



White Paper

PIC/S

The 10 Golden Rules of GMP

The Good Manufacturing Practice regulations that govern pharmaceutical and medical device manufacturing can seem overwhelming. Use these ten 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.

What are the 10 golden rules?

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 food, drug, and medical device manufacturer aims to operate their business in accordance with the principles of Good Manufacturing Practice (GMP). It's much easier to be GMP compliant if the design and construction of the facilities and equipment are right from the start. It's important to embody GMP principles and use GMP to drive every decision.

'Sometimes you need to step back and reconsider the whole production area'

Facility layout

Lay out the production area to suit the sequence of operations. The aim is to reduce the chances of cross contamination and to avoid mix-ups and errors. For example, don't have final product passing through or near areas that contain intermediate products or raw materials.

A logical and well-planned layout will improve productivity. Sometimes you need to step back and reconsider the whole production area rather than applying quick fix solutions.

Aim to:

- 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 zigzagged from one area to another. This meant that near-final product was exposed to early-stage product with the potential of 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 plant so that it does not impact product quality. You should design facilities to reduce the risk of contamination from the environment.

Make sure 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
- pipe work, light fittings, and ventilation points are easy to clean
- drains are sized adequately and have trapped gullies.

Equipment

Design, locate, and maintain equipment to suit its intended use. Make sure 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 (if necessary)
- clearly labelled.

Golden Rule #2

Validate processes

It's one thing to design and construct state of the art facilities and equipment, but how do you ensure that it's operated in a controlled manner? This is where validation comes into play.

To prove that equipment and processes consistently do what they are supposed to do, testing and documentation is required. Consistent performance is the key to maintaining safety and effectiveness of every product and enhances a company's reputation for quality and reliability.

Validation

By definition, validation is:

"Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."

It's a GMP requirement to prove control of the critical aspects of certain operations. New facilities and equipment, as well as significant changes to existing systems, require validation.

All validation activities should be well planned and clearly defined. This is usually by means of a Validation Master Plan, or VMP. Before you get to this stage consider all the critical parameters that may be affected and impact product quality; *what happens if the stirring speed is changed? How does this affect temperature or pH?* Once this is complete, define the testing and documentation required.

Validation usually involves:

- Installation Qualification, or IQ, which is testing to verify that the equipment is installed correctly
- Operational Qualification, or OQ, which is testing to verify that the equipment operates correctly
- Performance Qualification, or PQ, which is testing to verify that product can be consistently be 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's important to maintain its 'validated state'. Achieve this by correctly following written procedures, and properly maintaining and calibrating equipment. If a change to the validated state is required then it must be subject to change control.

A change control system should be in place to document all changes to facilities, equipment, or processes that may have an impact on product quality. You should evaluate the impact of the change and define the extent of re-validation.

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. No re-validation work had been performed and the system was no longer in its validated state. How did the company know that the system was operating in a controlled and consistent manner?

The answer is 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

Think about what happens in a workplace if written procedures are not available. People rely on longer-term employees to tell them how to do things and then do their job from memory. This is fine for a company making garden pots, but not so good when the products you are making can cause death!

In the food, drug and medical device industry it's critical that good procedures are in place to ensure a controlled and consistent performance; it's an essential part of GMP.

Procedures should be clear, concise, and logical. Consider hiring a professional technical writer to do the job. Unlike permanent employees they know how to write well and will perform usability tests to ensure that documents work. Having an independent party reviewing your procedures also leads to process improvements.

Documentation requirements

The following documents are typical in the food, drug, and medical device industry:

- Specifications: These detail the requirements with which products and 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
- Operating Procedures: These give direction for performing certain tasks and provide higher-level instruction than operating instructions.
- Records: These provide a history of each batch and provide a mechanism to check that you are following operating procedures and instructions.

'Procedures should be clear, concise, and logical'

Writing good procedures

Outline the task before you begin writing the procedure. 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; they tend to scan the document for key words.

Break the procedure into chunks and use:

- headings
- tables
- bullet points
- diagrams.

This makes the information easier to digest and follow.

When writing procedures try to visualise the person that will use it. Use language they will understand and don't include too much or too little information.

You can increase the readability of your procedures by using simple sentences and by writing in a conversational style. Use an online tool such as http://www.online-utility.org/english/readability_test_and_improve.jsp to test readability. Aim at a readability score that matches the educational level of the person using the document.

You can also check that the procedure is usable by performing a 'usability test'. Print out two copies of the procedure and ask someone unfamiliar with the task to follow it. Mark up the second copy with notes about where they found the document confusing. This will highlight problems with the document and is a great learning experience for the writer.

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 in the process that the document relates to.

Some operators resist following procedures because they think they have a 'better' way of working.

Introduce a "Better Operating Procedures" system within the work group where the team meets to discuss procedures that are not followed. Allow operators to suggest how they think a task should be performed and act on it as necessary.

Following procedures

It's all very well to have great written procedures in place but to ensure a controlled and consistent performance 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. Taking shortcuts may save time or make the task easier, but you should never deviate from a written procedure without the approval of a supervisor or the Quality Department.

There are two main reasons for this:

- Many 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 don't change procedures without assessing the impact on the entire process.

Golden Rule #4

Identify who does what

All employees should clearly understand what they have to do each day. It avoids misunderstandings and minimises the risk to product quality. You should create a job description for each role to define:

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

There should be no gaps or overlaps in responsibilities.

Create an organisational chart and display it on the intranet or a local notice board. This way everyone in the organisation can see who does what.

Some areas that are vulnerable to overlap include:

- cleaning
- validation
- calibration.

When preparing procedures for these areas carefully consider and define the responsibilities. It's also vital that employees are trained to undertake a task that they are assigned responsibility to; this is covered further in Golden Rule #6.

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 detailed in sampling procedures and the validation documentation.

Golden Rule #5

Keep good records

Good records enable you to track all activities performed during batch manufacture from the receipt of raw materials, to the final product release; they provide a history of the batch and its distribution.

It is an essential part of GMP to keep accurate records, and during an audit, it helps convey that you are following procedures. It also demonstrates that processes are known and under control.

‘If it’s not written down then it didn’t happen!’

Good record keeping

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. 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 in the pharmaceutical world. Employees are asked to sign so many records and can become complacent about what their signature actually means. Review your procedures to reduce the number of signatures to critical steps 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.

Some required records include:

- product master records
- batch or manufacturing records
- material / component control records
- personnel records
- training records
- equipment logs
- cleaning logs.

Keep documents that form GMP records for one year past the expiry date of the product or three years past the distribution date of the product, whichever comes later. You can define your own retention period for other documents and files.

If you follow these guidelines, you will easily be able to examine each step of the manufacturing process should you need to.

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 employees 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.

'Companies need people who know how to do the job right first time, every time'

Training

You should provide training for all employees whose duties take them into production areas or laboratories, and whose activities could affect the quality of the product. This includes basic training on the theory and practice of GMP as well as specific training relative to their role.

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

It's also important to ensure that training requirements are highlighted as part of the change control system. If you install a new piece of equipment then employees must know how to use it. You should check that training is complete during validation or add it as a separate change control task. The same also applies for updates to procedures or instructions. Usually the document control process will define the training requirements for document updates.

Demonstrating job competence

Employees must demonstrate their job competence every day by producing quality products in a safe and efficient manner. Companies need people who know how to do the job right the first time, every time.

Annual performance reviews are also a great way to formally discuss an employee's development and performance. It's a great way to review what the employee has achieved and to identify any gaps or areas for further development. Areas to discuss include:

- key performance indicators
- work plans
- roles and responsibilities
- position descriptions
- training
- financial compensation.

Document the outcome so that you can review it later.

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. Develop a program to meet the standards of cleanliness necessary for the product. As an example, you would have different cleaning standards for sterile products used in an operating theatre as opposed to products that you inject into your 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.

Keep these practices in mind:

- ALWAYS practice good personal hygiene by washing your hands and wearing the required protective garments.
- Inform your supervisor if you are ill; 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 appropriately.

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

Golden Rule #8

Maintain facilities and equipment

It's important to have a maintenance schedule for facilities and equipment. Regular equipment maintenance prevents equipment breakdowns, which can be costly. It also reduces the risk of product contamination and maintains the 'validated state' of the facility or equipment. Sometimes an unexpected event may affect the facility or equipment and under such circumstances, you need to carry out repairs immediately.

You should have written procedures for all scheduled and emergency maintenance. These should detail who does the work, the tasks involved, and define any lubricants, coolants, cleaning agents etc. required. It's also a GMP requirement to have a maintenance schedule in place with the frequency determined by the criticality of the equipment.

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. 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.

Walk around your plant and check all the calibration stickers you can see. If they are out of date then your maintenance process is not being controlled properly.

Golden Rule #9

Design quality into the whole product lifecycle

By working in the food, drug, and medical device industry you know that 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 that you build quality into the product lifecycle.

Every step in the product lifecycle requires effective controls to assure product quality. Here are four critical areas:

Controlling Components

Check all materials and components when they enter the plant to ensure they meet the defined specifications. Identify components and store them in a quarantine area for sampling and testing. All materials and components must be approved prior to release for manufacturing, or if rejected, they must be identified and stored in a secure area to prevent accidental use.

Controlling the Manufacturing Process

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 occur. To enable traceability, assign a batch or lot number to each product. Before a new batch or lot is processed, inspect packaging and labelling areas to ensure that it contains no material from a previous batch. Follow all procedures and carefully document your work.

Holding and Distribution Controls

The company must have controls against contamination, mix-up, and errors. Provide separate areas for quarantine and finished product testing. Prepare procedures for handling and storage of products and distribution records to help trace shipments.

Golden Rule #10

Perform regular audits

Audits must be conducted 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.

You should also conduct in-house audits, or self-inspections, to ensure GMP compliance. A 'Self Audit Checklist' is provided below. It's a good practice to undertake a self-audit a few times a year and to target different manufacturing areas and departments each time.

Tip:

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

Self-Audit Checklist

Written Procedures

- Are there procedures that provide "step by step instructions" to perform my job?
- Do I know and understand these procedures and do I carefully follow them?
- Do I regularly review my procedures to make sure they are accurate and up-to-date?
- Do I refrain from deviating from my written procedures? When I see an easier or better way to do my job do I discuss this with my supervisor?

Job Competence

- Do I have the necessary education, training, and on-the-job experience to perform my assigned function?
- Have I identified and acquired the necessary skills (i.e. been trained) that relate to my job?
- Do I perform my job right the first time and every time?

Documentation and Validation

- Do I carefully document my work by recording all necessary information immediately?
- Do I sign my name legibly and in ink, when and where a signature is required?
- If required, do I mark down the date and the time I started or completed the job?
- Do I check and double-check all critical operations to make sure there are no errors?

Sanitation and Cleanliness

- Do I always practice good personal hygiene?
- Do I always wear the proper garments in the workplace? Do I wear the garments correctly?
- Are my equipment and tools clean? Do I store them in the proper place?
- Do I report any conditions in the plant or equipment that could be potential sources of product contamination?

Maintenance of the Workplace

- Is there adequate space in my work area to safely and effectively perform my job?
- Do I minimize the chance of product contamination, mix-ups, and errors by helping to control the plant environment?
- Do I perform routine maintenance on my equipment? Do I check to see if my measuring and testing equipment is calibrated?
- Do I keep an accurate equipment log? Do I promptly report any maintenance problems to the supervisor?

Quality Control

- Do I carefully control the components used in the manufacture of our products?
- Do I pay close attention to the lot numbers assigned to components and finished products?
- Do I know and understand what responsibility the Quality Assurance/Quality Control Department has for assuring Product Quality?
- Do I know and understand my responsibility to build quality into our products?

If you have answered "no" to any of these questions, then raise a corrective action. Auditing is an important tool to help evaluate your progress toward the goals of GMP.

Remember, all employees have a personal responsibility to evaluate how closely they are working to the standards of GMP.

If you have answered "yes" to these personal audit questions, your work practices are compliant with the requirements of GMP.

About PharmOut

PharmOut is a professional consultancy offering product registration, engineering, validation and regulatory compliance solutions to the Medical Device, Pharmaceutical and Veterinary drug manufacturing industry from concept development, feasibility studies, scale up, engineering design, project management to final the product regulatory approval and GMP compliance certification.

How PharmOut can help

We offer the following range of services:

ISO, GMP & APVMA compliance consulting

Policies, SOP, and Forms. We can also help you obtain approval from the following international regulatory authorities (APVMA, FDA, MHRA, and TGA).

Engineering

Our experienced industry engineers can develop concept and detailed designs, around your production process ensuring full GMP compliance by careful project management and verification (validation) to ensure that the exacting GEP standards are met.

GMP Compliance

We can visit your site before or after a FDA or TGA GMP audit to assess and improve your quality management systems and/or validation documentation, business processes and physical operations.

Quality Management Systems

We can help you create a Quality Management System from scratch, or bring your current system into compliance.

Technical Document Writing

We can help you write procedures and work instructions that your staff will actually use and can follow.

ISO & GMP consulting

We can provide practical recommendations and advice on the implementation of ISO 9001 for Pharmaceuticals or ISO 13485 for Medical Device Quality Management Systems, Policies, SOP, and Forms. We can also help you obtain approval from the following international regulatory authorities (FDA, MHRA, and TGA). This includes Part 11 and Annex 11 compliance to FDA and TGA requirements.

Training

We run on-site or in-the-city classroom training on GLP, GMP compliance, validation and documentation writing. We also develop e-learning modules on topics such as Good Record Keeping that you can use for your ongoing training needs.

Validation

Our validation engineers / specialists can write validation plans, specifications and qualification protocols for i.e. cleaning validation, equipment validation, computers systems validation, analytical method validation or process validation.

Brought to you by



Bob Tribe is an experienced and approachable industry veteran who has been a key player in the development of the GMP standards and their application within Australia and internationally.

Bob was previously the Chief GMP Auditor for the Therapeutic Goods Administration (TGA), Australia (1980 – 2003) and Chairman of the Pharmaceutical Inspection Cooperation Scheme [PIC/S] (2000 – 2001).

He is a current regulatory advisor to the International Society of Pharmaceutical Engineers (ISPE) and a special advisor to a number of regulatory authorities seeking PIC/S accreditation.

Bob is an Executive Consultant with PharmOut.

PharmOut's Managing Director, **Trevor Schoerie** has 21 years of manufacturing and 8 years of consulting experience in the chemical, pharmaceutical, pesticides & veterinary drugs industries.

Trevor believes strongly in sensible, practical compliance that delivers business results, not just audit success.

His area of expertise is in combining Good Manufacturing Practice (GMP) compliance with continuous improvement methods such as Lean Manufacturing.



Gordon Farquharson is widely recognised as a world leader and expert in sterile products manufacture, clean room design and maintenance and utilities for the same.

Gordon is the Chair of British, CEN and ISO committees responsible for development and deployment of the ISO 14644 family of cleanroom standards.

He is also an advisor to the European Medicines Agency (EMA) concerning the revision to Annex 1 of the European Union's GMP in February 2008 and a member of the World Health Organisation (WHO) expert committee (WHO Pharmaceutical Water GMP; Sterile GMP Annex 1). Gordon is an Executive Consultant with PharmOut.



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