

## Guideline 49

# Data requirements and guidelines for variations to immunobiological products

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## 1. INTRODUCTION

The purpose of this guideline is to set out the procedures and requirements for making an application to the APVMA for variation to the particulars of a registered immunobiological product. The variations may include variation to the manufacturing or formulation of the product, an extension of use, or other variations that may affect the quality, efficacy and quality of the formulated product.

Most applications of this nature are evaluated under [Category 14](#).

In some instances, the proposed variation to the formulation of the product means that the product becomes a new product with a new product number. In these instances, the applications are evaluated under [Category 10](#). Examples of instances where such a variation will constitute a new product include:

- addition of an antigen to an existing product
- removal of an antigen from an existing product
- adding an adjuvant or varying the class of adjuvant
- major change to seed strains.

Categories 14 and 10 are both modular categories. Data requirements, the fee payable and timeframe for evaluation depend on which of the modules are required for evaluation of a particular application.

### 1.1. Some variations do not require application to the APVMA

Certain in-process manufacturing changes which are unlikely to have any detectable impact on product quality, safety or efficacy may be made without application to the APVMA. These changes are described in Table 2, in Section 3.

If a registrant implements one of the Table 2 changes to in-process manufacturing, within 30 days the registrant must provide to the APVMA a summary statement or notification of the changes which have been made. If a registrant has any doubt whether a proposed in-process change is covered by Table 2 they should consult the APVMA before implementing the change.

The APVMA will maintain the right to request a copy of the information used in the decision-making process to validate the change, or to require the registrant to make an application under Category 14 (or another category) if the APVMA believes this to be necessary.

## 2. DATA REQUIREMENTS

Data requirements for an application for a variation to manufacturing or formulation, or for an extension of use are derived from the following data Parts in MORAG Volume 3 ‘*Data requirements and data guidelines*’:

- Application and Overview (Part 1) <LINK>
- Chemistry and Manufacture (Part 2) <LINK>
- Efficacy and Safety (Part 8) <LINK>

Further general information on data requirements for applications relating to immunobiological products may be found in veterinary Guideline 47: Data requirements and guidelines for registration of new veterinary immunobiological products <LINK>.

Specific data requirements for each type of variation to manufacturing or formulation, or for an extension of use are set out in Table 1.

To facilitate APVMA evaluation, applicants are advised to summarise or supply full copies of previously submitted data.

**Table 1: Data requirements for each type of variation to manufacturing, formulation or extension of use requiring application to the APVMA**

Application type	Application request	Application category	Expected data modules	
1. Extension of use where there are no variations to the formulation (extension to the product claim)	1.1 Extension of use in/on a new food-producing animal	Category 14	Efficacy and Safety	Module 8.1
	1.2 Extension of use to a new disease/pest in/on the same food-producing animal	Category 14	Efficacy and Safety	Module 8.2
	1.3			
	1.4 Extension of use to a new companion animal species	Category 14	Efficacy and Safety	Module 8.2
2. Formulation change: Minor	2.1 Removal, addition and/or changes to preservatives, stabilisers and other non-active excipients	Category 14	Chemistry and Manufacture	Module 2.4
	2.2 Change of adjuvant within the same class	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.4 Module 8.3
3. Formulation change: Major	3.1 Addition or variation to the class of adjuvant (eg oil to water or vice versa)	Category 10	Chemistry and Manufacture Efficacy and safety	Module 2.2 Module 8.3

Application type	Application request	Application category	Expected data modules	
4. Major change to seed strains: change to source or site or process of manufacture of the antigen	4.1 Change to the source or site or process of manufacture of an antigenic component(s). This may include additional passaging beyond the registered particulars	Category 10	Chemistry and Manufacture Efficacy and Safety	Module 2.2 Module 8.3
	4.2 Change in the donor source of antibody for an immunoserological product	Category 10	Chemistry and Manufacture Efficacy and Safety	Module 2.4 Module 8.3
	4.3 Addition of an alternate source of manufacture of an antigenic component of a vaccine without change to the pharmacopoeial grade or acceptance specification for that antigen	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.2 Module 8.3
5. Change to in-process testing	5.1 Change to in-process testing not included in Table 2 (eg deletion of test)	Category 14	Chemistry and Manufacture	Module 2.4
	5.2 Change to other critical decision-making test			
6. Change to final product tests including change to potency	6.1 Change to final product tests including change to potency testing or other critical release tests	Category 14	Chemistry and Manufacture	Module 2.4
	6.2 Change to site of quality control testing	Category 14	Chemistry and Manufacture	Module 2.4

Application type	Application request	Application category	Expected data modules	
7. Change of site of manufacture of the final product	7.1 Change to, or addition of, a site of manufacture of the final product using the same active constituents	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.3 Module 8.3
	7.2 Change of site of manufacture involving the filling step of the product	Category 14	Chemistry and Manufacture	Module 2.4
8. Changes to release or expiry titre	8.1 Change to APVMA-approved release titre	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.4 Module 8.3
	8.2 Reduction in shelf-life associated with a decrease in the minimum release titre	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.4 Module 8.3
	8.3 Increase in the maximum release titre	Category 14	Chemistry and Manufacture Efficacy and Safety	Module 2.4 Module 8.3

Application type	Application request	Application category	Expected data modules
9. Other specific changes (refer also to Table 2)	9.1 Change to specification testing of raw materials (excluding changes to antigenic components) Change from pharmacopoeial to non-pharmacopoeial standard Deletion of existing test for raw materials Note: a change from pharmacopoeial to non-pharmacopoeial standard is not consistent with GMP	Category 14	Chemistry and Manufacture    Module 2.4
	9.2 Changes to the packaging material and/or closure of product containers (includes diluent container if this is part of the product presentation) where there are no implications for product stability or sterility	Category 12	Chemistry and Manufacture    Module 2.4
	9.3 Changes to the packaging material and/or closure of product containers (includes diluent container if this is part of the product presentation) where there are implications for product stability or sterility	Category 14	Chemistry and Manufacture    Module 2.4
	9.4 Change in the expression of units of potency in batch release specification where this changes the registration particulars	Category 14	Chemistry and Manufacture    Module 2.4
	9.5 New reference batch ie a new comparison batch of proven efficacy is established to determine <i>in vivo</i> the relative potency of the production batches	Category 14	Chemistry and Manufacture    Module 2.4

Application type	Application request	Application category	Expected data modules
10. Extension of product shelf-life	10.1 Extension of product shelf-life	Category 14	Chemistry and Manufacture Module 2.4
11. Change to the diluent	11.1 Change to the diluent where the diluent is packaged and supplied with the vaccine	Category 14	Chemistry and Manufacture Module 2.4 Efficacy and Safety Module 8.3
12. Fall-out product	12.1 Registration of a new product that is derived from an existing registered product by removal of one or more antigens and with reduced claim	Category 10	Chemistry and Manufacture Module 2.3 Efficacy and Safety Module 8.3 The requirement to provide efficacy and safety data may be waived where scientific argument and literature studies justify the absence of full animal efficacy and safety data
13. Build-up product	13.1 Registration of a new product that is created by addition of active constituents to an existing registered product. Any change to the claims for the product relate only to the new active constituents	Category 10	Chemistry and Manufacture Module 2.3 Efficacy and Safety Module 8.2
14. Changes to batch shelf-life	14.1 Change to the expiry date for a specific batch or batches of a product	Category 23 (Permit)	Chemistry and Manufacture Module 2.4
15. Resizing of batch	15.1 Re-sizing of batches (ie change to the number of doses per container based on potency tests)	Category 23 (Permit)	Chemistry and Manufacture Module 2.4 <ul style="list-style-type: none"> <li>include potency and batch release specifications</li> </ul>

Application type	Application request	Application category	Expected data modules
<p>16. Batch released below the approved titre and associated change in shelf-life</p>	<p>16.1 Batch of product to be released with a decreased minimum release titre and associated reduction in shelf-life</p> <p>Note: A reduction in shelf-life is required for all such batches. If the registrant repeatedly applies for a reduction in titre of the same antigen, an application should be submitted for a variation to the shelf-life of the product</p>	<p>Category 23 (Permit)</p>	<p>Chemistry and Manufacture Module 2.4</p> <ul style="list-style-type: none"> <li>include certificate of analysis to demonstrate antigen titres, stability data and batch release specifications</li> </ul>

### 3. VARIATIONS TO IN-PROCESS MANUFACTURING WHICH MAY BE MADE WITHOUT APPLICATION TO THE APVMA

Certain defined changes to the manufacturing process of immunobiological products which are unlikely to have any detectable impact on product quality, safety or efficacy, may be made application without application to the APVMA.

#### 3.1. Reliance on GMP

These changes will rely heavily on compliance with the Australian Codes of Good Manufacturing Practice (GMP), especially the Australian Code of GMP for Veterinary Medicines, with emphasis on the principles and function of quality management.

Manufacturers of immunobiological products must have in place a quality assurance system to ensure that finished products are fit for their intended use, comply with registration requirements and do not place treated animals or users at risk due to inadequate quality, safety or efficacy. The manufacturer's quality system must ensure that:

- appropriate procedures are in place to ensure that relevant quality standards are met
- all materials involved in the manufacturing process comply with required quality standards before they are released for use in manufacture
- there are safeguards and controls in place to prevent the occurrence of foreseeable errors or process failures
- finished products have been made and stored correctly and comply with batch release specifications before they are released for supply.

The quality assurance system is relevant to the nature and intended use of the immunobiological product. It must be fully documented, monitored for effectiveness and provide for continuous improvement.

GMP is concerned with both production and quality control, therefore all manufacturing processes must be clearly documented, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing the registered products of the required quality and in compliance with their specifications. Critical steps of the manufacturing process and significant changes to the process must be validated.

All variations from the registered particulars of manufacture, all critical steps in the manufacturing process, and any variations to these particulars or processes must be documented and subject to review by a company change control system which will be led by an appropriately qualified senior quality assurance designate. A change control team should include appropriate representatives from at least Quality Assurance, Regulatory Affairs and Production, each of whom is in a position to provide advice without constraint by company management.

Records of each final decision, including information or validation data reviewed as part of that decision process, must be maintained in a specific file available for audit. In all cases, validation data should be generated and made available to the APVMA on request.



**Table 2: Variations to in-process manufacturing which may be made without application to the APVMA**

Change to in-process manufacturing	Situations where application to the APVMA is not required	Validation documentation
1. Change of manufacturing location within the same site	<ul style="list-style-type: none"> <li>▫ Chemistry and manufacturing, efficacy and safety, and product specifications remain unchanged (provided the manufacturing site is licensed or recognised by the APVMA)</li> <li>▫ The manufacturing site is being purchased by another company; staff, equipment, documentation and procedures remain unchanged</li> </ul>	<ul style="list-style-type: none"> <li>▫ Manufacturer GMP compliance</li> <li>▫ Equipment and/or process validation as appropriate</li> <li>▫ Manufacturer change control committee consideration and assessment as appropriate</li> </ul>
2. Change to non-critical in-process tests	<p>The change involves:</p> <ul style="list-style-type: none"> <li>▫ adding a new in-process test; and/or</li> <li>▫ upgrading a previous test (eg upgrade of test equipment)</li> </ul>	<ul style="list-style-type: none"> <li>▫ Manufacturer change control committee consideration and assessment as appropriate</li> </ul>
3. Change to method of dispensing	<p>The change involves:</p> <ul style="list-style-type: none"> <li>▫ the same manufacturing site; and</li> <li>▫ the same active constituent; and</li> <li>▫ the same staff, provided there is no change in any other element of the Chemistry and Manufacture dossier</li> </ul>	<ul style="list-style-type: none"> <li>▫ Internal GMP compliance issue requiring, certificate of analysis, equipment and/or process validation as appropriate.</li> <li>▫ Manufacturer change control committee consideration and assessment as appropriate.</li> </ul>
4. Change to biological raw materials (eg material used in media)	<p>The new biological raw material is of <b>Australian origin</b>, is of an equivalent standard to the current raw material, and is used for the same purpose</p>	<ul style="list-style-type: none"> <li>▫ Vendor qualification</li> <li>▫ Evidence of compliance with recognised compendial standards, if appropriate</li> <li>▫ Confirmatory testing of a minimum of 3 batches to pharmacopoeial standard or company specification</li> <li>▫ Manufacturer change control committee consideration and assessment as appropriate.</li> </ul>

Change to in-process manufacturing	Situations where application to the APVMA is not required	Validation documentation
5. Change to biological raw materials (eg material used in media)	The new biological raw material is of <b>overseas origin</b> but is of an equivalent standard to the current raw material, and is used for the same purpose	<ul style="list-style-type: none"> <li>▫ Valid AQIS import permit</li> <li>▫ Confirmatory testing of a minimum of 3 batches to pharmacopoeial standard or company specification</li> <li>▫ Manufacturer Change Control Committee consideration and assessment as appropriate</li> </ul>
6. Change to non-biological raw materials (eg buffer salts)	The new non-biological raw material is of equivalent pharmacopoeial standard to the current raw material and is used for the same purpose	<ul style="list-style-type: none"> <li>▫ Vendor qualification</li> <li>▫ Manufacturer's certificates of analysis for a minimum of 3 batches</li> <li>▫ Evidence of compendial compliance, if appropriate</li> <li>▫ Confirmatory testing of a minimum of 3 batches to pharmacopoeial standard or company specification</li> <li>▫ Manufacturer Change Control Committee consideration and assessment as appropriate</li> </ul>
7. Change to manufacturing process including freeze-dry cycles, documentation editions, change to filter media, certain plant or equipment	<p>The change involves:</p> <ul style="list-style-type: none"> <li>▫ filter media changes e.g. from Millipore to Pall</li> <li>▫ manufacturing process changes eg freeze-dry cycles</li> <li>▫ changes to equipment within the manufacturing site</li> </ul>	<ul style="list-style-type: none"> <li>▫ Manufacturer GMP compliance</li> <li>▫ Equipment and/or process validation as appropriate</li> <li>▫ Manufacturer change control committee consideration and assessment as appropriate</li> </ul>
8. Change to raw material shelf-life	The shelf-life of an inorganic raw material is to be extended. However, if the extension involves biological raw material, APVMA assessment is required where there will be a change to registration particulars	<ul style="list-style-type: none"> <li>▫ Manufacturer GMP compliance, quality assurance and/or process validation as appropriate</li> </ul>

<b>Change to in-process manufacturing</b>	<b>Situations where application to the APVMA is not required</b>	<b>Validation documentation</b>
9. Change of site of manufacture involving the packaging and labelling steps of the product	Evidence that the new manufacturer is licensed/recognised by the APVMA to carry out these steps of manufacturing	<ul style="list-style-type: none"> <li>▫ Manufacturer GMP compliance</li> <li>▫ Equipment and/or process validation as appropriate</li> <li>▫ Manufacturer change control committee consideration and assessment as appropriate</li> </ul>

## Revision history

Revision date	Description of revision
September 2004	First edition
May 2006	Second edition <ul style="list-style-type: none"><li>• complete revision of the content</li></ul>