



White paper:
Preparing for GMP inspections

As a GMP licensed manufacturer, you should always be ready for an inspection - regulators can 'drop in' at any time.

This Whitepaper focuses on TGA GMP inspections, however, it provides useful tips for inspections carried out by other authorities, such as the US FDA.

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Introduction - Always be 'inspection ready'

As a Therapeutic Goods Administration (TGA) GMP licensed manufacturer, you should always be ready for an inspection as regulators can perform 'unannounced' inspections at any time.

First impressions count and it's important to convey to the inspector that you have your facility, pharmaceutical quality system (PQS) and manufacturing processes under control.

Establish an SOP

A key to success during any inspection is preparation. You may like to consider establishing a company procedure for the management of GMP inspections – from the opening to the closing meeting, including the steps to follow in the event of an unannounced inspection.

Your procedure should define the roles and responsibilities of all personnel likely to be involved in the inspection including:

- security and reception (remember first impressions count!)
- escorts
- scribes (note-takers)
- subject matter experts
- runners.

The procedure should also include the company policy on electronic data, entry into controlled areas, hygiene, sample collection and the use of cameras, videos and sound recording.

“The message that you want to convey is that you have your facility, PQS and manufacturing processes under control”

Preparing for the initial TGA licensing inspection

An initial inspection is usually carried out within 3-months of your application to the TGA and you should be 'inspection ready' on the date specified in your TGA licence application.

Before the inspection, the TGA lead inspector will contact you to discuss/request:

- the members of the inspection team
- documentation (e.g. Site Master File (SMF) and Quality Manual).

The inspector may also ask for copies of other records or documents such as SOPs, validation plans, products to be manufactured, etc.

The purpose of the licensing inspection is to verify your compliance with the relevant code of GMP, standards and regulations in relation to the scope of your application and the depth of the inspection will depend on the risk level of the products that you are manufacturing.

Before the inspection, you should have commissioned your facility, qualified equipment and completed validation reports. Your PQS documentation, including procedures, instructions, job descriptions and authorities for key personnel should be approved and personnel appropriately trained.

After the inspection, you will be issued with a post-inspection letter (PIL) (usually within 4 weeks of the inspection) that records any deficiencies identified during the inspection and whether you have passed the audit. You will be asked to respond to the listed deficiencies within 4 weeks and if the lead inspector accepts your response to the inspection findings, you will be issued with the TGA licence.

If your response is not accepted, you will get a second chance to address them, however, if your response is not accepted a second time your application may be rejected. This means that you will have to correct your deficiencies and re-apply for the licence and undergo another inspection.

To increase your chances of passing the inspection the first time, and shorten significantly the time between your application and receiving your TGA licence, you could request a pre-licensing /mock inspection from PharmOut. PharmOut has very experienced staff (i.e. staff with years of TGA inspection experience) and can inspect your facilities before the initial TGA inspection.

Re-inspection timeframes

The TGA uses a risk-management approach when determining the frequency for re-inspecting facilities. They take into account the type of products manufactured, results of previous inspections, product recalls, adverse reaction reports, complaints and significant changes within the company. As a general rule of thumb, the following periods for re-inspection apply:

Risk category	Frequency of re-inspection (months)			
	Acceptable compliance rating			Unacceptable rating
	A1	A2	A3	
High (e.g. sterile medicines)	24	18	12	Internal review panel decides
Medium (e.g. OTC medicines)	30	20	12	
Low (e.g. listed medicines)	36	24	12	

A1 = good compliance (no 'major' and \leq 10 'other' deficiencies)

A2 = satisfactory compliance (1-5 'major' and \leq 11 'other' deficiencies)

A3 = basic compliance (5-15 'major' deficiencies)

Unacceptable = unacceptable compliance (\geq 15 'major' or 1 or more 'critical' deficiencies)

The final compliance rating is determined after a formal response to the inspection findings is assessed by the TGA.

Know your documentation

Before an inspection, ensure that your team has reviewed any documentation that an inspector is likely to request. Make sure that all documentation is accessible and that all circulated documents are 'controlled copies' and up-to-date.

Some documents, such as the procedure for handling deviations, OOS, CAPA, change control and release of the product are viewed by the TGA as key procedures. Therefore it is recommended that these procedures are current and detail adequately your processes and controls.

Typically, the inspector will review the following documents before arriving on your site:

- SMF (if the inspector is new to your site)
- Validation Master Plan (VMP)
- previous inspection findings and your responses
- complaints and adverse events.

Site Master File and Validation Master Plan

You should review the content of your SMF and VMP when you have been notified of an upcoming inspection. If appropriate, the updated SMF should be sent to the inspector before the inspection.

The following link provides useful guidance on preparing SMFs:

<https://www.tga.gov.au/publication/site-master-file-preparation-pics-explanatory-notes-pharmaceutical-manufacturers>.

Define tour routes

It is useful to define routes through the facility for the 'inspection tour'. Ensure that you have designated 'hosts' at each area who are capable of answering questions.

To prepare your hosts, you may like to practice some mock questions and answers.

Train personnel

Before an inspection, you should choose which personnel will be interacting with the inspector(s) and train them on how to conduct themselves appropriately. Personnel should always be polite and helpful.

There are a couple of things that you shouldn't do:

- try to second guess the next request from the inspector
- be obstructive or argumentative
- say something when being given the 'silent treatment' from the inspector

- provide answers to questions not related to the area of your responsibility or expertise, especially when your knowledge may be limited.

It is also a good idea to train personnel on the different inspection techniques that an inspector may use. This will help them be more proactive, and help them to anticipate the next step in the inspection process. Techniques likely to be used include:

- trace forward – start with the raw material and follow the production flow
- trace backwards – start at the final product of a specific batch and go backwards
- random – start at points that appear significant (e.g. complaint, CAPA, change control, training).

During the inspection

Arrival to site

It is critical to make a good impression as the inspector arrive on-site. Security personnel should check the identification of the inspector and ensure that they register them in the visitor's book and provide them with appropriate ID badges.

You will also need to ensure that you have a room dedicated to the inspector for the duration of the inspection.

Opening meeting

The lead inspector will chair the opening meeting. The content of the opening meetings is likely to include:

- introduction of the inspection team
- confirmation of the inspection scope and objectives
- presentation and a brief discussion of the inspection plan
- discussion of the methods and procedures to be used during the inspection
- discussion of the communication links during the inspection
- confirmation that the resources and facilities are available
- establishing a tentative time and date for the closing meeting.

It is a good idea to request a summary session at the end of each day if the inspection is over several days.

During the opening meeting, you should advise the inspector about the:

- company policy on health, hygiene and safety
- company policy on photographs, video and sound recording (note that the TGA act allows the inspector to collect such evidence when deemed necessary)
- normal operating hours (e.g. 8am to 5pm)
- times for lunch, breaks, etc

The Ops room

The Ops room supports the personnel fronting the inspector and should be managed by senior personnel. The role of the Ops room is to:

- keep track of the inspectors' location
- keep the schedule on time
- provide an area to hold documents likely to be requested by the inspector
- line up the experts
- action requests for information
- follow-up questions that can't be answered immediately
- provide an area to review documents before they are given to the inspector.

The personnel in charge of the Ops room should also be responsible for reporting to senior management the progress of the inspection, and any areas of attention or significant deficiency.

During the inspection, ensure that all photocopies provided to the inspector for review are marked as 'uncontrolled' or 'commercial in confidence' as necessary, and provide the correct version.

All documentation (procedures, records, raw data etc.) provided to the inspector must be compliant with GMP standards – no sticky notes, incomplete fields or unchecked data.

If any deficiencies are observed during the inspection, you can attempt to correct these immediately, and demonstrate the effectiveness of your procedures for handling such deficiencies. However, although taking immediate corrective action is fine for many types of deficiencies, you may need to perform expert root cause analysis and demonstrate the implementation of measures to prevent reoccurrence for others.

Some other helpful hints to remember during the inspection are:

- when a document is requested, provide this and no more
- do not volunteer information that has not been requested unless it is to your advantage to do so
- do not guess an answer
- allow the inspector to question any staff member (i.e. do not steer the inspector away)
- do not hide information
- do not lie to the inspector
- do not argue or display anger towards the inspector
- do not cause a deliberate delay. If for some reason you cannot deliver a copy of a document quickly, explain the reason for the delay.
- always deliver something you have promised
- be confident and smile!

Closing meeting

At the closing meeting, the lead inspector will provide an overview of the inspection and its outcome. You will be presented with a list of observations that are likely to be listed as deficiencies in the inspection report. The scribe should attend the closing meeting to compare the observations presented by the lead inspector to those recorded during the inspection and discuss any discrepancies. It is important to be cooperative and to commit to providing a written inspection response to the inspection findings during the closing meeting.

There will be some time allocated by the lead inspector to further clarify the observations noted during the inspection, however, most of them should have been discussed and accepted or otherwise at the time they were observed. If any deficiencies are wrong, you can suggest that these are re-visited or documented as such.

If serious deficiencies were noted during the inspection, and the inspector is likely to request a product recall or report a critical deficiency (that may result in a request to vary or suspend your licence) you should start working on your response immediately and be prepared to present it to the TGA in person. You may wish to seek assistance from an appropriately experienced PharmOut consultant to prepare such a response.

After the inspection

Assign one person to be the company's contact for receiving the inspection report and answering any follow-up questions that the inspector may have after leaving your site. A person should also be delegated as responsible for coordinating any correction actions and compiling the inspection report.

A post-inspection review should be conducted to address any areas of weakness identified by your personnel during the inspection (and not detected by the inspector). It is better to correct these weaknesses now rather than wait for the inspector to identify them next time around.

Secrets for success

The secrets to success at any inspection include:

- being well prepared
- providing a good first impression
- having good inspection management
- ensuring that personnel who front the inspector have the required technical knowledge and expertise, confidence and presentation skills
- establishing an SOP and training personnel.

Internal inspections

It is important to conduct internal inspections to ensure compliance with the Code of GMP. If a significant number of deficiencies are noted during a TGA inspection that was not identified during the internal inspection, the lead inspector is likely to conclude that your quality system and measures taken to monitor the performance of the quality system are weak and ineffective.

It is also worthwhile focusing your efforts on areas receiving the majority of GMP deficiencies.

This PharmOut blog details common deficiencies and inspection findings: <https://www.pharmout.net/audit-deficiencies/> and is summarized below:

The common deficiencies reported by the TGA in 2019-2020 were:

Deviations:

- Poor investigations and poor root cause analysis
- No root cause analysis performed
- Poor Corrective and Preventative Action Plan (CAPA)

Computerised Systems:

- Electronic systems used for PQS processes that are not validated
- Back up of data not performed
- Lack of inspection trails
- Inadequate procedures and access control

Environmental monitoring:

- Inadequate environmental controls specified
- Inadequate frequency of environmental monitoring

Validation:

- Inadequate cleaning validation
- Poor process validation
- Poor equipment validation
- Poor validation identification
- Validation not performed to procedures
- Validations do not always demonstrate full control of the manufacturing process

The US Food and Drug Administration (FDA) publish its annual inspection observations on its website. The most recent data set for the 2020 financial year reported the following common deficiencies:

CAPA:

- Inadequate procedures for corrective and preventive action
- CAPA activities and/or results not adequately documented

Complaints:

- Inadequate procedures for receiving, reviewing and evaluating complaints by a formally designated unit
- Inadequate maintenance of complaint files
- Poor investigation of complaints
- Rationale not documented for no investigation

Quality Control Unit:

- Inadequate quality control personnel
- Quality Control Unit responsibilities not documented or fully followed
- Production discrepancies/failures:
- Inadequate investigation of discrepancies
- Investigations do not always include conclusions and follow up

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) reported in 2019 that the highest number of inspection deficiencies related to:

- Quality Systems
- Documentation
- Production
- Qualification and Validation
- Premises and Equipment

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

<https://www.pharmout.net/audit-deficiencies/>

<https://www.tga.gov.au/sites/default/files/good-manufacturing-practice-annual-report-2019-20.pdf>

<https://www.tga.gov.au/book-page/licensing-and-certification-process>

<https://www.tga.gov.au/manufacturing-inspections-risk-based-approach-frequency>

<https://www.tga.gov.au/publication/site-master-file-preparation-pics-explanatory-notes-pharmaceutical-manufacturers>



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