

## **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 to prepare for a GMP audit. This White Paper focuses on TGA GMP Audit readiness; however it provides useful tips for audits carried out by other authorities, such as US FDA.

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## Always be 'audit ready'

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 process under control.

## Establish an SOP

A 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 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 display is that you have your facility and processes under control, and that you know what you are doing'*

## Preparing for an 'initial audit'

An initial audit is usually carried out within 3-months of your application to the TGA, and may be conducted at relatively short notice. You should 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 should have commissioned your facility, qualified equipment and completed validation reports. Your QMS documentation, including procedures, instructions, job descriptions and authorities for key personnel should be approved and personnel appropriately trained.

After the initial audit, you will be issued with an audit report (within 20 working days). You will be informed that you have passed the audit, or asked to respond to the listed deficiencies within 4 weeks. If the lead auditor accepts your response to the audit findings, you will be issued with the TGA license.

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 require another licensing audit.

To increase your chances in passing the audit the first time, and shorten significantly the time between your application and receiving your TGA licence, you could request a pre-regulatory audit from PharmOut. PharmOut has very experienced staff (i.e. staff with years of TGA audit experience) and can carry out an audit of your facilities prior to the initial audit. PharmOut can also help you to address any audit deficiencies noted during the initial audit, and prepare a response to the TGA.

## Preparing for a 're-audit'

The TGA uses a risk-management approach when determining the frequency for re-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 company.

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

Risk category	Frequency of re-audit (months)			Unacceptable rating
	Acceptable compliance 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)

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

## Do some research

Unless you have a reason to expect to have unannounced audit, you will be notified by the lead auditor within 2 month of the scheduled audit. It is a good idea during this time, to review previous audit reports (your own and other companies) to gain some insights. Ensure that all deficiencies, even those for which evidence of close-out was not required, were in fact closed, and that this is documented.

You may also like to gain some 'intelligence' on the auditors to find out their areas of expertise and focus. The web also 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 the audit, ensure that your team has reviewed any documentation that an auditor 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 product are viewed by the TGA as key procedures. Make sure that these are current and detail adequately your processes and controls.

A new requirement for Annual Product Review (APR) will be audited from the 1<sup>st</sup> July 2010. This is considered by the TGA one of the most important documents and indeed, you should also consider it as such. Be mindful, that the information from APRs and the deviation and change control registers (logs) will 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)
- Validation Master Plan
- previous audit findings and your responses
- complaints and adverse events.

## Site Master File and Validation Master Plan

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

The following link provides useful guidance on preparing SMFs:

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

## Define tour routes

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

## Train personnel

Before an audit, you should choose which personnel will be interacting with the auditor(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 auditor
- be obstructive or argumentative
- say something when being given the 'silent treatment' from the auditor
- 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 audit techniques that an auditor may use. This will help them be more proactive, and help 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 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. If you are audited prior to July 1, you will be asked by the TGA auditor if you wish to be audited against the new guide.

The TGA expectation is that you are well prepared to comply with all the new requirements from July 01. When preparing for 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:

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
Counterfeiting	December 2005	August 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 <sup>1</sup>	January 2009	July 2010
Media fill simulations	February 2008 <sup>1</sup>	January 2009	July 2010
Bio-burden monitoring	February 2008 <sup>1</sup>	January 2009 <sup>1</sup>	July 2010
Capping aseptically filled vials	February 2008 <sup>2</sup>	January 2009 <sup>2</sup>	July 2010
Adoption of ICH Q9	February 2008	January 2009 <sup>3</sup>	July 2010

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1 Enforcable March 2009

2 Enforcable March 2010

3 As Annex 20. The use of this annex is voluntary where the PIC/S Guide applies.

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## 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 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. The lead auditor may or may not include this during the opening meeting.

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 act allows auditors to collect such evidence, when deemed necessary)
- normal operating hours (e.g. 8am to 5pm)
- times for lunch, breaks etc.

*'A key to success during any audit is preparation'*



## The Ops room

The Ops room supports the personnel fronting the auditors and should be managed by senior personnel 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 they are given to the auditor.

The 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 or significant deficiency.

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

If any deficiencies are observed during the audit, 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 implementation of measures to prevent recurrence for others.

- 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 lie to the auditor
- do not argue or display anger towards the auditor
- do not 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!

## Closing meeting

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

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

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. You may wish to seek assistance from an appropriately experienced PharmOut consultant in preparation of such response.

## 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 your site. A person should also be delegated as responsible 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.

## Secrets for success

The secrets to success at any audit include:

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

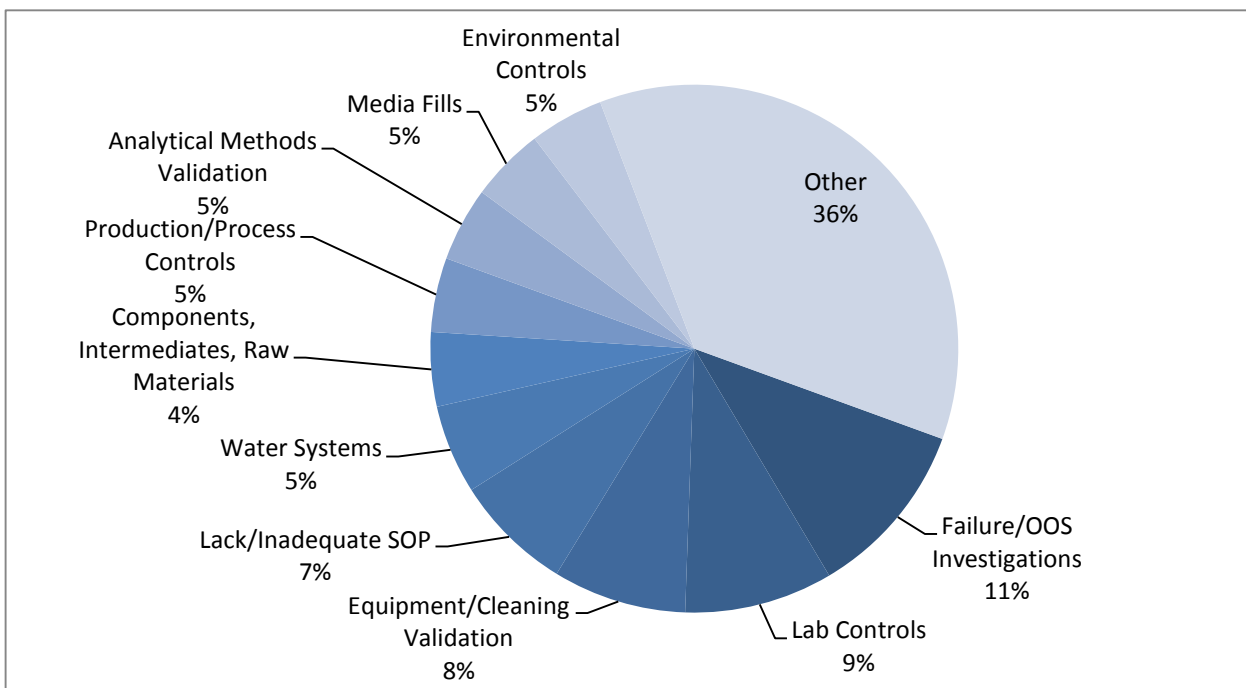
The message that you want to convey during an audit is that you have everything under control and that you know what you are doing.

## Internal audits

It is important to conduct internal audits to ensure compliance with the Code of GMP. If a significant number of deficiencies are noted during a TGA audit that were not identified during internal audits, the lead auditor 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.

The FDA reported failure / OOS investigations as the most common GMP deficiency for 2004<sup>4</sup> as detailed in the chart below. The TGA may release similar type of information in the future.



4 [www.fda.gov/cder/about/smallbiz/Presentations/6.ppt](http://www.fda.gov/cder/about/smallbiz/Presentations/6.ppt)

## References

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

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

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## Sources

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PharmOut is an international GMP consultancy serving the Pharmaceutical, Medical Device and Veterinary industries. PharmOut specialises in PIC/S, WHO, United States FDA, European EMA, and Australian TGA GMP consulting, engineering, project management, training, validation, continuous improvement and regulatory services.

Our team includes international GMP experts who have previously held leadership roles within regulatory bodies.

For more information please visit [www.pharmout.net](http://www.pharmout.net) or contact us at [info@pharmout.net](mailto:info@pharmout.net).

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