Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public consultation on Proposed update of the Good Manufacturing Practice Audit Procedure

Submissions received

August 2024

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23 August 2024

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By email only: enquiries@apvma.gov.au (cc: mls@apvma.gov.au)

Dear MQL team,

Re: Updated GMP Audit Procedure

Thank you for the opportunity to provide feedback on the updated GMP Audit Procedure. Our members have reviewed the updated procedure and we are pleased to provide the following comments to APVMA.

General comment:

The greater level of detail added to the procedure is appreciated. AMA notes that the inclusion of greater detail does not reflect 'new' processes, but rather, formalises and clarifies what is already current practice and aligns with current APVMA expectations.

Other audits:

The recognition of TGA and NATA audits is welcomed. Information on the process for TGA and NATA audits and the requirements for notifications by both registrants and APVMA is an important addition to the GMP Audit Procedure guidance.

Audit duration:

The audit duration will be determined using a risk-based approach, taking into account non-conformities and license variations, in addition to the product category. AMA supports a risk-based approach to determine audit durations that are proportionate to the risks being assessed by the audit process.

Auditor selection:

Auditors are to be selected 6 weeks prior to the audit, rather than the current 4 weeks. We anticipate this will support better planning and workflow management for both registrants and the regulator.

Communications:

Auditors are expected to provide their report within 10 working days of audit completion. Although this has not changed, AMA members note that auditor compliance with this requirement is variable.

The expectations on timeframes for key communications during the audit process are identified in this audit procedure. AMA expects that these timelines will be respected for all key communications from APVMA to the registrant, and from the registrant to APVMA. This will improve predictability and efficiency of the audit process, and support better management of timeframes and resources for all parties.

I hope that this feedback is of assistance in finalising the GMP audit procedure guidance material. Please let me know if we can provide any further information or clarification.

We look forward to further engagement with the MQL team on future consultations, including the updated GMP Code.

Yours sincerely,

[redacted]

[redacted]

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22 AUGUST 2024

VMDA SUBMISSION RE AUDIT PROCEDURES

The VMDA has only two comments in addition to those already made via ILCF.

1. Under 'Duration of Audit' there is a note that the duration "…may be modified on account of additional intelligence…"

   The VMDA believes that this requires clarification as to the nature and provenance of the 'intelligence'.

   In the experience of at least one of our members, the audit period was extended because of 'adverse reaction reports'.

   The manufacturer in question does not hold any registrations, and therefore may not be advised by the registration holder/s of any such reports (and in this case was not).

   In addition, the nature of the reports is not disclosed and therefore there is no evidence provided to the manufacturer as to whether their processes and procedures were in any way involved in the suspected adverse reactions.

   The manufacturer has no opportunity to provide any argument as to whether the extended audit time is justified.

   The VMDA suggests that this procedure is clarified and modified so that manufacturers can clearly see and defend the basis of extended audit times.

2. On the cover sheet for additional information the word 'APPENDIXES' is used. While there may be some casual use of this form of words for documentation, it is generally considered to be incorrect. For documentation the plural of APPENDIX is APPENDICES.

Australian Government

Australian Pesticides and Veterinary Medicines Authority

JULY 2024

Good Manufacturing Practice Audit Procedure

Draft for Public Comment

Comments and enquiries regarding copyright:

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CONTENTS

INTRODUCTION

The purpose of this document is to provide detailed instructions on how routine (full or partial) GMP audits of veterinary chemical manufacturing premises are to be planned, conducted and reported to the Australian Pesticides and Veterinary Medicines Authority (APVMA).

This manual covers the procedure to be followed by APVMA-authorised GMP auditors when auditing an **Australian veterinary chemical manufacturing facility** for compliance with the Agricultural and Veterinary Chemicals (Manufacturing Principles) Determination 2014 (Manufacturing Principles), the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products, 2007 (and relevant annexes—GMP Code), Part 8 of the Agricultural and Veterinary Chemicals Code Act 1994 (AgVet Code) and Part 7 of the Agricultural and Veterinary Chemicals Code Regulations 1995 (AgVet Code Regulations). It covers procedures to be followed for routine (full and partial) audits, and for verification (on-site) audits and desk reviews of corrective actions arising from routine audits. It also covers the procedures to be followed by Licence Holder when selecting an auditor and when responding to and forwarding the GMP Audit Report to the APVMA.

The procedure should also be followed for audits of **overseas veterinary chemical manufacturing facility** by APVMA-authorised GMP auditors, however some differences in processes, forms, etc may apply. These differences are summarised in Section 5. For a list of all forms and templates, refer to Appendix A (page 29).

The procedure also covers other recognised GMP accreditation from Therapeutic Goods Administration (TGA) and the National Association of Testing Authorities, Australia (NATA). The TGA will audit a veterinary chemical manufacturing facility against the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Testing laboratories can be audited by NATA to ISO17025 General Requirements for the Competence of Testing and Calibration Laboratories.

The APVMA may attend audits as an observer(s) or may periodically conduct announced and unannounced audits to assess day-to-day GMP compliance.

All GMP Audit Reports are reviewed by the APVMA to ensure that a veterinary chemical manufacturing facility is compliant with the Agricultural and Veterinary Chemicals (Manufacturing Principles) Determination 2014 (Manufacturing Principles) and the GMP Code for the purpose of licensing.

1 GENERAL PRINCIPLES

Supplying manufactured goods to Australia

No batch of veterinary chemical product manufactured prior to licensing or issuance of a GMP compliance letter can be sold or supplied within Australia, or exported from Australia, unless prior approval has been obtained.

Note that the manufacture of excluded nutritional or digestive (END) products can be exempted from this requirement. For a product to be an END product, the product must be manufactured under one of the following QA systems:

- Meet the requirements of the APVMA GMP Code of Practice and manufacturing principles
- An Australian animal feed industry code of practice (such as FeedSafe or the FIAAA CoP)
- An Australian Standard for animal feed manufacture (in particular, AS 5812-2011), or
- An animal feed quality standard of the United States of America or the European Union (such as FAMI-QS).

The QA system must be appropriate for the product. For example, a stock feed QA system will not apply to a pet food, and vice versa.

	Do not commence manufacturing for validation or supply to Australia until a manufacturing licence or GMP compliance letter has been granted, unless prior approval has been obtained or those chemical products are listed, reserved or exempt.

Confidentiality

APVMA treat information about applications and manufacturers as official information. Find out more about confidentiality at APVMA approach to disclosure of commercially confidential information.

The APVMA publishes a list of licensed Australian manufacturers.

Determining whether a licencing or GMP compliance letter is required

Under the AgVet Code and the AgVet Code Regulations, an APVMA manufacturing licence is required to manufacture veterinary chemical products for supply in, or export from, Australia, unless otherwise exempt.

GMP compliance is how the APVMA determines that veterinary chemical products manufactured overseas and intended for import and supply to Australia, and manufactured domestically, comply with Australia's GMP requirements.

Independent advice

If a Licence Holder has no previous experience with manufacturing veterinary chemical products within Australia, they may seek the services of a GMP consultant or a regulatory affairs consultant. **The APVMA also recommends that Licence Holders seek independent legal advice to ensure they comply with all relevant requirements.**

Responsibilities of key persons

The AgVet Code Regulations, the Manufacturing Principles and the GMP Code outline specific responsibilities for the key persons nominated by the Licence Holder and listed in APVMA records as being responsible for controlling production and quality.

Under the AgVet Code Regulations, it is a condition of the licence that the key people maintain their control of production and quality. If a key person is replaced, the Licence Holder must advise the APVMA of the name, qualifications and experience of their replacement as soon as practicable.

Variations to a licence or its conditions

Licence Holders are responsible for notifying the APVMA of any changes or variations that may affect their licence or its conditions. This can apply to changes in the product (types), the manufacturing site and processes or to key persons.

Licence Holders must submit an application to vary their licence, in accordance with the requirements set out in the AgVet Code.

Recalls

Licence Holders are responsible for having a system in place to recall a product after it has been supplied to the Australian market and for implementing that system when required.

Recall action can be instigated by the Licence Holder, registrant or by the APVMA when:

- A chemical product may not meet the safety criteria, the trade criteria or the efficacy criteria
- The constituents of stocks of a registered chemical product or of a particular batch of a registered chemical product differ by more than the prescribed extent from the constituents stated in relation to the product in the Register
- The concentration of the constituents of stocks of a registered chemical product or of a particular batch of a registered chemical product differs by more than the prescribed extent from the concentration of the constituents stated in relation to the product in the Register, or
- The composition or purity of any constituent of stocks of a registered chemical product or of a particular batch of a registered chemical product differs by more than the prescribed extent from the composition or purity of that constituent stated in relation to the product in the Register.

The APVMA has published recall guidelines to provide more details on the responsibilities of Licence Holders and other parties when undertaking recalls.

2 AUDIT PATHWAYS: OVERVIEW

Audits may be undertaken by the APVMA's authorised auditors, by the TGA or by NATA. The choice of which audit pathway a Licence Holder takes to ensure GMP accreditation is an individual business decision. Please note that there are different costs associated with the different audit pathways.

2.1 APVMA Audits

APVMA-authorised auditors may undertake an audit of a Licence Holder's manufacturing facility for four key reasons:

- Routine GMP audit
- Audit to add a manufacturing site(s)
- Audit to vary a licence
- Verification audit (Section 3.3).

In addition to audits undertaken by APVMA-authorised auditors, the APVMA may utilise its own staff to conduct audits as needed. These may include routine GMP audits, unannounced GMP audits, variation to licence or verification audits. At the discretion of the APVMA, a fee for these audits may be requested from the Licence Holder.

[redacted] These staff should be trained to do a GMP Audit

[redacted] Where will the fee structure be listed?

Routine GMP audits

Prior to each APVMA audit, the APVMA will notify the Licence Holder three (3) months before the audit due date of the required audit duration. The Licence Holder must arrange for an APVMA-authorised auditor to conduct the audit before the audit due date. The pre-audit notification and information form must be provided to the APVMA at least six (6) weeks prior to the audit being conducted. The APVMA-authorised auditor will verify during the audit that ~~all~~ aspects of veterinary chemical manufacture are carried out within the scope of the Licence Holder's APVMA licence. The Licence Holder must also provide the APVMA with signed APVMA forms within required timeframes i.e. GMP Audit Reports, responses to non-conformances, related to the conduct and closure of such audits, unless granted extensions by the APVMA.

[redacted] Not realistic for an auditor to cover all aspects

It is important for a Licence Holder to advise the APVMA of any changes to site, key personnel or any variation of licence prior to related correspondence between the Licence Holder and APVMA-authorised auditor. This is to enable the APVMA to provide relevant correspondence to the APVMA-authorised auditors in a timely manner.

	Advise the APVMA in writing before three (3) months of the audit due date with any changes in the scope of the licence. If this doesn't occur, audit duration may be changed, and the Licence Holder will be notified of the change.

An APVMA audit may be required for an overseas site if other acceptable evidence is not available for the purposes of APVMA product registration (see Section 5).

Adding a new manufacturing site(s)

You may request pre-application assistance to discuss the application requirements for a new licence or to vary a licence. There is a fee for this service.

To be ready for an audit, the Licence Holder must have:

- Completed constructing or fabricating the premises
- Taken functional control of the site (APVMA may ask to see a certificate of occupancy or equivalent)
- Documented and implemented a quality system, in accordance with the requirements of the manufacturing principles and specifically tailored to the Licence Holder's proposed manufacturing operations, that includes procedures, records and instructions for the management of:
    - Quality Management Systems (QMS) such as deviation, change control, risk management, product quality review systems
    - Documentation
    - Materials
    - Production operations, including master batch records
    - Personnel matters including training, clothing and hygiene
    - Validation and qualification
    - Equipment assembly and calibration
    - Maintenance, cleaning and sanitisation
    - Environmental monitoring
    - Pest control
    - Complaints
    - Recalls
    - Returns
    - Self-inspection
    - Laboratory controls and operations
    - Release for supply.
- Qualified all relevant facilities, utilities and equipment to at least the operational qualification (OQ) stage

- Employed, nominated and trained all key staff responsible for controlling manufacturing operations and quality assurance.

Varying a licence

To change details on a manufacturing licence – or to change its conditions – Licence Holders must apply to the APVMA for a licence variation.

Changes can include:

- A change to the company name where the ACN / ABN remains the same (not a change to the legal entity)
- The change to a product type within an already licensed manufacturing category (and applicable steps)
- A change to steps of manufacture covered by the licence (addition / deletion)
- The inclusion of a subcontractor under the provisions of Regulation 59A (analysis and testing, packaging or labelling only)
- Any other change not already specified.

The requirement for a variation is because licences to manufacture chemical products in Australia are issued with certain details and licence conditions that are specific to each Licence Holder. The licence will specify, among other things, precisely what steps of manufacture, at which sites and what products can be manufactured as part of the licence. Any change to a licence or its conditions must be approved by the APVMA, meaning Licence Holders must submit an application well ahead of the audit.

The process for receiving, assessing and deciding the outcome of a variation application is similar to the process for new licence applicants, and is undertaken in accordance with APVMA legislation.

Observing audits

APVMA staff will observe audits as part of quality assurance for both the auditing process and the individual APVMA-authorised auditors. TGA and NATA audits (below) may also be observed. Broadly, the reasons for observing audits may include:

- Auditor qualification and quality control
- Auditor wishes to audit to a new category of manufacture
- Complex audit history or new sites / steps of manufacture
- Training staff.

If an audit is to be observed by APVMA staff, the Licence Holder and the auditor / inspector will be notified, and the role of the observer will be underscored. In particular, it will be explained that when an APVMA staff member is present as an observer, that person will not actively take part in, or otherwise influence, the audit. There will be no cost to the manufacturer for the APVMA staff to attend the audit as an observer.

[redacted] The purpose/role of the observer should be explained in detail i.e training of staff or observing consistency of auditors etc

2.2 TGA Audits

APVMA-TGA memorandum of understanding

The TGA and the APVMA have a Memorandum of Understanding (MoU) on Good Manufacturing Practice Licensing and Inspection of Australian Manufacturers (APVMA-TGA MoU).

Manufacturers holding both TGA and APVMA licences may elect to have routine inspections conducted by the TGA. The Licence Holder must notify the APVMA of this decision. If the purpose of the inspection is to underpin licence renewal or change (see also certification, below), then the TGA will not inspect a facility that is dedicated to the manufacture of veterinary products only.

The APVMA recognises authorities in Europe, including the United Kingdom, through Mutual Recognition Agreements (MRAs). The APVMA also recognises authorities in New Zealand, Canada and the United States as having requirements equivalent to the APVMA's good manufacturing practice (GMP) standards. On a case-by-case basis, the APVMA may recognise GMP evidence from a PIC/S participating authority / member.

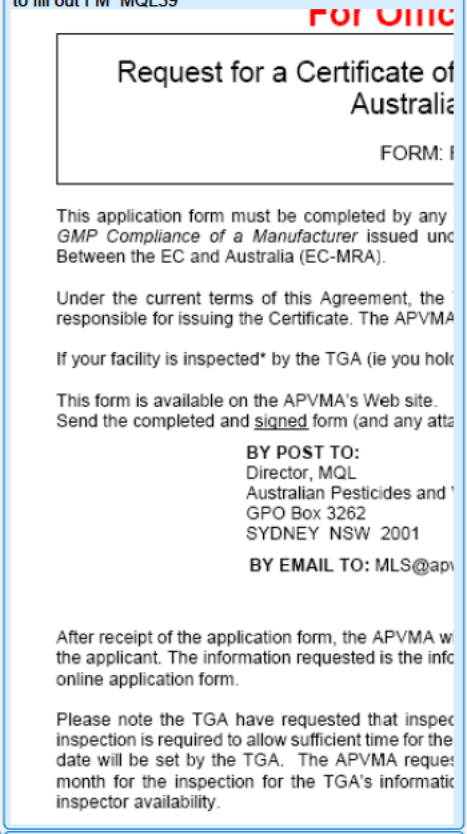
Manufacturers licensed by the APVMA, who wish to export veterinary chemical products to Europe or the UK, must be inspected by the TGA. This inspection must be requested by the APVMA, not by the manufacturer. The APVMA will assess the TGA inspection results and can then issue a GMP certificate to the manufacturer. Under the EU or UK MRAs, the authority in the recipient country recognises the TGA as the authority for inspecting veterinary premises in Australia and the APVMA as a certifying body. Note that in contrast to inspections undertaken for the purpose of licensing (above), the TGA will inspect a facility dedicated solely to the manufacture of veterinary products if the purpose of the inspection is to certify a product under an MRA.

TGA Audit process

Prior to each TGA audit, the Licence Holder must arrange for the TGA inspector to verify during the audit that all aspects of veterinary chemical manufacture are carried out within the scope of that audit (European Community-Australian Mutual Recognition Agreement; EC-MRA) or TGA licence. The Licence Holder must maintain their TGA licence and advise the APVMA in writing, within 10 working days, of any changes in the scope of that licence. The Licence Holder must also provide the APVMA with copies of all TGA audit reports and correspondence i.e. responses to non-conformances, related to the conduct and closure of such inspections, within 10 working days of receipt of those reports or correspondence.

It is important for a manufacturer to advise the APVMA of any related correspondence between the manufacturer and TGA. This is to enable the APVMA to provide commercially confidential information (CCI) to the TGA in a timely manner.

[redacted] Do you need to add the instruction to fill out FM MQL39


For Offic

Request for a Certificate of Australia

FORM: I

This application form must be completed by any *GMP Compliance of a Manufacturer* issued unc Between the EC and Australia (EC-MRA).

Under the current terms of this Agreement, the responsible for issuing the Certificate. The APVMA

If your facility is inspected* by the TGA (ie you hol

This form is available on the APVMA's Web site. Send the completed and signed form (and any atta

BY POST TO:
Director, MQL
Australian Pesticides and
GPO Box 3262
SYDNEY NSW 2001

BY EMAIL TO: MLS@ap

After receipt of the application form, the APVMA w the applicant. The information requested is the info online application form.

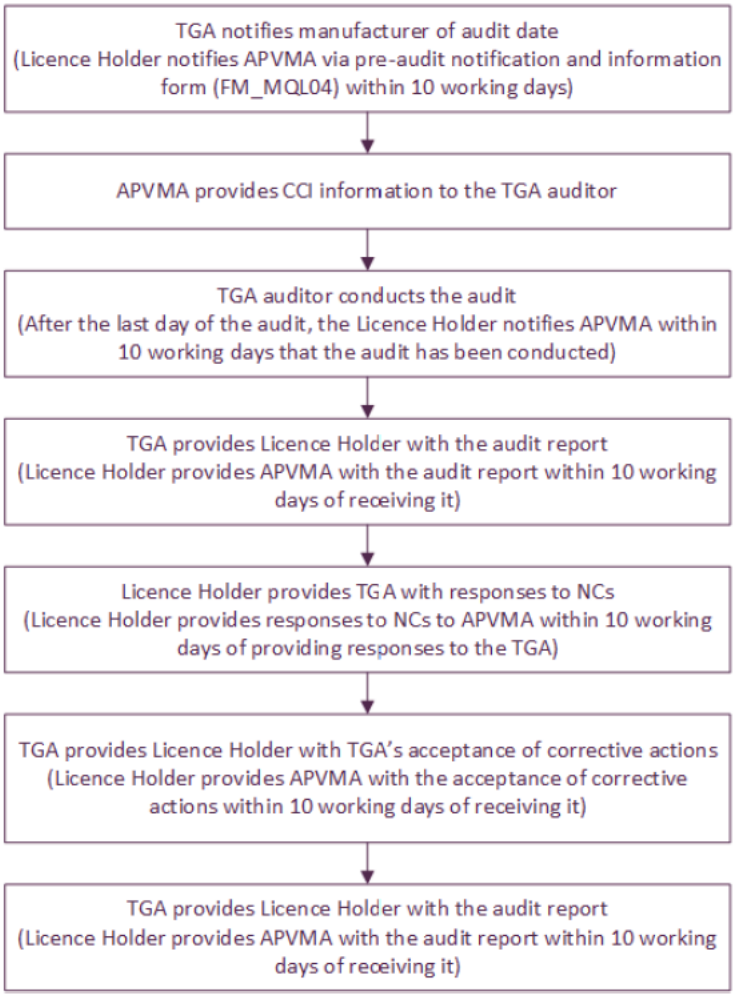
Please note the TGA have requested that inspec inspection is required to allow sufficient time for the date will be set by the TGA. The APVMA reque month for the inspection for the TGA's informatic inspector availability.

[redacted] Sentence doesn't make sense. How can the this be done prior to the audit but also during the audit?

[redacted] The licence holder also does not arrange TGA audits- this is done by APVMA

Figure 1: TGA audit process

[redacted] Is the FM_MQL04 the correct form to be filled out? I thought this was for arranging APVMA audits. What about FM MQL39?

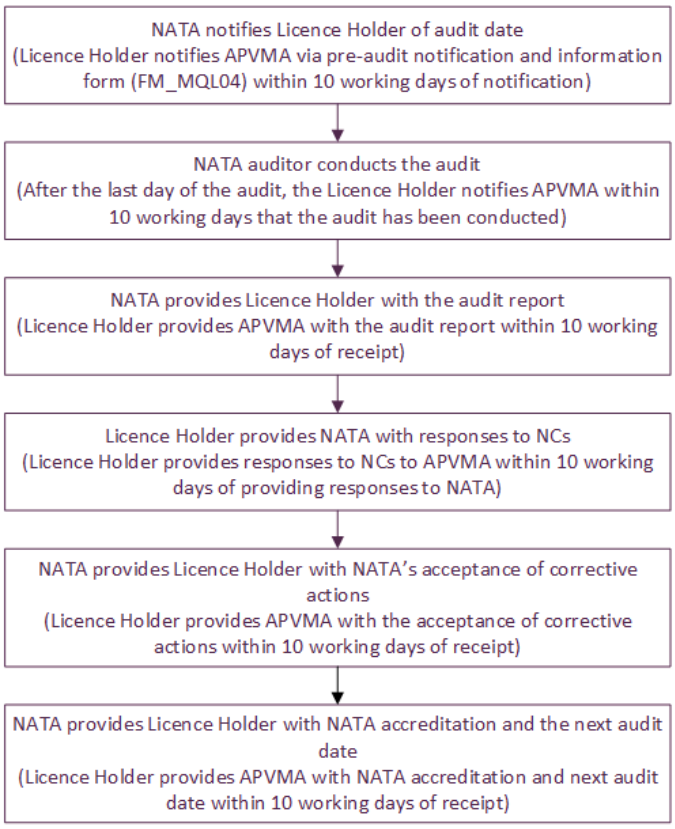


	Advising the APVMA in writing within 10 working days of any changes in the scope of the licence and correspondence is a condition of a Licence. If this doesn't occur, regulatory action may be taken which may result in suspension or cancellation of the licence.

2.3 NATA Audits

The Licence Holder must maintain their NATA accreditation and advise the APVMA in writing, within 10 working days, of any changes in the scope of that accreditation that are likely to impact on the analysis or testing or both of veterinary chemical products. The Licence Holder must also provide the APVMA with copies of all NATA assessment reports and correspondence i.e. responses to non-conformances, related to the conduct and closure of such assessments, within 10 working days of receipt of those reports or correspondence. Providing this correspondence is important as the APVMA does not have an agreement with NATA and cannot retrieve or provide information to NATA.

Figure 2: NATA audit process

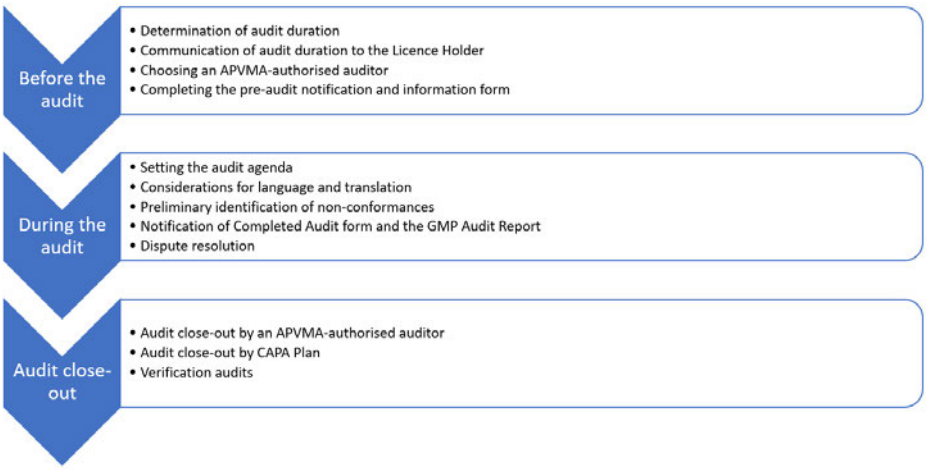


Advising the APVMA in writing within 10 working days of any changes in the scope of the licence and correspondence is a condition of a Licence. If this doesn't occur, regulatory action may be taken which may result in suspension or cancellation of the licence.

3 APVMA AUDITS: PROCEDURE

An overview of the audit and review procedure for APVMA audits is given in Figure 3 below. Each of the items in this figure is discussed in the following three sections.

Figure 3: APVMA audit process



3.1 Before the audit

APVMA determines audit duration

When determining audit duration, the APVMA will take into account the type of products manufactured, the complexity of the manufacturing process, the size of the manufacturing facility, the Licence Holder's audit history, and any manufacturing-related adverse experiences or voluntary recalls. In addition, the APVMA will consider any changes to key personnel (appointments or resignations), operations or to buildings, key equipment or product lines.

As a baseline, however, audit duration will be calculated as the sum of the following three parts:

a) Risk-based audit duration, plus

b) Non-conformity additional duration, plus

c) Licence variation additional duration.

Risk-based audit duration ranges from Low (1 day) to High (3 days), as set out below:

a) High risk – audit duration 3 days

High risk products and processes include:

- Category 1 - Sterile products
- Category 1 - Immunobiological products
- Multi-category manufacturing.

b) Medium risk – audit duration 2 days

Medium risk products and processes include:

- Category 2 or 3, only non-sterile products
- Products containing antibiotics.

c) Low risk – audit duration 1 day

Low risk products and processes include:

- Category 4, Premix / supplements
- Laboratories
- Single step – labelling / packaging, release for supply, or storage.

A day will be added to this risk-based starting point for audit duration, if either of the following non-conformity scenarios applies:

- 10 or more total non-conformities, and/or
- 5 or more Major non-conformities from the previous audit.

A further day will then be added to the calculated audit duration if the license is to be varied for either of the following reasons:

- A new facility is to be added to the license (i.e., a new building for storage, manufacturing or laboratory services)
- A new step of manufacture / product dosage form / category is to be added to the license, increasing the base risk (e.g., the current licence covers non-sterile products, and a variation is sought to add a sterile step of manufacture).

The APVMA will use this three-step formula to obtain a baseline estimate for audit duration. At the APVMA's discretion, this baseline calculation may then be modified to a maximum of 5 days on account of additional intelligence about the Licence Holder or manufacturing site.

Communicating audit duration to the Licence Holder

At the close of the preceding audit (see below), the APVMA will issue an audit outcome letter that includes, amongst other things, the due date for the next audit and the first estimate of audit duration (as described above).

Four (4) months ~~prior to the date of the next audit~~before the audit due date, the APVMA will collate and review any relevant s161 notices, adverse experiences or recalls; relevant conditions attached to any new product registrations or permits; and relevant license variation applications. Based on this information adjustments may be made to the first estimate for audit duration.

Three (3) months before the audit due date, the APVMA will issue an audit reminder notice to the Licence Holder. This reminder notice will cite the final audit duration. The reminder notice will also request that if the Licence Holder is wanting to change the scope of their licence i.e. new facilities, categories or steps of manufacture, then a licence variation application must be submitted. This licence variation application should be submitted within two (2) weeks of the date of the audit reminder.

Choosing an APVMA-authorised auditor

At least six (6) weeks prior to the audit due date, the Licence Holder must select an auditor from the current list of APVMA-authorised GMP auditors, arrange for the audit to be conducted by the required time, and notify the APVMA on a signed 'Pre-audit notification and information form'. Overseas sites should use the 'Pre-audit notification and information form—overseas sites'. The form should be emailed to the APVMA. Unsigned forms will not be accepted by the APVMA.

[redacted] From the comments from the auditors at CAPSIG meeting 6 weeks is very short notice

If the APVMA has not received notification that an audit has been arranged prior to six weeks of the due date for audit, the APVMA will contact the Licence Holder to remind them that an audit is due and to ensure the audit schedule is maintained. Failure to arrange an audit, as directed by the APVMA, may result in suspension or cancellation of the licence for breach of licence condition.

The auditor must also submit a signed 'Confirmation of audit booking form' to the APVMA as soon as possible after the audit date is confirmed with the Licence Holder. The 'Auditor's declaration' at the foot of the document, confirming the auditor has no actual or perceived conflict of interest in performing the audit **MUST** be signed by the auditor. Unsigned forms will not be accepted by the APVMA. Submission of this form by email is acceptable provided the form contains an electronic signature in the 'Auditor's declaration' section, and the form does not contain any commercially sensitive information.

The APVMA may reject the Licence Holder's choice of auditor if:

- The auditor has carried out the previous two consecutive routine full audits on the facility
- The auditor has carried out consultancy services for the Licence Holder within the preceding three (3) years or there is any other potential conflict of interest
- The APVMA considers that the auditor is not suitably qualified to audit the nominated type of manufacturing facility or manufacture
- The APVMA considers that a substantive conflict of interest may exist

- The APVMA considers that under the circumstances, for whatever reason, another auditor is more appropriate.

In most cases, the APVMA will liaise with the Licence Holder and the auditor and advise the Licence Holder to select an alternative auditor. However, as indicated above, the APVMA reserves the right to appoint an auditor of its own choice if considered appropriate. This may include the appointment of a suitably qualified and experienced APVMA staff member.

[redacted] How is this defined?

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Prior to the audit, the APVMA GMP Officer may send to the auditor:

- Relevant particulars of the Licence Holder, including the pre-audit notification and information form submitted by the Licence Holder
- Copy of the completed application form (for new applicants for a licence or licence variation)
- Copy of the previous audit reports other relevant correspondence from the Licence Holder's file
- Copy of the current APVMA licence and schedule of conditions (if an existing licensee)
- Copy of any documents relevant to an audit
- Copy of other relevant correspondence from the Licence Holder's file.

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[redacted] Duplication of same information

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The auditor should ~~normally~~ prepare an audit plan with a proposed timetable, which should be provided to and discussed with the Licence Holder prior to the audit, to verify whether it is suitable and whether relevant staff will be available and/or that the plant will be operating, etc.

Pre-audit notification and information form

If a Licence Holder fails to provide the notification that an audit has been arranged, after the APVMA GMP officer has followed up with the Licence Holder to remind them that an audit is due, the APVMA may take action. This may result in suspension or cancellation of the licence.

3.2 During the audit

Audit agenda

The agenda on the day of audit will be at the auditor's discretion, although should be consistent with ISO 19011: 2018 Guidelines for Auditing Management Systems. Key elements should include:

- An initial meeting with the Licence Holder and staff for introductions, to confirm the scope of the audit, discuss the audit plan and how it will be conducted, and a brief introduction / familiarisation with the personnel, plant and procedures
- The confirmation of the scope of manufacture to be inspected (categories, steps of manufacture, product types, licence conditions)
- A review of any changes in the company structure, quality management system, the facility and/or key personnel since the last audit

- A review of previous audit outcomes and steps taken to address the required corrective actions
- Inspection of the facilities, procedures, records, etc
- Confirmation with the Licence Holder during the audit about the relevance and accuracy of observed non-conformances
- Preparation of a draft report (if practical)
- An exit interview where all non-conformances are highlighted and options for corrective action(s) assessment are canvassed.

On completion of the audit, the auditor should hold an exit interview with the Licence Holder and staff to discuss the outcome of the audit. As part of that discussion, the auditor must identify the Critical non-conformances observed and discuss with the manufacturer various options, priorities and appropriate timelines for corrective action. Major and Minor non-conformances, as well and observations / areas for improvement, should also be highlighted to the Licence Holder. The auditor is encouraged to provide positive feedback regarding compliance as well as identifying any non-conformances.

[redacted] These are not always classified at this time

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Language and translation

Audits will be conducted in English. If the APVMA needs to talk to people who cannot speak or understand English, the Licence Holder will need to:

- Provide a guide with some technical understanding who can act as a translator
- Translate any documents that the APVMA requests into English.

	**The translator**: Please ensure the translator can translate technical language. The translator needs to be able to translate a technical question asked by the auditor in English into the relevant language, as well as translate technical information into English. The auditor may terminate the audit if they cannot communicate effectively or if the provided documents are not in English. If the information cannot be properly translated to the auditor, this may adversely affect the inspection outcome.

The Licence Holder may also appoint observers.

Preliminary identification of non-conformances

The auditor will inform the Licence Holder of all potential non-conformances that have been observed and will give the Licence Holder an opportunity to provide any additional relevant information.

	If the auditor notifies the Licence Holder of an observed non-conformance, the Licence Holder can provide additional information for the auditor to review. However, if the Licence Holder has additional information, the APVMA preference is that this is provided to the auditor during the audit.

Notification of completed Audit form and the GMP Audit Report

The auditor must use approved, current versions of audit documents, in the standardised format, as provided by the APVMA. Audit documents to be completed by the auditor include:

- The Notification of Completed Audit form (FM_MQL06), within three (3) working days of audit completion (24 hours where Critical non-conformances are observed).
- The GMP Audit Report (FM_MQL05), within ten (10) working days of audit completion.
- The GMP Audit Report supplements for annexes 1 to 6 to (as required), within ten (10) working days of audit completion.

The auditor must complete and forward a Notification of Completed Audit form to the APVMA **within three working days of completion of the audit**. Where Critical non-conformances have been identified, this form must be submitted to the APVMA within 24 hours of the audit. If additional comments are warranted, they can be provided as a covering letter. The form should be uploaded to Objective Connect (preferred) or sent to the APVMA by email.

The auditor must provide the Licence Holder with the GMP Audit Report and any associated documents (e.g. report supplements for annexes, product audit checklists) within 10 working days (2 calendar weeks) of the last day of the audit. A copy of the GMP Audit Report and associated documents are to be submitted to the APVMA by the auditor at the same time through Objective Connect (preferred) or sent to the APVMA by email.

Auditors should note that the GMP Audit Report has four (4) sections:

- **Manufacturer and audit details**: details of the manufacturer, facility and key audit information.
- **Compliance report**: should contain sufficient detail, based on the observations made, to allow the APVMA to make an informed licensing decision.
- **Non-conformances identified**: lists Minor, Major and Critical non-conformances identified in detail and close-out requirements (desk or verification audit and due dates); estimate of audit rating from non-conformance score
    - Non-conformances must be accurately classified and clearly written in a way which would allow the Licence Holder, the APVMA and/or another auditor to identify what was non-compliant. They should also be written in a way which would allow another auditor to review and confirm the corrective actions at a subsequent audit.
    - Each non-conformance must be assigned an identifying reference number, and the relevant GMP code clause or Manufacturing Principle must be cited. The most relevant one should be referenced (maximum 3) (refer Appendix B).
    - The agreed date for submission of corrective actions / plan for desk-review and/or date for verification audit should be included in this section.
    - Section C also includes the auditor's calculation of the non-conformance score and audit rating/level. The rating or score may be subject to change once the APVMA have assessed the provided information. While the APVMA does not normally alter the NC rating provided by an auditor, the APVMA may de-aggregate distinct non-conformances when determining a non-

conformance score. Similarly, if a NC reported is not clearly expressed—or it is challenged by the Licence Holder—the APVMA may ask the auditor to provide further information to justify the score and rating assigned.

- Where there is any disagreement, the Licence Holder will need to negotiate the matter with the APVMA (see below).

- **Auditor's Summary**: auditors should comment on the Licence Holder's level of compliance with the Manufacturing Principles and GMP Code. The auditor must sign the form.

The GMP Audit Report should accurately reflect both the auditing activities undertaken and observations made as well as the compliance status of the facility. Terms such as 'assessed', 'examined', 'checked', 'read' and 'reviewed' will be interpreted as indicating a more thorough assessment of the procedures and/or records and as such the relevant documents need to be individually cited. In contrast, terms such as 'scanned', 'sighted', and 'viewed' will be interpreted as indicating a superficial assessment of the procedures and/or records and as such the documents do not need to be individually cited. Phrases such as 'sighted six raw material specifications' would be acceptable. Due to the necessity for the auditor to pursue non-conformances, the extent to which individual requirements and guidelines are investigated will be left to the auditor's discretion.

Individual requirements and guidelines not examined should be left blank or marked 'not assessed' and these areas can be followed up as a priority at the next audit. Any areas or sections of the GMP code that were not audited should be listed in Section A, question 15 of the audit report. Any GMP requirements rated as being 'Non-Compliant' in Section B should be mirrored by non-conformances (Critical, Major, Minor) in Section C. For clarity, auditors should provide reference numbers to non-compliant requirements in Section B and link them with the non-conformances in Section C.

The APVMA requires that the auditor securely retains copies of the GMP Audit Report and associated documents acquired in connection with or produced in the performance of the GMP Audit for at least seven (7) years post the audit as per document retention requirements. This will assist in the situation where later comment is sought by the APVMA.

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[redacted] How is confidential storage governed ? Consultants are sole traders- what happens if they pass away? Propose that APVMA should be holding all documents as it is not appropriate for consultants to be holding confidential company IP

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The auditor is expected to meet all obligations with respect to the terms of their agreed contract with the Licence Holder, and in accordance with the requirements of this procedure and their deed of authorisation. The Licence Holder is expected to meet all obligations with respect to the terms of the agreed contract with the auditor. This includes payment for audit services rendered and Licence Holders should note that further payments may be required for verification audits or desk reviews of corrective actions.

	Where Critical non-conformances have been identified, the Licence Holder must notify the APVMA of those **within 24 hours**. This is a condition of the licence.

Dispute resolution

If the Licence Holder does not accept one or more of the auditor's findings at the audit and is unable to reach agreement with the auditor subsequently, the Licence Holder should state their reasons / justification in Part 1 of the Response to GMP Audit Report form (or separate letter), offering alternative corrective actions or solutions and timeframes for correction (where applicable). Similarly, if the Licence Holder is not satisfied or has concerns with

the auditor's assessment of their corrective actions addressing non-conformances identified, the Licence Holder should write to the APVMA detailing their concerns and the reasons why they then consider corrective actions to be adequate.

In these and other cases of dispute, the APVMA will convene an APVMA Review Panel. This Panel will be chaired by the APVMA delegate for the issuance of licenses (the MQL Assistant Director: or the MQL Director in the A/Director's absence) and will include the Senior GMP Officer with oversight for the audit review. The Panel will discuss the matter at hand with both the manufacturer and the external authorised auditor and will make a determination that can then be taken forward in the audit review and close-out procedure.

3.3 Audit close-out

As noted above, auditors must provide the Licence Holder with the GMP Audit Report and any associated documents within 10 working days (2 calendar weeks) of the last day of the audit. Licence holders will then have an additional 15 working days (3 calendar weeks) in which to respond to this in writing and provide corrective action evidence and/or a plan for review. Including a further 15 working days (3 calendar weeks) for the auditor's assessment of this response results in an overall 8-calendar-week window for the immediate rectification of non-conformances.

- Where non-conformances can be corrected within this 8-week window between the end of the audit and the APVMA-authorised auditor's assessment of the Licence Holder's response to the audit outcomes, the audit will be closed out by the auditor. As required, this may include a verification audit (see below).
- Where the correction of non-conformances cannot be completed within this 8-week window, a Corrective and Preventive Action (CAPA) Plan will be developed by the Licence Holder. Once the auditor and the APVMA have agreed to the CAPA Plan, audit close-out will then be transitioned to the APVMA. As required, this may include a verification audit (see below).

The two pathways to audit close-out are discussed below.

Note, however, that where **Critical** non-conformances have been identified, the APVMA and the auditor will work together with the Licence Holder to develop a CAPA Plan that can be implemented immediately and, thus, will immediately address any risk to animals, humans or environment.

Audit close-out by APVMA-authorised auditor

Within 15 working days of receipt of the GMP Audit Report (which should also be within 25 working days of the audit completion), Licence Holders must sign FM_MQL05 confirming they have read and agree to the report, and with any non-conformances noted. Licence Holders must then return a copy of the GMP Audit Report to both the APVMA (mls@apvma.gov.au) and to the auditor.

If no non-conformances are identified, the Licence Holder must complete only the GMP Audit Report (FM_MQL05). Although not compulsory, the APVMA also requests that Licence Holders complete Part 2: Manufacturer's Feedback to APVMA.

If non-conformances have been identified in the GMP Audit Report, the Licence Holder must also complete, sign and return to the auditor and to the APVMA (as above) Part 1 of a Response to GMP Audit Report form, providing

a response and corrective action evidence for each and all of the non-conformances identified in the GMP Audit Report. This will include details of proposed corrective actions. If these corrective actions cannot be undertaken within the 8-week period following from completion of the audit, Licence Holders should develop a CAPA Plan. This is discussed in more detail in the following section (Audit close-out by CAPA Plan).

- If the Licence Holder does not accept some or all of the auditor's findings, they should raise these with the auditor in the first instance. If an agreement cannot be reached, the Licence Holder should then discuss their concerns with the APVMA – as discussed in Section 3.2.
- Licence Holders are encouraged to also complete **Part 2** 'Manufacturer's feedback to APVMA (online form here – please contact the APVMA if difficulty accessing this form) of the Response to GMP Audit Report form. Licence Holder should answer the questions in this section and provide comment on the auditor's conduct, preparation, and any other relevant information. This section remains confidential and will be viewed by the APVMA only. Although specific issues of concern may be discussed with the auditor, this will be at a level above the detail provide by the Licence Holder. Responses will be de-identified and de-aggregated for sharing with other internal and external stakeholders.

Once the APVMA has received the auditor's written confirmation that all corrective actions arising from the audit have been completed, an internal review of the audit will be undertaken. The APVMA will then send written advice to the Licence Holder of its decision with respect to audit closure, licensing, and notification of the due date for the next audit and the first estimate of audit duration (Section 3.1).

Once the audit is closed out, the auditor must notify the APVMA that audit materials are securely stored.

[redacted] These should be returned to APVMA, not appropriate for consultants to store confidential company information

	It is a condition of all licences that Licence Holders must sign and submit all audit reports and related documentation to the APVMA within 25 working days of the audit completion date. Failure to provide the documentation within the required timeframe may result in suspension or cancellation of the licence for breach of licence condition.

Audit close-out by CAPA Plan

Where the correction of non-conformances cannot be undertaken within the 8-week period between completion of the audit, and the auditor's review of the Licence Holder's Response to GMP Audit Report form (see above), a CAPA Plan will be developed by the Licence Holder.

For Critical and Major non-conformances, the CAPA Plan must include the following:

- An investigation of the root cause of all Critical and Major non-conformances
- The details of the corrective action(s) to address the root cause(s) of non-conformances
- The details of the preventative action(s) to address the root cause(s) of non-conformances
- The corrections to address the non-conformances
- The date by which all actions will be completed.

For Minor non-conformances that cannot be resolved within 8-weeks of the audit, the CAPA Plan must include the corrective actions to be taken and the date by which they will be completed. As relevant, and for all non-conformances, the Plan should also include a list of any documents and their reference numbers, and may include

a requirement for a verification audit. Guidance for Licence Holders on the information that should be included in the Plan is given in Appendix C.

The CAPA Plan should be discussed with the auditor, finalised, and submitted to the APVMA by the Licence Holder within the stated 8-week period. The auditor must also provide the APVMA with a signed copy of the Plan, endorsing its corrective actions and timelines. The APVMA will then review the Plan and, if acceptable, audit close-out will at this point be transitioned to the APVMA. If changes to actions or timelines are required, these will be negotiated with the Licence Holder and auditor.

Failure to submit an acceptable CAPA Plan: in the situation where the Licence Holder and auditor cannot agree to a Plan that is acceptable to both, the APVMA will form an APVMA Review Panel (Section 3.2). If a prolonged disagreement appears unavoidable, the APVMA will terminate the auditor's ongoing involvement and will take responsibility for development of the Plan. If a Plan cannot be developed to a standard that is acceptable to the APVMA within 16 calendar weeks (four months) of completion of the audit, the facility will be considered non-compliant with Regulation 61 (3A) and will be managed accordingly.

Audit close-out: once transitioned to the APVMA, the APVMA will assume responsibility for monitoring completion of the tasks within the timelines detailed in the Licence Holder's CAPA Plan. Note that Licence Holders are expected to observe these timelines unless written advice to the contrary is obtained from the APVMA. Note also that failure to complete the tasks described within the timelines stated may result in regulatory action by the APVMA. This may include, as relevant, licensing action or adjustment of the Licence Holder's audit interval (Section 4). Once the CAPA Plan has been completed to the satisfaction of the APVMA, the APVMA will review the audit and close it out. At this point, the APVMA will issue an audit outcome letter that includes, amongst other things, the due date for the next audit and the first estimate of audit duration (Section 3.1).

Verification audits

Verification audits involve an on-site inspection or visit by the auditor. The verification audit differs from routine audits in that the scope of the audit will be restricted to confirming that non-conformances identified at the previous full audit have been satisfactorily addressed.

The procedure for a verification audit will be similar to that for a full audit, except that a product-specific evaluation will not usually be required and the APVMA will not usually provide the auditor with any further information unless it is specifically requested.

Where the non-conformances are of a Critical nature, or where the Licence Holder disputes the auditor's findings, the Licence Holder is advised to use the dispute resolution process (Section 3.2).

Each time a verification audit or desk review is performed to review corrective actions or plan, the auditor must complete a Corrective Action Review form (MQL_24) noting the non-conformance number, specific evidence reviewed, and its acceptability. If further corrective action is required, the auditor should note the new due date for re-submission of evidence on the form. In most cases, the maximum period allowed should be 15 working days. The auditor will send the form to the Licence Holder and a copy to the APVMA within 15 working days of receipt of submissions for desk review.

Once all non-conformances are closed out to the auditor's satisfaction (by evidence or plan), this should be indicated on the Corrective Action Review form by ticking the 'YES' box.

In the event that a verification audit or desk-review is delayed, or submissions are not received by the due date, the auditor should advise the APVMA of the status of the arrangements for closure. The APVMA will follow-up with the Licence Holder where necessary.

4 AUDIT INTERVAL AND SCHEDULING

Audit intervals will be allocated to Licence Holders based on the scheme outlined in Table 1 below. This scheme classifies Licence Holders according to the following four audit levels:

- Audit level 1: assigned when the audit has reported no Major non-conformances and the non-conformance score is less than 7. When a manufacturing site is assigned an audit level 1, the high levels of compliance with the manufacturing standards provide a basis for allocating longer audit intervals.

- Audit level 2: assigned when an audit has reported no more than 5 Major non-conformances and their non-conformance score is between 7 and 20. This means the APVMA considers manufacturing sites with an audit level 2 rating to have a functioning quality management system, although with some identifiable weaknesses to address.

- Audit level 3: assigned when non-conformance scores total 21 to 40, with no more than 10 Major non-conformances. For manufacturers assigned an audit level 3 rating, the audit intervals will remain similar to those applied prior to 1 March 2016.

- Audit level 4: assigned when the audit reports more than 10 Major non-conformances and/or a non-conformance score greater than 40.

Extension to audit interval: Licence Holders who consistently demonstrate high levels of compliance may be given an extension on their audit interval. The consistency extension will only be granted where the facility has maintained a rating of audit level 1 for 2 or more consecutive audits.

Exception for Critical non-conformance: in situations when an audit identifies a Critical non-conformance the Licence Holder must implement immediate corrective actions, irrespective of their established audit rating or category. The schedule anticipates that other compliance and enforcement tools may be used to support auditing where appropriate.

Rescheduling audits: in exceptional circumstances, Licence Holders can formally request to reschedule an audit. Written request should be submitted to the MLS email address (mls@apvma.gov.au) more than 14 days prior to the audit due date. Requests may be based on:

- Recent major changes to management and/or staffing

- Factory fires or other unscheduled asset crises and any associated maintenance or repair activities

- Other circumstances, such as voluntary licence suspension where cessation of manufacture may mitigate many of the risks associated with the postponement of an audit.

[redacted] Define what this means?

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Table 1: Risk-based audit interval calculation

	Risk Rating			
Category	Low (< 7) Level 1	Medium (7-20) Level 2	High (21-40) Level 3	Very High (> 40) Level 4
Cat 1	30 Months	24 Months	12 Months	≤12 Months
Multiple categories	30 Months	24 Months	12 Months	≤12 Months
Cat 2	36 Months	30 Months	12 Months	≤12 Months
Cat 3, 4 and 6	36 Months	30 Months	18 Months	≤12 Months

5 APVMA AUDITS OF OVERSEAS SITES

Registrants of intermediate or finished products manufactured overseas are required to provide acceptable evidence of overseas GMP compliance to the APVMA. Conditions of registration require the registrant to ensure all sites involved in any step of manufacture—whether in Australia or overseas—maintain compliance with GMP. Registrants also need to ensure appropriate evidence of compliance is kept and submitted to the APVMA on request.

If a product applicant or registrant is unable to provide existing acceptable evidence of GMP compliance for an overseas manufacturing site used, then an audit by an APVMA-authorised auditor may be required.

For overseas audits, the majority of the audit processes and procedures described above apply, with the following differences:

- The audit may be arranged and/or paid for by the product applicant / registrant rather than the manufacturer
- The auditor may require additional notice for overseas audits, to allow for travel arrangements to be made
- The pre-audit notification and information form for overseas sites should be used (fm_mql45)
- The audit will usually focus on the products to be imported to Australia, rather than the full range of products manufactured at the site
- Additional time may be required for the audit if interpreters or translation of documents are required
- The APVMA cannot issue a licence for overseas sites; instead, the APVMA provides a letter of confirmation of GMP compliance for the site, to whoever commissioned the audit.

Information on APVMA audits of overseas sites can be found on the website.

6 SUMMARY: KEY RESPONSIBILITIES

The **Licence Holder / manufacturer** is responsible for:

- Arranging the audit well in advance of the due date advised by the APVMA.
- Sending a signed and completed Pre-audit Notification and Information form to the APVMA promptly, at least six (6) weeks ahead of the audit date.
- Reviewing the final 'GMP Audit Report' and signing the last page within 25 working days of the audit date. By signing the report, the Licence Holder is agreeing to the list and level of non-conformances observed during the audit.
- Advising the APVMA as soon as possible in the case of disagreement or dispute with the auditor's findings, or assessment of corrective actions.
- Advising the APVMA in writing, and within 24 hours of the audit completion date, of any Critical non-conformances identified and detailing root cause and proposed corrective actions.
- Completing Part 1 of the Response to GMP Audit Report form (compulsory) and Part 2 (encouraged but not mandatory) within 25 working days of the audit date and submitting both to the APVMA.
- Sending a copy of the completed Part 1 of the Response to GMP Audit Report form to the auditor within 25 working days of audit completion.
- Signing and sending the original version of the completed GMP Audit Report and all associated documents (eg report supplements for annexes, if used) to the APVMA within 25 working days of audit completion.
- Paying the auditor for the primary audit and all desk and/or verification audits required to close.

The **APVMA-authorised GMP auditor** is responsible for:

- Completing correct, current versions of all audit documents, using only standard authorised formats, as supplied by the APVMA.
- Sending a signed Confirmation of Audit Booking form to the APVMA when audits are booked.
- Conducting the audit in a thorough, professional manner in accordance with this procedure.
- Sending a Notification of Completed Audit form to the APVMA within three (3) working days (24 hours where Critical non-conformances are observed) of completion of the audit.
- Providing the Licence Holder with the original version of the completed GMP Audit Report plus all associated documents (eg report supplements for annexes, if used) within 10 working days of the audit, and providing copies to the APVMA at the same time.
- Reviewing corrective actions by either desk-review (objective evidence or plan) or verification audit and completing and submitting a Corrective Action Review form, to the Licence Holder and the APVMA, within 10 days of receipt of the evidence / plan.
- Notifying the APVMA when they are satisfied that all non-conformances have been satisfactorily addressed, by review of objective evidence or satisfactory plan.

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[redacted] Should this be final audit report?

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- Advising the APVMA if a verification audit is postponed, or corrective action submissions are not received within the agreed timeframes.
- Returning confidential Licence Holder and product information to the APVMA, or providing written confirmation to the APVMA that all information has been securely stored, once the audit is closed out.

[redacted] Propose that all confidential documents be returned to the APVMA. It is a conflict of interest to have consultants holding proprietary information

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[redacted] Propose all company information be returned to the License holder or APVMA. It is a conflict of interest for consultants to be storing proprietary information

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The **APVMA GMP officer / reviewer** is responsible for:

- Monitoring audit timeframes and initiating regulatory action as appropriate.
- Reminding Licence Holders when audits are due or overdue.
- Vetting the suitability of the auditor.
- Collating audit information in consultation with any other relevant APVMA sections, where necessary.
- Forwarding information on the Licence Holder to the auditor prior to the audit.
- Monitoring the progress of the audit and close-out processes and intervening where necessary.
- Providing confirmation of whether an audit can be closed based on an agreed plan.
- Recommending whether licences should be issued, continued, suspended or cancelled, conditions imposed / removed.
- Facilitating early resolution of disputes between the Licence Holder and auditor regarding non-conformances and/or corrective actions.
- Attending the APVMA Review Panel in the event that dispute resolution is required.
- Recommending when the next audit is due and advising the Licence Holder of that next due date upon close-out of the current audit.

The **APVMA Assistant Director / Director, MQL** is responsible for:

- Reviewing recommendations on licensing, audit duration and re-audit timeframes, as necessary.
- Chairing the APVMA Review Panel in the event that dispute resolution is required.
- Approval of closure of non-conformance by plan.

APPENDIXES

APPENDIX A – FORMS AND TEMPLATES

[redacted] Add FM_MQL39?

Table 1:

Reference No	Title
FM_MQL04	Pre-audit notification and information form——Australian sites
FM_MQL45	Pre-audit notification and information form——overseas sites
FM_MQL05	GMP Audit Report form
FM_MQL06	Notification of completed audit form
FM_MQL23	Confirmation of audit booking form
FM_MQL24	Corrective action review form
FM_MQL26	Response to GMP Audit Report form
FM_MQL27	GMP Audit Report supplement annex 1
FM_MQL28	GMP Audit Report supplement annex 2
FM_MQL29	GMP Audit Report supplement annex 3
FM_MQL30	GMP Audit Report supplement annex 4
FM_MQL31	GMP Audit Report supplement annex 5
FM_MQL32	GMP Audit Report supplement annex 6

APPENDIX B – GUIDANCE ON WRITING NON-CONFORMANCES (FOR AUDITORS)

The following guidance outlines the APVMA's expectations of auditors when reporting non-conformances from GMP audits.

Non-conformances are considered to be signs of weakness in a quality system and may be identified during APVMA audits where Licence Holders are not able to demonstrate compliance with the Manufacturing Principles and GMP Code.

The role of the auditor is to systematically and objectively collect and analyse sufficient relevant evidence to allow them to make an assessment of the Licence Holder's compliance with the APVMA's GMP requirements.

The auditor must clearly differentiate between identifying a non-conformance with the requirements of the Manufacturing Principles and/or GMP Code, and making suggestions for improvement.

Non-conformances are identified and reported during the auditing process. They are important for communicating what the problem is so that it can be corrected and should be written in a clear and concise manner, ensuring that they are not misinterpreted or ambiguous. In some cases additional details to support the non-conformance may be recorded in the body of the GMP Audit Report, eg a description of evidence viewed.

Careful attention should be given to identifying the manufacturing principle or clause of the GMP Code to which the non-conformance relates. While there may be a number of references that could be related to one non-conformance, the most relevant one should be referenced (maximum 3).

Writing up non-conformances

- **Ensure the Licence Holder understands *why* the issue is non-compliant**

What is the problem / issue?

What was observed / how was this identified? What is the objective evidence to substantiate the non-conformance?

Consider: will the Licence Holder understand what the problem / issue is that needs to be corrected?

- **Check the non-conformance—will the next auditor understand the non-conformance?**

Other auditors will be receiving a copy of the GMP Audit Report in the audit information packs provided by the APVMA.

Consider:

Does the non-conformance make sense, would you understand what was reviewed and what was non-compliant with the Manufacturing Principles / Code?

Would you understand what needs to be implemented as the corrective action?

Would you be able to check that the corrective actions have been implemented and are appropriate to address the non-conformance?

Remember, is the non-conformance clear enough to be understood by someone who was not at the audit when it was raised / identified?

- **Identify the appropriate manufacturing principle / GMP code clause(s) (maximum of 3).**

There may be a number of clauses / Manufacturing Principles that may be applicable to the non-conformances identified, however it is not necessary to list each reference, but to identify the **most relevant** one (max 3).

- if the cause of the non-conformances are related and will be closed through the provision of a single SOP i.e. if they link back to a problem with the SOP then they should be grouped as one.
- if the cause of the non-conformances are diverse and will result in different corrective actions being undertaken then they should be reported separately.

- **Identify the classification (Minor, Major or Critical and/or repeat).**

Classifications of non-conformances:

- ***MINOR non-conformance***—Minor or less serious non-conformance which is *unlikely* to pose a risk to product quality.

May be less serious but not trivial.

Depends on the type of product, and context in which the issue is identified.

If significant numbers of Minor non-conformances are identified in one system area, it could be indicative of a system breakdown and may be more appropriately classified as Major.

- ***MAJOR non-conformance***—failure to satisfy a key or mandatory requirement and/or one which ***may pose*** a risk to product quality.

Major deviation from the manufacturing principles and/or GMP Code

May consist of several Minor non-conformances, which on their own may not be Major, but together may represent a Major non-conformance—should be explained and reported as such.

- ***CRITICAL non-conformance***—a Major non-conformance which ***poses*** a risk to treated animals or users and must be corrected immediately.

Need to identify a clear link to use this classification.

Notify APVMA **immediately** (within 24 hrs)

May result in regulatory action being considered by the APVMA.

[redacted] Propose more flexibility for grouping of NCs. A single SOP is very strict and this could create large numbers of NCs. Suggest following the TGA audit reporting method where it is not unusual to group up to 10 items all under the same clause. These are listed for example as one NC (eg. NC1 with each example marked with a, b, c, etc

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[redacted] What is the definition of diverse? GMP principles/topics should be able to be grouped together. Same comment as above. TGA allow grouping of several examples even when there are different corrective actions for each example.

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Although the auditor may discuss various options for corrective action, it is the responsibility of the Licence Holder to determine the most appropriate course of action to address identified non-conformances.

APPENDIX C – GUIDANCE ON PREPARING A CAPA PLAN (FOR LICENCE HOLDERS)

The following guidance should be considered when preparing a plan for assessment.

Licence Holders will have a maximum of three opportunities to submit a satisfactory plan to the auditor for assessment. If no agreement is reached, the APVMA will take over the process to implement the plan or require submission of objective evidence, to close the audit. This may also result in the Licence Holder's audit interval schedule to be reduced.

It is therefore in the Licence Holder's best interests to provide as much detail and relevant information as possible in their plan to allow the auditor to make an effective assessment.

- The plan should include a detailed and clearly cross-referenced description of the specific corrective actions in response to each of the non-conformances identified. The plan must include.
  - an investigation of the root cause of all Critical and Major non-conformances
  - the details of the corrective action(s) to address the root cause
  - the details of the preventative action(s) to address the root cause
  - the corrections to address the non-conformances
  - the date all actions will be complete
- The APVMA expects that where documents are to be amended, a detailed description of the change to be made, the names of the documents affected and their document reference and revision numbers should be recorded (preferably using a change control process). The description of the change should advise which point / clause / section is to be amended for example:

  "…point 1 will be amended to include a reference to the positions which may undertake this role, specifically the Quality Assurance Manager and their delegate, being the Quality Assurance team leader for powder products".

- An indication of **proposed dates** associated with completion of drafts, review of documents and publishing of final documents should also be included.
- Details of when training will be undertaken and what the training will include should be provided along with the people to be included within the training (position titles).
- If validation activities are to be undertaken then a detailed description of what the validation will cover (ie validation protocol) and the timeframes to be met should be provided.
- If building works are to be undertaken then a description of the key events and target completion dates should be included.
- There may also be situations where a risk assessment should be undertaken in order to support the proposed activities.

[redacted] Do corrective & preventative actions need to be identified separately? What if they are the same, i.e. the corrective action also functions as the preventative action in some cases.

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[redacted] Note that the current APVMA CAPA form does not include preventative actions

RESPONSE to GMP AUD	
Non-Conformance Number *(from Section C of Audit Report)*	Manufacturer's response including proposed CORRECTIVE A *Please provide details on what specific a to address each non-conformances, inc of the root cause.*

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APPENDIX D – GUIDANCE ON ASSESSING CAPA PLANS (FOR AUDITORS)

The following guidance outlines the APVMA's expectations of auditors when undertaking an assessment of and approving a 'plan' for the closure of non-conformances for Licence Holders.

Expectations:

- Auditors should use the **Corrective Action Review (CAR) form** to record their assessment and a copy of final version of the plan provided by the Licence Holder should be attached.
  The documents should be sent to the APVMA within eight weeks of the audit being completed.
- Auditors should assess and confirm that the Licence Holder has identified the 'root cause' where applicable.
- Auditors should ensure that timeframes have been stipulated, are reasonable and practical.
- Auditors should confirm that there is sufficient detail provided to allow the next auditor to understand what was agreed to for the closure. Think about how you would interpret the response and what you would expect to see if you were provided with only the CAR form for the plan three years after the last audit—would you be able to understand what has been assessed and accepted? Will it result in the NC being closed?
- A clear description of **what** has been agreed to should be included in the CAR form to allow the APVMA and the next auditor to clearly identify what you have considered and why the response is accepted.
- If the auditor is not satisfied that an acceptable plan has been provided after three attempts by the Licence Holder (within the stated allowable timeframe), this should be noted accordingly on the CAR form.
- Please note ambiguous information or comments included within CAR reports must be avoided.