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Discussion paper: Managing release for supply of contract manufactured veterinary medicines

Manufacturing Quality and Licensing

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EXECUTIVE SUMMARY

The APVMA would like to hear your views on alternative approaches to undertaking the step of '*release for supply'* for contract (or toll) manufacturing arrangements. The issue is also relevant to products manufactured at different geographic sites, controlled by the same company, such as a large multinational corporation.

This discussion paper presents a proposal, where the manufacture of veterinary chemical products occurs in stages at different manufacturing sites, the authorised person at each site would be responsible for releasing the intermediate or bulk product for the next step in the manufacturing process. Each release would include a declaration of compliance consistent with clause 547 of the *Australian Code of Good Manufacturing Practice for Veterinary Chemical Products* (Code of GMP). The declaration of compliance would address the same quality checks as would normally occur with '*release for supply'*, but limited to the manufacturing steps undertaken.

The potential benefits of a streamlined and integrated process include:

- a reduction in the administrative cost of copying and moving batch records from one site to another,
- more effective product quality reviews based on information supplied by the registrant and
- greater transparency for ease of auditing.

1 BACKGROUND

Veterinary chemical products are subject to a registration process that requires them to be fit for their intended use and to not place treated animals or users at risk due to inadequate safety, quality or efficacy. Veterinary chemical products must also be manufactured in such a way that they comply with their registered particulars and that there is batch-to-batch consistency. In order to achieve these objectives, the manufacturer must have in place a comprehensively designed, adequately resourced and correctly implemented system of quality assurance, incorporating the principles of good manufacturing practice (GMP).

The *Agricultural and Veterinary Chemicals Code Act 1994* provides for the licensing of the manufacturers of veterinary medicines by the APVMA, where the manufacturer complies with the APVMA's Manufacturing Principles and the Code of GMP. Australian manufacturers of veterinary medicines must be licensed by the APVMA to perform the relevant steps of manufacture for nominated categories of product, while overseas manufacturers must provide acceptable evidence of GMP compliance that is recognised by the APVMA.

'*Release for supply*' is a '*step of manufacture*' that involves a comprehensive review of batch and related records to ensure that all the necessary procedures have been followed, all equipment calibrated, and all raw materials (including packaging), intermediate and finished product complies with specifications. '*Release for supply'* is an important quality check that helps ensure the quality, safety and efficacy of the finished product being supplied into the market. '*Release for supply'* is not the same as the release from manufacture (or partial release), where bulk material or unfinished product is authorized to go from one stage in the process to the next. A manufacturer performing '*release for supply'* in Australia must hold an APVMA GMP licence to perform this step of manufacture for the relevant product category.

The requirements for '*release for supply'* are occasionally misunderstood by registrants and manufacturers, particularly when this step is performed by a contract manufacturer who may or may not be involved in the actual production of the product batch.

To provide clarification on the term '*release for supply*' and its requirements, the APVMA proposes guidance that describes alternative approaches for performing release for supply of veterinary chemical products where parts of the manufacturing process are undertaken at different sites, often as part of a sub-contracting arrangement.

This discussion paper focuses on situations where products manufactured—in part or whole—by one manufacturer are released for supply by another. It is also intended to cover situations where products are manufactured and released by a licensed manufacturer, other than the registrant.

2 RELEASE FOR SUPPLY

2.1 Current Requirements

When '*release for supply'* is performed, the authorised person is responsible for the quality of the finished product batch being released. It is essential that a *GMP Agreement* between the contract giver and contract accepter is in place and clearly stipulates which party is responsible and accountable for specified activities, taking into account possible consequences of such responsibilities. The agreement should also detail the type of documents required to ensure that the person conducting '*release for supply'* has access to all of the required documentation.

It is an offence under section 84 of the *Agricultural and Veterinary Chemicals Code Act 1994* for registrants or manufacturers to supply chemical products where the constituents differ by more than the prescribed extent from the particulars contained in the APVMA's Register. Similar offences apply to breaches of the conditions of registration (s 79) or the supply of registered product with an unapproved label (s 81). The '*release for supply*' arrangement does not negate the registrant's (contract giver's) responsibility for (Code of GMP 909(c) and 918):

a) inspecting the contract manufacturer (e.g. supplier's audits),

b) ensuring that the finished product had been manufactured correctly and complies with their registered particulars and specifications, and

c) ensuring that they have been released appropriately by a competent authorised person.

Under the Code of GMP (c547) 'Batch records should show the name of the person responsible for releasing the product for supply and confirm by way of a person's signature that:

a) all manufacturing documents have been reviewed

b) all entries are complete

c) there are no unexplained or unresolved deviations

d) the product meets all specifications

e) a final packed item has been visually examined.'

Where the manufacturing process is undertaken at different manufacturing sites, the procedures in place should ensure that the finished product has been made correctly and meets all the required quality tests before it is released for supply or sale. Any declarations of compliance for the release of 'intermediate' or 'bulk' products by third-party contractors or subsidiaries of multinational companies should still be consistent with Code of GMP clause 547, especially when a comprehensive review of all relevant documents is not undertaken as part of the final release step. The level of detail should also be consistent with the GMP Agreement and other relevant documents.

The arrangements for contract manufacture must not compromise the quality of the finished product. GMP agreements must be in place and must stipulate responsibilities and accountability of each party involved.

Sub-contractors must undertake the various steps of manufacture in compliance with the GMP Agreement, GMP code, written procedures and the relevant product related information.

2.2 The Need for Change

In cases where all the steps of manufacture are conducted on a single site operated by the registrant, '*release for supply'* is relatively straight forward. The person conducting *'release for supply'* has ready access to all the relevant particulars in the application for product registration as well as all of the batch manufacturing and supportive quality assurance records (including equipment and process validation). Under these circumstances it is considered that current practices should continue.

Applicants for product registration, frequently nominate multiple manufacturing sites in order to:

- access manufacturing capabilities not available at a single site
- ensure supply chain flexibility and reliability, and
- maintain competitive pricing between service providers.

For these and other reasons, nominated sites may represent duplication in manufacturing capability or different stages (or steps) in a sequential manufacturing process (eg blending, packaging and labelling, QC testing and analysis and/or release for supply) or a combination of these.

As the manufacturing arrangements become more complex, *'release for supply'* becomes more difficult to conduct. Challenges include access to the relevant registration particulars, the logistics of transferring batch and other records between different sites (particularly when these sites may be in different global regions) and gaps in technical expertise between different sites. As an example of the latter, staff in a specialist packaging facility may not have the technical expertise to assess batch records related to the production of bulk antigen produced using fermentation technology. It could be argued that the review of the compliance of each stage may best be done by personnel familiar with the specific manufacturing facility.

Over the course of a product's life, registration details themselves can become further complicated by progressive variations to formulation, process, packaging materials, label, shelf-life and/or sites of manufacture. As a consequence, it may be more effective for some registrants to provide sub-contractors with a consolidated summary of 'product-related information' relevant to the steps of manufacture being undertaken, rather than copies of numerous applications and approvals. If such product-related information was dated it would be easier for both corporate technical personnel and APVMA auditors to be satisfied that the information within the documents before them is current. The difficulty in supplying copies of applications is that it can be difficult to know whether any other variations to registration have occurred since the document was provided.

3 PROPOSED GUIDANCE FOR CONDUCTING RELEASE FOR SUPPLY

3.1 Responsibilities of the Registrants and Manufacturers

Under this proposal, registrants may provide each sub-contractor with a dated outline of the process being undertaken, as well as all relevant product-related information. This information must be consistent with the application for product registration submitted to and approved by the APVMA.

The manufacturer/person conducting '*release for supply'* should be provided with a dated overall product statement, an outline of the sub-contracting arrangements and all necessary product-related information. Generally the registrant or manufacturer may provide the product-related information, but confidentiality restrictions may result in alternative arrangements being made. If all the necessary information cannot be provided to the person responsible for release from manufacture, a certificate of compliance should not be issued.

The product-related information, where appropriate, may include approved label, raw material and product specifications, formulation, packaging specifications, manufacturing process control parameters, test methods, equipment and process validation in process control testing, and finished product testing.

Where the manufacture of veterinary products occurs in stages at different manufacturing sites, the authorised person at each site is responsible for releasing the bulk or intermediate for the next step of manufacture. Each release should include a declaration of compliance that is consistent with the Code of GMP 547 and addresses relevant product related information, codes and standards that apply to that part of the process. In other words, this step of '*release from manufacture'* should include the same quality checks as would occur with '*release for supply'*, within the scope of the manufacturing steps undertaken.

The authorised person responsible for providing declarations of compliance must be able to demonstrate that they have all the relevant information and technical capability necessary to perform this review step.

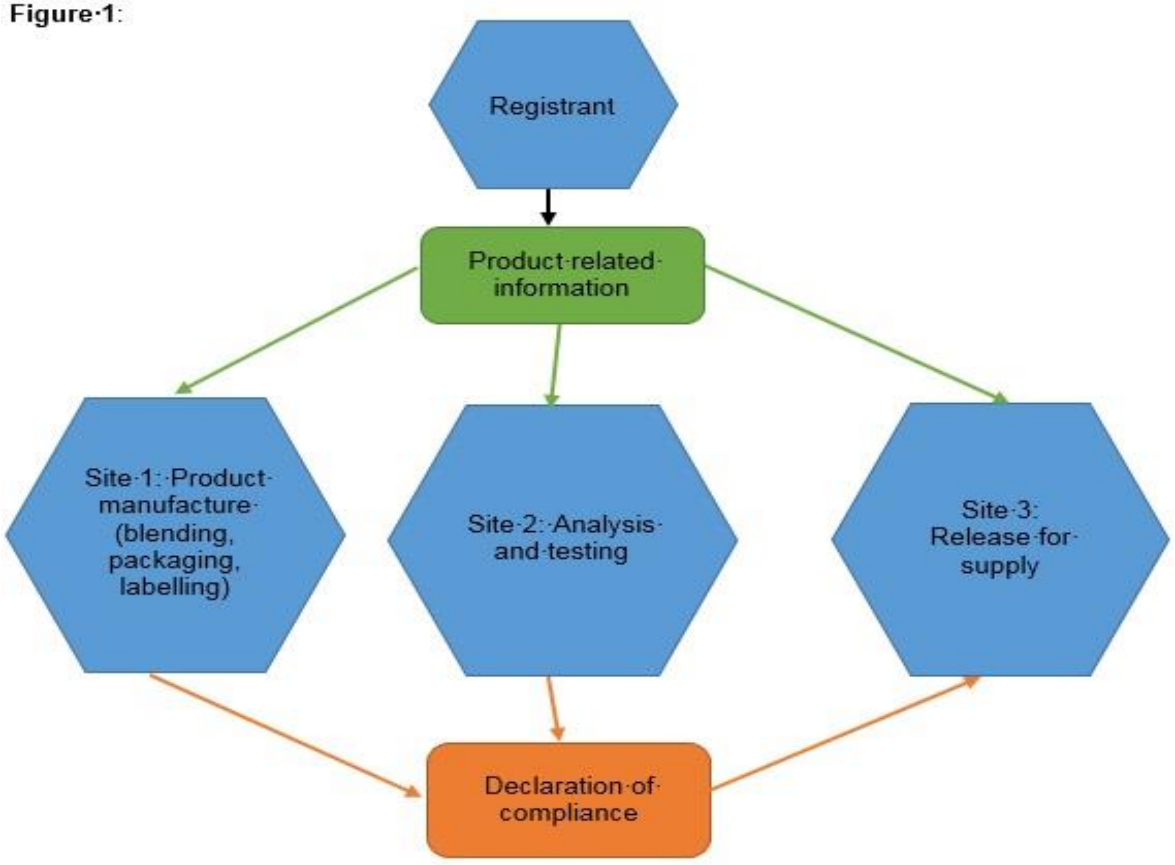
Each Australian manufacturer must be licensed by the APVMA to perform the relevant steps of manufacture for the product involved, or in the case of an overseas manufacturer, hold current GMP compliance recognition by the APVMA to perform the relevant steps of manufacture of the relevant product. Any manufacturer, engaged in the release of finished product must be licensed by the APVMA to perform '*release for supply'* in accordance with their manufacturing licence. Consideration will be given to adding '*release from manufacture'* to the scope of licences not already licensed for '*release for supply'*.

3.2 Performing Release for Supply

Under the proposal, manufacturers will have the option of releasing veterinary medicines on the basis of declarations of compliance against the product-related information, or through a comprehensive review of batch and related records against copies of the relevant product registration documents. Where it is impractical for the contractor conducting the (final) '*release for supply'* to review all of the relevant manufacturing and quality control documents in accordance with the requirements, it is anticipated that they would review declarations of compliance for each of the contracted stages of manufacture. The person

authorised to perform '*release for supply'* must check the declarations of compliance against the overall product statements (see Figure 1). Products could be released under a combination of both processes. For example, the '*release for supply'* of a finished product may take into account a declaration of compliance for the imported bulk chemical as well as a review batch and other records for the packaging and labelling activities undertaken at the site performing release for supply.

Figure 1:



The person conducting '*release for supply'* can only rely on decisions by other sub-contractor authorised person/s to release intermediate, or bulk, or finished product if the following conditions are met:

- All partial manufacturers in the manufacturing chain are covered by valid GMP agreements which comply with the APVMA's Manufacturing Principles and GMP Code (refer to the APVMA GMP Code Chapter 9 and also to PIC/S Guide to GMP). These agreements should specify the release to the next manufacturer or '*release for supply'.*
- Authorised persons at each site of manufacture are provided with full access to all parts of the relevant particulars of the product for the steps of manufacture performed at the site.
- All manufacturers have a document which outlines details regarding the release process for the relevant manufacture performed.
- All decisions to release to the next step of manufacture or '*release for supply'* are documented in accordance with GMP requirements.

- The authorised person performing '*release for supply'* of the finished product batch has accepted the quality management system used for partial release or release to the next step of manufacture, e.g. through a supplier audit.

The authorised person performing '*release for supply'* is ultimately responsible to ensure that the above conditions are met when relying on other party's compliance declaration and release decisions.

The supporting GMP Agreement should clearly define the responsibility of the parties for release. The Agreement should also stipulate the responsibility of the provider of bulk or intermediate or unfinished product to notify the recipients of any significant process deviations, change controls, out of specification results, non-conformances, investigations, complaints or other matters which should be taken into account by the person who is responsible for '*release for supply'* of the finished product batch. Responsibility for recall and recall management should also be stated in the GMP agreement.

COMPARISON OF CURRENT AND PROPOSED APPROACHES		
Current	**Proposed**	**Benefit**
Guidance is limited to contract giver (registrant) providing 'all the information necessary to carry out the contracted operations' (Code of GMP clause 908).	Registrants should provide each sub-contractor with a dated outline of the process being undertaken, as well as all relevant product-related information (details included).	Greater transparency in the requirements. The dated process outline helps ensure currency of the information being provided through periodic review.
Current guidance on release for supply is focussed on the review of all manufacturing documents (Code of GMP clause 547) which may result in copies of all the relevant batch documents being passed onto the person responsible for 'release for supply'.	Relevant records are reviewed for the steps of manufacture being undertaken at each site and a declaration of compliance provided to the person performing 'release for supply' on the finished product'. 'Release for supply' may either be based on a comprehensive review of batch records or on declarations of compliance provided by other sites.	More flexible arrangements to suit different manufacturing circumstances. Reduced need to copy and transfer quantities of batch documents between different manufacturing sites. Site with best knowledge conducts the review assessment. Greater alignment of APVMA guidance with that provided by the TGA. Greater transparency for ease of auditing.

4 IMPLEMENTATION AND TRANSITIONAL ARRANGEMENTS

4.1 Implementation

The proposal is consistent with the Government's Regulator Performance Framework. The risks associated with the implementation of this proposal are considered to be minimal as the changes proposed are designed to increase the effectiveness of the '*release for supply'* process, particularly when the manufacturing process involves multiple sites. The potential benefits of a streamlined and integrated process also include a reduction in the administrative costs associated with copying and transferring quantities of documents between sites as well as greater transparency for ease of auditing.

It is anticipated that guidance on the '*release for supply'* process would be published on the APVMA website by 1 January 2016, following a period of public consultation in August-September 2015. At the same time, guidance would also be developed and provided to auditors and manufacturers on the outcome of the consultation process.

Where it is considered appropriate, conditions may be added to APVMA licences, where the site is undertaking release for supply on the basis of declarations to ensure transparency and compliance. The imposition of conditions will need to be considered on a case-by-case basis, taking into account the circumstances relevant to the licensed site. As an example it is anticipated that such conditions may be similar to '*For all manufacturing steps not conducted by the licence holder, the person in charge of quality control must not release for supply any batch of veterinary unless there are declarations of compliance testifying that all steps of manufacture have been conducted in conformance with the registered particulars approved by the APVMA*'.

4.2 Transitional Arrangements

Due to the optional nature of the proposal, no transitional period is considered necessary.

It is recommended that a formal review of the change be undertaken 2 years after commencement to assess the effectiveness of the changes. Such a review should be undertaken in consultation with the APVMA's Manufacturers Licensing Scheme - Industry Liaison Committee (MLS-ILC).

4.3 Questions for Consultation

The APVMA invites comment on this discussion paper. Comments should be addressed to Manufacturing Quality and Licensing submitted via email to mls@apvma.gov.au by 21 August 2015. Any submissions will be published unless a written request is received to the contrary. In preparing your submission you may wish to consider the following questions:

- Do you have any comments on the proposed approach to '*release for supply*'?
- Do you consider that there will be an unintended consequences of the proposed approach?
- Do you have any suggestions for improvements to the proposed approach?

- Do you have any comments on conditions which may be added to APVMA licences in relation to the proposal?
- Do you consider that a transitional period is necessary for implementation of the proposal?

ABBREVIATIONS

Code of GMP	*Australian Code of Good Manufacturing Practice for Veterinary Chemical Products* (Code of GMP)
GMP	Good Manufacturing Practice

GLOSSARY

Authorised person	A person recognised by the manufacturer as having the necessary basic scientific knowledge and technical experience to carry out specified tasks associated with quality control.
GMP Agreement	A written agreement between the primary manufacturer or registrant of a veterinary chemical product and another manufacturer or laboratory that carries out a step in the manufacture of that product, that clearly specifies each party's responsibility in relation to every aspect of the manufacturing process, assurance of product quality and compliance with product registration particulars.
Manufacture	Means to produce a chemical product or to engage in any part of the process of producing the chemical product, or any component or ingredient of the chemical product as part of that process, or of bringing the chemical product to its final state, including by formulating, processing assembling, packaging, labelling, storing, sterilising, testing, supplying or releasing for supply.
Step of manufacture	A single, discrete manufacturing activity, eg quality assurance of raw materials, blending, processing, primary and secondary packaging, labelling, analysis and testing, sterilisation, release for supply.
Toll manufacture	Toll manufacture is where all or part of the manufacture of a veterinary chemical product is contracted to another party. Toll manufacture is also called contract manufacture.

REFERENCES

Agricultural and Veterinary Chemicals Code Act 1994

Australian Code of Good Manufacturing Practice for Veterinary Chemical Products. Published by the Australian Pesticides and Veterinary Medicines Authority, 29 March 2007.

Agricultural and Veterinary Chemicals Code (Manufacturing Principles) Determination 2014