



White Paper

Preparing for GMP audits

As a GMP licensed manufacturer, you should always be ready for an audit – regulators can ‘drop-in’ at any time. This White Paper provides some hints for preparing for a GMP audit.

Whilst this white paper focuses on TGA GMP audit readiness, it provides useful tips for audits carried out by other regulatory authorities such as US FDA.

Before the audit

As a Therapeutic Goods Administration (TGA) GMP licensed manufacturer, you should always be ready for an audit - regulators can perform 'unannounced' audits at any time. First impressions count and it's important to convey to the auditors that you have your facility, quality management system (QMS) and manufacturing processes under control.

Initial audit

These are usually carried out within 3 months of your application and may be conducted at relatively short notice. Make sure that you will be "audit ready" on the date specified in your licensing or certification application.

During your first or licensing audit, you must demonstrate capacity to manufacture within the scope of your application. You would have commissioned your facility, qualified equipment and have completed all relevant validation reports. Your QMS documentation, including procedures, instructions, job descriptions and authorities of key personnel should be approved and your personnel appropriately trained.

After the TGA audit, you will be issued with an audit report within 20 working days and either told that you have passed the audit (no deficiencies) or asked to respond to the deficiencies listed in the report. If the lead auditor accepts your response to the audit findings you will be issued with the TGA licence.

If your response is not accepted, you will get a second chance to address the deficiencies. However, if it is still not accepted, your application may be rejected, meaning you will have to correct your deficiencies and re-apply for the licence. Another audit will be required and the process will start again.

To increase your chances in passing the audit the first time and reduce the time between your application and receiving the TGA licence, we recommend that you have a third party perform a GMP compliance audit of your facility. This will uncover any gaps between your current level of compliance and what is needed to pass an audit by a regulator.

Re-audit

The TGA uses a risk management approach for the frequency of auditing facilities. They take into account the type of products manufactured, results of previous audits, product recalls, adverse reaction reports, complaints and significant changes within the manufacturing facility or processes.

As a general rule of thumb, the following periods for re-auditing apply:

Risk category	Frequency of re-audit (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 <10 ‘other’ deficiencies)

A2 = satisfactory compliance (1-5 ‘major’ and <11 ‘other’ deficiencies)

A3 = basic compliance (5 - 15 ‘major’ deficiencies)

Unacceptable = unacceptable compliance (> 15 “major” or 1 or more ‘critical’ deficiencies)

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

Do some research

With the exception of unannounced audits, you will be notified by the lead auditor approximately 2 months prior to a scheduled audit.

At this point it is a good idea to review previous audit reports to gain some insights. Ensure that all deficiencies, even those for which evidence of close out was not required, were appropriately closed and documented.

You may also like to gain some ‘intelligence’ on the auditors to find out their areas of expertise and focus.

The TGA web provides some information and the following links may be useful:

<http://www.tga.gov.au/docs/html/auditmed.htm>

<http://www.tga.gov.au/docs/html/gmpcodes.htm>

<http://www.tga.gov.au/docs/html/gmpcodqa.htm>

Know your documentation

Prior to an audit, ensure that your team has reviewed any documentation that an auditor is likely to request. Make sure the documents are accessible and that all circulated documents are 'controlled copies' and up to date.

Some procedures, such as the procedure for:

- handling deviations
- out of specification (OOS)
- corrective actions and preventative actions (CAPA),
- change control, and
- release of product

are regarded by the TGA as key quality management system procedures. Make sure that these are current and adequately detail your processes and controls.

A new requirement for Annual Product Review (APR) will be audited from 1st July 2010. This is considered by the TGA one of the most important documents. Be mindful that the information from APRs and the deviation and change control registers (logs) may be used by the TGA auditors to focus their audit activities.

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

- **Site Master File** (if the auditor is new to your site or there were significant changes)
- **Validation Master Plan**
- Previous audit findings and your responses
- Recalls, complaints and adverse events

Site Master File / Validation Master Plan

When you have been notified of an audit you should review the content of your Site Master File (SMF) and Validation Master Plan (VMP). If appropriate, the updated SMF should be sent to the authority prior to the audit.

The following link provides useful guidance on preparing SMFs:

<http://www.tga.gov.au/docs/html/siteinfo.htm>

'The message that you want to display during an audit is that you have your facility and processes under control and that you know what you are doing'

Define tour routes

It is useful to define routes through the facility during the 'audit tour'. Ensure that you have designated 'hosts' for each area and that they are capable of answering auditors' questions. To prepare your hosts you may like to prepare some mock questions for them to answer.

Train personnel

Before an audit, you should choose personnel that will be interacting with the auditor and train them on how to conduct themselves in front of an auditor. 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
- be obstructive or argumentative
- say something when being given the 'silent treatment' from the auditor
- provide answers to a question not related to the area of your responsibility/expertise, especially when your knowledge may be limited

It is also a good idea to train personnel on the different audit techniques that an auditor may use. This will help them be more proactive and allow them to anticipate the next step in the audit 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).

Be pro-active

GMP auditors will be impressed to see early implementation of any expected changes to the Code of GMP. All manufacturers should be aware that the TGA has adopted the P009-8 version of the PIC/S GMP Guide, and that compliance with this guide is mandatory from July 1, 2010. This version of the PIC/S Guide could be downloaded from the TGA web site. The TGA expectation is that you were well prepared to comply with all the new requirements from the 1st of July. When implementing such changes, it's a good idea to get audit ready as early as possible.

Recent and expected changes to GMP guides and codes include:

New GMP requirement	EU GMP Guide	PIC/S GMP Guide	Australian Code of GMP
Product quality review	October 2005	January 2006	July 2010
Ongoing stability program	October 2005	June 2006	July 2010
Reference and retention samples	December 2005	April 2007	July 2010
Quality risk management	February 2008	January 2009	July 2010
Clean-room classification	February 2008 ¹	January 2009	July 2010
Media fill simulations	February 2008 ¹	January 2009	July 2010
Bio-burden monitoring	February 2008 ¹	January 2009 ¹	July 2010
Capping aseptically filled vials	February 2008 ²	January 2009 ²	July 2010

During the audit

It is critical to make a good impression as the auditors arrive on-site. Security personnel should check the identification of the auditors 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 auditors for the duration of the audit.

Opening meeting

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

- introduction of the audit team
- confirmation of the audit scope and objectives
- presentation and brief discussion of the audit plan
- discussion of the methods and procedures to be used during the audit
- discussion of the communication links during the audit
- confirmation that resources and facilities are available

¹ Enforcable March 2009

² Enforcable March 2010

- 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. The lead auditor may or may not include this in his/her audit plan.

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

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

The Ops room

The Ops room supports the personnel fronting the auditors. Senior personnel should be in charge to support staff during the audit. The role of the Ops room is to:

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

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

Conduct the audit

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

If deficiencies are observed during the audit, you could attempt to correct immediately the deficiencies that do not need investigation of root causes – it may impress the audit team if you demonstrate the effectiveness of your procedures for handling such deficiencies. You can also ask the auditors to acknowledge such actions in their final audit report.

Taking immediate corrective actions to address a deficiency that requires expert root cause investigation, is best to be left after the audit. A full response should include the investigation of root causes and implementation of measures to prevent reoccurrence. Otherwise, you may create an impression that it is acceptable to do a patch up work and this will not be viewed favourably by the audit team.

Some other helpful hints to remember during the audit 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 auditors to question any staff member (i.e. do not steer the auditor away)
- do not hide information
- do not argue or display anger towards the auditor
- never cause a deliberate delay. If for some reason you cannot deliver a copy of a document quickly, explain the reason for delay.
- always deliver something you have promised
- look confident and smile!

'A key to success during any audit is preparation'

Closing meeting

At the closing meeting, the lead auditor will give an overview of the audit and its outcome. You will be presented with a list of issues. These are not yet deficiencies, but are very likely to be listed as deficiencies in the audit report. A scribe should attend the closing meeting to compare the deficiencies presented by the lead auditor to those recorded during the audit, and discuss any discrepancies.

There will be some time allocated by the Lead Auditor to further clarify the issues noted during the audit but most of them should have been discussed and accepted or otherwise at the time they were observed and noted. Do not leave important issues till the closing meeting as there may not be sufficient time to discuss them.

It is important to be co-operative and to commit to providing a written audit response to the audit findings. If serious deficiencies were noted during the audit and the auditors are 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.

After the audit

Assign one person to be the company's contact for receiving the audit report and answering any follow up questions that the auditors may have after leaving the site. A person should also be delegated the responsibility for coordinating any correction actions and compiling the audit report.

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

Internal audits

It is important to conduct self-inspections, or internal audits, to ensure compliance with the code of GMP. If deficiencies are noted during the TGA audit that were not identified during internal audits, the lead auditor is likely to conclude both your quality system and measures taken to monitor the performance of the system are weak and ineffective. This would be a very undesirable audit outcome.

It is also worthwhile focusing on the areas receiving the majority of GMP deficiencies, as reported by other regulatory authorities.

Establish an SOP

The key to success during any audit is preparation. You may like to consider establishing a company procedure for the management of GMP audits – from the opening to closing meeting. This should also include the steps to follow for an ‘unannounced’ audit.

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

- security & reception (remember first impressions count!)
- escorts
- scribes (note takers)
- subject matter experts
- runners (people to fetch requested documents and other items)

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.

Secrets for success

The secrets to success at any audit include:

- being well prepared
- creating a good first impression
- having good audit management
- ensuring that personnel who front the auditors have the required technical knowledge and expertise, confidence and presentation skills
- establishing an SOP and training personnel on that SOP
- having effective quality and GMP systems

The message that you want to convey during an audit is that you have your facility and processes under control and that you know what you are doing.

About PharmOut

PharmOut is Australia's consultancy to the Pharmaceutical, Medical Device, and Veterinary drug industries.

PharmOut specialises in GMP compliance, validation and continuous improvement consulting, and training.

How PharmOut can help

Audit readiness / GAP Assessments

We have experienced consultants (including ex-TGA and PIC/S auditors) able to perform GMP Audit Readiness / GMP GAP assessments for your facility against TGA, PICS and US FDA GMP requirements.

Audit report response

If deficiencies are found during a regulatory audit, we can offer assistance in correcting any deficiencies and preparing responses to audit findings.

International regulatory assistance

We can assist you with preparation of application for registration of medicines and obtaining approval from the following international regulatory authorities –TGA, EMA and US FDA.

Quality Management System

We have consultants experienced with designing a QMS to suit your operations or re-designing your existing QMS in compliance with relevant standards.

Training

We offer GAMP/ GLP/ GMP and audit training services and can specifically tailor these to meet your business needs.



www.pharmout.com.au