testing is complete, a report written.

Change control

Once testing is complete and the equipment or process is known to be controlled, it is important to maintain its 'validated state'. This can be achieved by correctly following written procedures,

and properly maintaining and calibrating the equipment. If a change to the validated state is required, then it must be subject to change control.

Equipment, facilities, utilities, and systems should also be evaluated at an appropriate frequency to confirm that they remain in a state of control.

Example

A computer system was validated after it was first installed on site. Some years later an auditor discovered that changes had been made to the system, however, no re-validation work had been performed and the system was no longer in its 'validated state'.

Question: How did the company know that the system was operating in a controlled and consistent manner?

Answer: They didn't. The oversight was due to a weak change control system that allowed changes to be made without formal evaluation and re-validation.

Golden Rule #3

Write good procedures and follow them

In the pharmaceutical and medical device industries, good procedures must be in place to ensure that processes are conducted in a controlled and consistent manner. Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements.

Documentation requirements

The following documents are typical in the pharmaceutical and medical device industries:

- Specifications: These detail the requirements with which products or materials have to conform, i.e. they serve as a basis of quality evaluation.
- Operating Instructions: These detail material and equipment requirements and describe the steps to complete a task.
- Procedures: These give direction for performing certain tasks and provide higher-level instruction than operating (or work) instructions.

Writing good procedures

Procedures should be clear, concise, and logical. Before you begin to write a procedure, you should outline the tasks and create a brief breakdown of the important steps and key points related to the task. A flow chart is a useful tool.

Remember that people don't usually read procedures from start to finish and tend to scan the document for keywords. Subsequently, it is advised to break the procedure into chunks and use headings, tables, bullet points and diagrams to make the information easier to digest and follow.

When writing procedures, you should also try to visualise the person that will use them and use language they will understand.

You can increase the readability of your procedures by using simple sentences. You may like to use an online tool such as http://www.online-utility.org/english/readability_test_and_improve.jsp to test readability.

You can also check that the procedure is usable by performing a 'usability test' and asking someone unfamiliar with the task to follow it. Make notes about where they found the document hard to follow.

It is a GMP requirement to regularly review documentation to ensure that it's up to date. Most companies have a three-year review cycle for their documents however this can be set according to the likelihood of change or criticality of the process that the document relates to.

Following procedures

It's all very well to have great procedures in place but they need to be followed; it's a GMP requirement. Frequently, the steps described in a written procedure may not appear to be the most efficient way of working, however, you should not deviate from a written procedure without the approval of a supervisor or the Quality Department.

There are two main reasons for this:

- shortcuts may create pitfalls that can be costly in the end
- each step in a procedure has been included for a purpose.

Even though the sense of a particular step may not be directly apparent, it may be there as a check for another stage of the process.

Ideas for improvement should always be encouraged but the entire process should not be changed without first conducting an impact assessment.

Golden Rule #4

Identify who does what

The correct manufacture of medicinal products relies upon people. All employees should clearly understand what they have to do each day to avoid misunderstandings and to minimise the risk to product quality.

A job description should be created for each role to define:

- job title
- job objective
- duties and responsibilities
- skill requirements.

In addition, the responsibilities for performing a specific task should be clearly defined in a procedure. Some areas that are vulnerable to overlap in responsibilities include cleaning, validation and calibration.

An organizational chart may be displayed (on an intranet or a local notice board) so that everyone in the organisation can see who does what.

Example

During a validation batch, a series of samples were not taken as the operators thought that validation staff would take them, whilst validation thought that the operators would take them.

The sampling responsibilities should have been appropriately detailed in the sampling procedures and validation documentation.

Golden Rule #5

Keep good records

Good records enable you to track each activity performed during batch manufacture from the receipt of raw materials, to the final product release. It is an essential part of GMP to keep accurate records, and during an audit, it helps to convey to the auditor that you are following procedures and demonstrates that processes are known and under control.

'If it's not written down then it didn't happen!'

Good record keeping

You should follow these guidelines to ensure that good record keeping is part of your everyday culture:

- Record all necessary information immediately upon completion of a task.
- Never trust your memory or write results on loose pieces of paper.
- Write your name legibly in ink.
- Remember that by signing records you are certifying that the record is correct and that you have performed the task as per the defined procedure.
- Draw a single line through any mistakes, and initial and date the correction. Include a reason for the correction at the bottom of the page.
- Record details if you deviate from a procedure and ask your supervisor or the Quality Department for advice should a deviation occur.
- Don't document someone else's work unless you are designated and trained to do so.
- Never assume that undocumented work has been properly completed – if it's not written down then it didn't happen!

Tip

Signature fatigue is a problem; employees are asked to sign so many records that they can become complacent about what their signature means. You should review your procedures and limit the number of signatures to critical steps only and only include a 'checked by' signature when it's required by a predicate rule.

Retention requirements

You should keep records for every stage of the manufacturing process including:

- product master records
- batch or manufacturing records
- material/component control records

- personnel records
- training records
- equipment logs
- cleaning logs.

You should clearly define which record relates to which manufacturing activity and where the record is located. Secure controls must also be in place to ensure the integrity of records throughout their retention period.

Specific retention requirements apply to batch documentation. These must be kept for one year after the expiry of the batch to which it relates or at least five years after certification of the batch by the Authorised Person, whichever is the longer.

For other types of documentation, the retention period will depend on the business activity which the documentation supports.

Golden Rule #6

Train and develop staff

To meet GMP requirements it's essential to have the right people to do the right job.

Do your employee's have the skills and knowledge to complete their job?

Have you equipped them with the right tools?

If so, then you can be proud that your people are doing the right thing to make GMP a culture.

Training

You should provide training for all employees whose duties take them into production and storage areas or laboratories (including maintenance and cleaning employees), and whose activities could affect the quality of the product.

Besides the basic training on the theory and practice of GMP, employees should receive specific training relative to their role.

Sometimes it's unavoidable to take an untrained visitor into a production area and if this happens, you should provide them with some information in advance (particularly relating to personal hygiene) and closely supervise them at all times.

Golden Rule #7

Practice good hygiene

It's critical to reduce the risk of product contamination to a minimum by putting in place a sanitation program. The program should meet the standards of cleanliness necessary for the product, for example, different cleaning standards would apply for sterile products used in an operating theatre as opposed to products that are injected into the bloodstream.

The fight against contamination is a constant battle and is one that requires the attention of every single employee, every day.

To convince staff of the importance of washing their hands after toileting, ask the microbiology department to take fingerprint samples from each operator after they have washed their hands. They can then see how much bacteria is present on their 'clean' hands.

Always keep these practices in mind:

- Practice good personal hygiene by washing your hands and wearing the required protective garments.
- Inform your supervisor if you are ill as you may not be allowed to enter the manufacturing area until you are well again.
- Minimise contact with product or product contact surfaces and equipment.
- Never eat, drink, smoke or chew in manufacturing areas.
- Always follow cleaning and sanitation procedures.
- Report any condition that may cause product contamination.
- Remove trash and waste materials, and store them appropriately.

These practices are nothing more than common sense and are your best defence to reduce the risk of product contamination.

Golden Rule #8

Maintain facilities and equipment

It's important to have a maintenance schedule for facilities, utilities and equipment. Regular maintenance prevents breakdowns, reduces the risk of product contamination and maintains the 'validated state'. Sometimes an unexpected event may occur and under such circumstances, repairs should be carried out immediately.

You should have written procedures for all scheduled and emergency maintenance activities. These should detail who does the work, the tasks involved, and define any lubricants, coolants, cleaning agents, etc. required.

Tip

When writing maintenance procedures consider whether the work can be performed outside the manufacturing area so that it doesn't affect the remainder of the facility. If this can't be achieved, remember to detail the cleaning requirements to get the plant back to a GMP standard.

Maintenance records

GMP requires you to keep accurate records relating to maintenance activities. This can be achieved by using use equipment logs to record information such as:

- when the equipment was last used
- what is was used for
- when it was cleaned

- when it was last inspected or repaired
- when it was last calibrated.

Golden Rule #9

Design quality into the whole product lifecycle

By working in the pharmaceutical and medical device industries, the health and safety of the customer depends on the quality of the product. The QC department can only inspect for quality so it's critical to build quality into the product lifecycle.

Controlling components

You should check all materials and components when they enter the plant to ensure they meet the defined specifications. All materials and components must be approved before being used in manufacturing, or if rejected, they must be identified and stored in a secure area to prevent accidental use.

Controlling the manufacturing process

You should establish records and procedures to ensure that employees perform the same job every time. Each product must have:

- a master record that outlines the specifications and manufacturing procedures
- individual batch or history records to document conformance to the master record
- written schedules and procedures for cleaning and maintaining the equipment and areas.

Packaging and labelling controls

Packaging and labelling are areas where mix-ups and errors often occur. To enable traceability, a batch or lot number should be assigned to each product.

Before a new batch or lot is processed, you should inspect packaging and labelling areas to ensure that they do not contain material from a previous batch.

Holding and distribution controls

You should have controls against contamination, mix-up, and errors, and provide separate areas for quarantine and finished product testing. You should also prepare procedures for handling and storage of products and distribution records to help trace shipments.

Golden Rule #10

Perform regular audits

Audits will be conducted by regulatory authorities to assess whether you are following the GMP rules. External bodies such as the Food and Drug Administration (FDA) or the Therapeutic Goods Association (TGA) will conduct these audits.

In addition to these external audits, you should also conduct in-house audits, or self-inspections, to ensure GMP compliance. It's good practice to undertake a self-inspection a few times a year and to target different manufacturing areas and departments each time.

Tip

You'll need a Corrective Action Preventive Action (CAPA) system to manage and fix anything found during an audit.

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at

www.pharmout.net

[PE 009-15 \(Part I\) 1 May 2021 GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART I](#)

[PE 009-15 \(Annexes\) 1 May 2021 GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEXES](#)



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