Australian Government

Australian Pesticides and Veterinary Medicines Authority

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Good Manufacturing Practice (GMP) Audit procedure

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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 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 (MPs) and the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products, 2007 (and relevant annexes—Code of GMP). 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 manufacturers when selecting an auditor and when responding to and forwarding the audit report to the APVMA.

The procedure should also be followed for audits of **overseas manufacturing sites** by APVMA-authorised GMP auditors, however some differences in processes, forms, etc may apply. These differences are summarised in Section 6. For a list of all forms and templates, refer to Appendix A (page 18).

1 GENERAL PRINCIPLES

Manufacturers are required under a condition of their licence to engage, at the request of the APVMA, an APVMA-authorised GMP auditor to inspect the premises, equipment, processes and facilities that will be used in any step in the manufacturing process in the manufacture of veterinary chemical products, and to forward a signed copy of that authorised person's inspection report to the APVMA.

An APVMA audit may be also required for an overseas site if other acceptable evidence is not available for the purposes of APVMA product registration—see Section 6.

The main objectives of an audit are to determine the extent of a manufacturer's compliance with APVMA requirements, to ensure products are consistently manufactured to required safety and quality standards, and to identify areas where the quality system needs to be improved.

The role of the auditor is to systematically and objectively collect and analyse sufficient relevant evidence to allow him/her to make an assessment of the manufacturer's compliance with the APVMA's GMP requirements.

The auditor must clearly differentiate between identifying non-conformance with the requirements of the Manufacturing Principles (MPs) and/or Code of GMP, and making suggestions for improvement. Although the auditor may discuss various options for corrective action, it is the responsibility of the manufacturer to determine the most appropriate course of action to address identified non-conformances.

For new applicants for a licence, the APVMA will advise of audit requirements upon acceptance of the licence application.

For existing licence holders, the APVMA will notify the manufacturer of the date of the next audit, once the current audit is closed out. Failure to meet this deadline may result in the APVMA issuing a notice of proposal to suspend or cancel the licence. Manufacturers may bring an audit forward, if they wish, to suit operational requirements.

From time to time, manufacturers may also request or be required to have a 'partial' audit of specific aspects of manufacture for reasons such as extension of scope of their APVMA licence. Such audits should be arranged within the required timeframe by the manufacturer and should follow the same procedure as outlined below.

In accordance with the terms of their accreditation deed, auditors may not, without the prior permission of the APVMA, audit any manufacturing facility associated with any company or other organisation with which the auditor was employed or in which they have a financial interest, or to which the auditor provided consultancy services within three (3) years prior to the GMP audit. A declaration to that effect must be signed by auditors upon accepting audits, on the 'Confirmation of audit booking form'.

It is also APVMA policy that an auditor may not conduct any more than two consecutive full audits of a particular manufacturing facility without the prior permission of the APVMA.

Under normal circumstances, manufacturers may select their own auditor from the current list of APVMA-authorised GMP auditors. However, the APVMA reserves the right to participate in the audit or reject the manufacturer's choice of auditor and nominate an auditor of its choice if considered appropriate (eg if the conditions above have not been met).

The manufacturer is responsible for meeting the costs of the audits and any follow-up work required to assess corrective actions (eg verification audits or desk-reviews). The APVMA is not involved in or responsible for setting or collecting these fees or payments.

Audits of new facilities (or new areas) should only be arranged once installation of equipment is completed and the facility/area is ready to commence manufacture (ie ‘audit-ready’). Audits conducted too early in the licensing process may result in lengthy audit closure times.

2 BEFORE THE AUDIT

At least four weeks prior to the audit due date, the manufacturer is required to 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 (preferred), faxed or mailed to the APVMA. Sufficient time should be allowed for the audit, taking into account the size and nature of operations involved. If the audit will include review of corrective actions from the previous audit, additional time should be allocated. The above documents are available on the APVMA website.

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 GMP officer or reviewer will contact the manufacturer to remind them that an audit is due to ensure the audit schedule is maintained. Failure to arrange an audit 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 manufacturer. The 'Auditor's declaration' at the foot of the document, confirming the auditor has no 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.

If required, the auditor may contact the APVMA for guidance on the expected audit duration for that manufacturer.

The APVMA may reject the manufacturer'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 manufacturer 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 under the circumstances, for whatever reason, another auditor is more appropriate.

In most cases, the APVMA GMP reviewer will liaise with the manufacturer and the auditor and request the manufacturer 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.

Prior to the audit, the APVMA GMP reviewer may send to the auditor, through an authorised delegate:

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

The auditor should normally prepare an audit plan with a proposed timetable, which should be provided to and discussed with the manufacturer 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.

The auditor may arrange a pre-audit visit to meet key staff, familiarise themselves with the premises in order to be satisfied that sufficient time has been allocated in the audit plan. Such a visit must not involve advice that can be interpreted or potentially perceived as ‘consulting’ per se.

In certain circumstances, APVMA staff may participate in the audit (joint audit) or attend the audit as an observer for training and/or auditing quality assurance purposes (observed audit). In such cases the APVMA GMP Reviewer will notify both the auditor and the manufacturer well in advance of the audit, and clearly explain the role of APVMA staff. Such attendance by the APVMA is at no cost to the manufacturer.

For audits of **overseas sites**, please also refer to Section 6.

3 AUDIT PROCEDURE

The procedure on the day of audit is always at the auditor's discretion, but should be consistent with AS/NZS ISO 19011:2003 Guidelines for Quality and/or Environmental Management Systems Auditing or subsequent revisions. Key elements should include:

- an initial meeting with the manufacturer 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 plant and procedures
- confirmation of the scope of manufacture to be inspected (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 required corrective actions
- inspection of the facilities, procedures, records, etc
- confirmation with the manufacturer 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 manufacturer and staff to discuss the outcome of the audit. As part of that discussion, the auditor must identify the critical and major non-conformances observed and discuss with the manufacturer various options, priorities and appropriate timelines for corrective action. Minor non-conformances should also be highlighted to the manufacturer. The auditor is encouraged to provide positive feedback regarding compliance as well as identifying any non-conformances.

If a verification audit or desk review is required to check corrective actions for non-conformances identified, a date for that audit/review should be agreed between the auditor and manufacturer at the exit interview. The possibility of closing corrective actions on the basis of a detailed plan (rather than submission of objective evidence) may also be discussed (if applicable). Please refer to the APVMA's website for information on audit ratings and scores.

The outcome of the audit and exit interview should be reported clearly, conclusively and within 10 working days of the last day of the audit, using the GMP audit report form.

For audits of **overseas sites**, please also refer to Section 6.

4 POST AUDIT PROCEDURE

4.1 For the auditor

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:

- Notification of completed audit report form (FM_MQL06)
- GMP audit report (FM_MQL05)
- GMP audit report supplements for annexes 1 to 6 to (as required)

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 emailed (preferred), faxed or mailed.

The auditor must provide the manufacturer with the 'GMP Audit Report' and any associated documents (eg report supplements for annexes, product audit checklists) **within 10 working days 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 (email preferred).

Auditors should note that the GMP audit report has four (4) sections:

- **Section A** – Manufacturer and audit details: details of the manufacturer, facility and key audit information.
- **Section B** – Compliance report: should contain sufficient detail, based on the observations made, to allow the APVMA delegate to make an informed licensing decision.
- **Section C** – Non-conformances (NCs) identified: lists minor, major and critical deficiencies 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 manufacturer, 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 MP must be cited. (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/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 we 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

manufacturer—the APVMA may ask the auditor to provide further information to justify the score and rating assigned.

- Where there is any disagreement, the manufacturer will need to negotiate the matter with the APVMA (refer Section 7).

- **Section D** – Auditor's Summary: auditors should comment on the manufacturer's level of compliance with the MPs and Code of GMP. The auditor must sign Section D.

The 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 and these areas can be followed up as a priority at the next audit. Any GMP requirements rated as being 'Non-Compliant' in Section B should be mirrored by non-conformances (critical, major, minor) in Section C.

The auditor should securely retain copies of the GMP audit report and associated documents until review of the audit report has been finalised by the APVMA, in case follow-up comment is sought by the APVMA.

The auditor is expected to meet all obligations with respect to the terms of their agreed contract with the manufacturer, and in accordance with the requirements of this procedure and their deed of authorisation.

4.2 For the manufacturer

The manufacturer should review the audit report and sign Section D confirming they have read the report.

> Where ***critical*** non-conformances have been identified, the manufacturer must notify the APVMA of those **within 3 working days of the audit**. This is a condition of licence.

If non-conformances are identified in the audit report, the manufacturer must also complete and sign Part 1 of a 'Response to GMP audit report' form (Manufacturer's response to audit report), providing a response to each and all of the non-conformances identified in Section C of the audit report, including details of proposed corrective actions and/or detailed plan (if eligible).

Where a desk review of corrective actions is appropriate (as indicated in Section C of the report), the manufacturer should indicate whether they intend to address the non-conformances by submission of:

a) objective evidence of corrective actions for review by auditor

b) detailed plan (if eligible)

c) combination of detailed plan and objective evidence of corrective actions completed (if eligible).

If no non-conformances are identified, the APVMA requests that the manufacturer complete and return **Part 2** of Response to GMP audit report form—'Manufacturer's feedback to the APVMA'—see below. The form is available on the APVMA's website.

If the manufacturer does not accept any or all of the auditor's findings they should raise these with the auditor in the first instance. If agreement cannot be reached, the manufacturer should discuss their concerns with the APVMA—refer Section 7.

The manufacturer is also requested to complete Part 2 of the 'Response to GMP audit report' form (Manufacturer's feedback to APVMA). Manufacturers are requested to 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 APVMA staff only. Specific issues of concern may be discussed with the auditor however, in most instances only trends or percentages will be reported. This information is utilised for the quality assurance of APVMA's auditing program.

The signed GMP audit report, associated documents, and Response to GMP audit report form must be sent the APVMA **within 25 working days of the audit**. A copy of Part 1 of the Response to GMP audit report form must be sent to the auditor along with evidence of corrective actions/or plan, as agreed. Manufacturers should note that where an auditor requests a verification (on-site) audit, the manufacturer has the option of having the documentary corrective actions assessed during the verification audit. It should also be stressed that changes to SOPs and documents may also require a verification audit, especially where they relate to fundamental and critical practices.

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

The manufacturer 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 manufacturers should note that further payments may be required for verification audits or desk reviews of corrective actions.

For audits of **overseas sites**, please also refer to Section 6.

5 ASSESSMENT OF CORRECTIVE ACTIONS AND CLOSING OUT OF THE AUDIT

Where appropriate, auditors should assess correction of non-conformances either by reviewing submitted documentation and/or detailed corrective action plan (desk review), or by conducting an on-site verification audit where the type, number and extent of corrective actions warrants one. It is the APVMA's expectation that all non-conformances will be addressed and closed out within eight weeks of the audit. If a closure plan is approved, then the APVMA expects that all NCs will be addressed within six months,
in accordance with that agreed plan.

5.1 Desk reviews—objective evidence

- Desk reviews involve the assessment of documentary or other objective evidence, to address the non-conformances identified during audit. Such evidence is to be provided to the auditor within the agreed timeframe. Claims by the manufacturer of action undertaken should not be accepted by the auditor in the absence of actual documentary or other appropriate evidence.

5.2 Desk reviews—detailed plan of corrective actions (eligible manufacturers only)

- If the **manufacturer** is eligible and opts to address non-conformances by plan, they will be required to indicate this on their Manufacturer's response to GMP audit form, and then submit a detailed plan to the auditor and a copy to the APVMA which will include timeframes for addressing the NCs, particularly for more serious NCs that may impact on product quality. The plan should also include a detailed description of the changes to be made, list any documents and their reference numbers to be amended. The plan should be completed and provided to the auditor and APVMA within 25 workings days of the last day of the audit.
- It is expected that under most circumstances (where closure by plan has been approved) all NCs will need to be addressed within six months, unless granted written approval from the APVMA for further extension (in cases of construction, facility renovation or major equipment purchase). Where the corrective actions include risk assessment or validation, the plan needs to include an outline of parameters to be considered.
- Guidance for manufacturers on the information that should be included in the plan is in Appendix C.
- **The auditor** will be required to assess the plan and confirm whether it contains the required information. The auditor may liaise with the manufacturer where the original plan does not contain sufficient information to allow them to be satisfied that all corrective actions will be implemented successfully and the non-conformance addressed. The auditor will need to provide a copy of the final plan with his/her endorsement to the APVMA for approval.
- Guidance for auditors on the assessment of corrective action plans is at Appendix D.
- **The APVMA** will consider both the audit report and auditor-endorsed corrective action plan or corrective action assessment as part of the audit review and closure process.
- If the plan that has been assessed by the auditor is **not** approved by the APVMA (due to the information contained being either unclear or insufficient for another auditor to know what corrective actions have been implemented) the manufacturer will be allowed to lodge up to two more submissions—with three weeks

allowed for each—in order to provide any unclear or missing information. If an acceptable plan has not been provided to the APVMA after three attempts, or within four months of the audit, the facility will be considered non-compliant with Regulation 61 (3A) and managed accordingly.

5.3 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 is usually 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 specific product audit 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 manufacturer disputes the auditor's findings, the APVMA GMP reviewer will advise both the manufacturer and the auditor of what action is required within a specified timeframe.

Each time a verification audit or desk review is performed to review corrective actions or plan, the auditor is required to complete a 'Corrective action review' 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 10 working days. The auditor will send the form to the manufacturer and a copy to the APVMA within
10 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' 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 manufacturer where necessary.

The auditor is required to return the pre-audit information to the APVMA once the audit is closed out or provide written confirmation to the APVMA that the information has been securely stored or destroyed.

The APVMA GMP reviewer will monitor progress in closing out the audit to ensure that the task is completed within required timeframes. It is a condition of all licences that manufacturers must address all non-conformances within the timeframes agreed or specified by the APVMA. Failure to address non-conformances in a timely manner may result in suspension or cancellation of the licence for breach of licence condition.

5.4 APVMA review and closure

Once the APVMA has received the auditor's written confirmation that all corrective actions arising from the audit have been completed (or a satisfactory plan has been approved), and has completed its review, the APVMA will send written advice to the manufacturer of its decision with respect to audit closure and licensing and notification of the due date for the next audit.

If the APVMA has accepted closure of the audit by plan (for eligible manufacturers) within six months of the audit, the licence holder or authorised person is required to notify the APVMA in writing (statutory declaration), confirming that that all of the NCs identified have been duly addressed in accordance with the approved plan. If a statutory declaration is not received by the due date, the manufacturer may be considered non-compliant.

All corrective actions will be formally reviewed at the next audit. If found to have not been completed according to the plan and statutory declaration, the APVMA may consider the manufacturer non-compliant.

Information on how the APVMA closes audits and assigns audit intervals is on the APVMA's website.

6 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, we provide 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.

7 DISPUTE RESOLUTUION

If the manufacturer does not accept any or all of the auditor's findings at the audit, and has been unable to reach agreement with the auditor, the manufacturer should state their reasons/justifications 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). In such instances, the APVMA will arbitrate, however submissions should be forwarded to the APVMA as soon as possible after the audit report is received by the manufacturer.

Similarly, if the manufacturer is not satisfied or has concerns with the auditor's assessment of their corrective actions addressing non-conformances identified, the manufacturer should write to the APVMA detailing their concerns and the reasons why they then consider corrective actions to be adequate.

In each case, the APVMA will consider the issues, which may include discussions with the manufacturer and/or the auditor, then advise the manufacturer and the auditor of its decision.

8 RESPONSIBILITIES

8.1 The manufacturer is responsible for:

- arranging the audit by the due date advised by the APVMA, well in advance of the due date
- sending a signed and completed 'Pre-audit notification and information form" to the APVMA promptly
- reviewing the final 'GMP audit report' and signing the last page
- advising the APVMA as soon as possible in the case of disagreement or disputes with the auditor's findings, or assessment of corrective actions
- advising the APVMA in writing within three days of the audit date, of any critical non-conformances identified and detailing proposed corrective actions
- completing Part 1 of the 'Response to GMP audit report form' (mandatory) and completing Part 2: 'Manufacturer's feedback to APVMA' (encouraged but not mandatory)
- signing and sending the original version of the completed 'GMP audit report form' and all associated documents (eg report supplements for annexes, if used) to the APVMA within 25 working days of the audit
- sending a copy of the completed Part 1 of the 'Response to GMP audit report form' to the auditor within 25 working days of the audit
- arranging with the auditor to close out the audit within eight weeks of the audit (including submitting corrective actions/plan to the auditor or undergoing a verification audit within agreed timeframes)
- paying the auditor for the primary audit and all desk and/or and verification audits required to close
- submitting a statutory declaration to the APVMA within six months of the audit (if closing the audit on the basis of an approved plan) confirming that all corrective actions have been implemented in accordance with the approved plan.

8.2 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' form to the APVMA within three working days (24 hours where critical non-conformances are observed) of completion of the audit
- providing the manufacturer with the original version of the completed 'GMP audit report' form 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 or verification audit and completing and submitting a 'Corrective action review' form, to the manufacturer and the APVMA, within 10 days of receipt of the evidence/plan

- notifying the APVMA when they are satisfied that all NCs have been satisfactorily addressed, by review of objective evidence or satisfactory plan (eligible manufacturers).
- advising the APVMA if a verification audit is postponed or corrective action submissions are not received within the agreed timeframes
- returning confidential manufacturer and product information to the APVMA, or providing written confirmation to the APVMA that all information has been securely stored or destroyed, once the audit is closed out.

8.3 The APVMA GMP officer/reviewer is responsible for:

- Monitoring audit timeframes and initiating regulatory action as appropriate
- Reminding manufacturers 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 manufacturer 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
- Resolving disputes between the manufacturer and auditor regarding non-conformances and/or corrective actions
- Recommending when the next audit is due and advising the manufacturer of that next due date upon close-out of the current audit

8.4 The APVMA Director, MQL is responsible for:

- Reviewing recommendations on licensing and re-audit timeframes, as necessary
- Resolution of disputes in some cases.

APPENDIXES

APPENDIX A – FORMS AND TEMPLATES

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 manufacturers are not able to demonstrate compliance with the Manufacturing Principles and Code of GMP.

> The role of the auditor is to systematically and objectively collect and analyse sufficient relevant evidence to allow him/her to make an assessment of the manufacturer's compliance with the APVMA's GMP requirements.
>
> The auditor must clearly differentiate between identifying non-conformance with the requirements of the MPs and/or Code of GMP, 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 audit report, eg a description of evidence viewed.

Careful attention should be given to identifying the manufacturing principle or clause of the code of GMP 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 manufacturer 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 NC?

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

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

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

  Consider:

  Does the NC make sense, would you understand what was reviewed and what was non-complaint with the MPs/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 NC?

Remember, is the NC 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/MPs that may be applicable to the NCs identified, however it is not necessary to list each reference, but to identify the most relevant one (max 3).

  - if the cause of the NCs 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 NCs are diverse and will result in different corrective actions being undertaken then they should be reported separately.

- **Identify the classification (minor/major/critical).**

Classifications of NCs:

- ***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 NCs 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 Code of GMP

  May consist of several minor NCs, which on their own may not be major, but together may represent a major NC—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

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

APPENDIX C – GUIDANCE ON PREPARING A PLAN FOR CORRECTIVE ACTIONS (FOR MANUFACTURERS)

If a manufacturer is eligible to close non-conformances from an audit on the basis of a plan, the following guidance should be considered when preparing a plan for assessment.

Manufacturers will have a maximum of three opportunities to submit a satisfactory plan to the auditor for assessment, before the APVMA will reject the plan and require submission of objective evidence to the auditor for assessment, to close the audit.

It is therefore in the manufacturer'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. Corrective actions should identify and address the root cause of the NC, where applicable.
- 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. 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 matrix needs to be prepared in order to support the activities to be undertaken. An indication of when the risk matrix will be finalised and the aspects to be considered in its preparations should be submitted.

APPENDIX D – GUIDANCE ON ASSESSING PLANS FOR CORRECTIVE ACTIONS (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 eligible manufacturers (audit level rating of 1 or 2 only).

The current requirements for closure based on objective evidence and the reporting of this will remain in place for all manufacturers identified as receiving an audit level rating of 3 or 4 or where the APVMA has determined that the audit may only be closed upon provision of objective evidence. Audit level 1 and 2 manufacturers will also have the option to request that the objective evidence be reviewed by the auditor to allow the closure of the non-conformances.

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 manufacturer 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 manufacturer 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 manufacturer (within the stated allowable timeframe), this should be noted accordingly on the CAR form.
- Please note ambiguous information or comments included within CAR reports may result in the APVMA requiring the closure of non-conformances based on objective evidence.