



**Australian Government**  
**Australian Pesticides and  
Veterinary Medicines Authority**



**Technical guideline for Out of Specification (OOS) veterinary  
vaccine permit applications**

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## BACKGROUND

The APVMA administers a permits scheme that allows for the legal use of chemicals in certain ways that are contrary to the label instructions or, in certain circumstances allows for the limited use of an unregistered chemical product.

The scheme allows for the legal use of products that may:

- be contrary to the label instructions of a registered vaccine
- be intended for the limited use of an unregistered chemical product (minor use, emergency use or research)
- allow the manufacture and sale of a product that would otherwise be an offence to manufacture
- be for other purposes or circumstances that are product or batch specific.

The time taken for APVMA to complete an evaluation of any given permit application can vary from less than three months to eight months' depending on technical assessment modules, involving either significant chemistry, toxicology, residues, efficacy or safety reviews. In many cases this permit evaluation process may only relate to a specific batch or serial of a vaccine.

This technical guideline (GL) outlines the technical requirements for the assessment of certain permit applications that are common to a range of veterinary vaccines, providing specific examples and associated technical requirements that would facilitate the issuing of a permit with minimal technical assessment whilst ensuring the quality, safety and efficacy of vaccines on the market.

Permits issued under the scheme are expected to be rare or occasional. The APVMA can request a formal variation to the registered product should such applications become frequent.

Specific examples applicable to the issue of multi-batch permits are described below.

# 1 EXTENSION OF BATCH SPECIFIC PRODUCT SHELF LIFE

## 1.1 Technical assessment of extension of batch specific product shelf life

Stability data supplied in support of the specific batch or batches does not need to predict the shelf life of the batch(es). Rather, the most recent testing need only demonstrate that the batch(es) conforms to the stability expectations for the product and is above the end of shelf life specification.

Real time stability data for a veterinary vaccine manufactured at production or pilot scale and filled into the final marketed primary container is used to support the registered shelf life. The data determines the release specifications of each and every batch and ensures that the end of shelf life specification is met.

For batch specific shelf life extensions, linear regression for live biological organisms and inactivated antigens is limited due to the uncertainty surrounding the stability of biological materials and retention of immunogenicity of the antigenic material. However, by regular monitoring of a veterinary vaccine over the period of extended stability, the risks can be managed and appropriate action taken should the potency fall below the registered end of shelf life potency.

The risk that potency of a veterinary vaccine will fall below the end of shelf life specification within the duration of the permitted extension will be managed by regular testing of final product samples from the specific batch. The frequency of testing will be agreed with the APVMA, typically two to six months depending on the characteristics of the product and informed by the registered stability data itself or additional information provided by the applicant that may be relevant to the technical review.

Once a specific shelf life extension has been granted and the frequency of monitoring agreed and risk-mitigation measures established, it should be possible to grant additional batch specific extensions for the same registered product using the same criteria with minimal technical input to ensure the product remains safe and efficacious. Any subsequent batches granted shelf life extensions should be monitored at the same frequency.

The applicant should provide a communication strategy to ensure users of the vaccine are in receipt of sufficient information to use the vaccine safely and effectively, such as a letter of advice to customers. The permit would indicate the new shelf life subject to the ongoing stability studies meeting the registered specifications.

Technical considerations for conventional classes of veterinary vaccines (live and inactivated viral, bacterial vaccines, subunit or toxoids vaccines, live recombinants and peptide vaccines are within the scope of this guidance.

Vaccines considered novel or unconventional or other immunobiological classes would be subject to product specific assessment for the maximum permitted extension of shelf life and the frequency of monitoring eg specific criteria may be indicated for products normally stored in liquid nitrogen or at,  $-70^{\circ}\text{C}$ , where antigens may be stable for > five years.

The following criteria is for guidance only and the APVMA may restrict or extend the frequency of monitoring on a case-by-case basis. Potency tests involving animals, in the interests of 3Rs, will be restricted to the mid-point of the agreed extension, unless justified or agreed with APVMA, without need for an End of Shelf Life [EOS] Time 0.

- registered shelf life of  $\leq 18$  months:
  - test at EOS and at three months for a six month extension
  - test every two months for any further extension beyond the six month initial extension up to 12 months beyond the registered shelf life (maximum 12 month extension)
- registered shelf life of  $\geq 18$  months up to 36 months:
  - test at EOS and at six months for a 12 month extension
  - test every four months for any further extension up to an additional 12 months (maximum 12 months extension)
- registered shelf life  $\geq 36$  months:
  - test at EOS and every six months for a 24 month extension, and every six months for any further extension up to an additional 12 months (maximum 24 month extension).

## 2 REDUCTION OF BATCH SPECIFIC PRODUCT SHELF LIFE

A batch of product can fail to achieve the minimum batch release specification (titre or potency) without any specific identifiable cause, without a measurable impact on the efficacy of the product depending on the nature of the product and the minimum titre/potency demonstrated to be efficacious. A minor change to a growth factor or media nutrient may cause the titre or potency of a vaccine antigen to be suboptimal, without effect on the antigen itself, which is especially true for a live vaccine that multiply or replicate in the host as part of its mechanism to generate sustained or lifelong immunity.

A benefit-risk assessment should be undertaken to justify the basis for the release of the product on the Australian market, taking account the availability of identical or similar vaccines for the disease condition, the market share and the consequences for the sector if vaccination schedules are adversely impacted. If the APVMA is mindful to consider an application for a reduction in shelf life the applicant will need to ensure the users of the vaccine are aware of the reduction if the intention is not to re-label the product, such as a letter of advice to customers.

Technical considerations for conventional classes of veterinary vaccines (live and inactivated viral and bacterial vaccines, subunit or toxoids vaccines) and live recombinant and other novel vaccines are within the scope of this guidance. Vaccines considered novel or unconventional or other immunobiological classes would be subject to product specific assessment.

Each application will be treated on its merits taking into account the registered potency test (or current potency test should the potency test be different from the registered test). The applicant should justify the reduction in shelf life using the data generated to support the registered product and any additional supporting data. The applicant should take into account the release and end of shelf life specifications and the characteristics of the potency test (sensitivity, Limit of Detection [LOD], range of linearity etc).

The applicant should provide a communication strategy for marketing the product. Where possible vaccine should be re-labelled to indicate the reduced shelf-life.

A possible approach for managing a reduction of batch-specific product shelf life:

- for every 10 per cent reduction in 'potency' of minimum release specification versus expiry specification, approved shelf life to be reduced by 15 per cent. For instance, the approved minimum release potency measure is 100 units, the approved expiry potency is 70 units, and the approved shelf life of the product is 36 months. At the time of manufacture and proposed release, the potency measure is 94 units, a six unit or 20 per cent reduction versus the expiry titre of 70 units. The batch shelf life would be reduced by 30 per cent or 11 months.

### 3 POTENCY EXCEEDS MAXIMUM BATCH RELEASE SPECIFICATION

As part of a registration dossier for live or inactivated veterinary vaccines, three specifications of finished product titre or potency are generally established;

- end of shelf life specification based on pivotal efficacy studies
- minimum batch release specification based on pivotal efficacy and stability studies
- maximum batch release specification based on pivotal safety studies.

On occasion, during batch manufacture an antigen fraction may exceed the approved maximum release specification. Under the current regulatory requirement such a deviation would require a batch specific permit, dependent on the results of an additional batch safety test, for the release of the specific batch to the market.

Given that target animal batch safety testing is no longer required in the interest of 3Rs, safety tests to support a higher release specification than the registered maximum release specification, will be restricted to exceptional situations following discussion with the APVMA.

The applicant should provide a risk-mitigation strategy for releasing product that exceed the maximum release specification. For livestock products, the vaccine should be administered to a small group of animals prior to a wider administration in the field. For companion animal products this should not be required.

In accordance with the results of the pivotal safety studies (overdose study for live vaccine or single dose, repeat dose for inactivated vaccine) a multi-batch permit could be issued with the following notes and conditions:

- (note) this batch of <product name> is formulated to contain a higher potency of <antigen name> than the registered Australian product. The <overdose or repeat dose> safety study indicates injection site swelling may (or may not) occur
- (note) reports of any adverse experiences associated with the use of the product may be provided to the APVMA Adverse Experience Reporting Program. Free call: 1800 700 583 (within Australia)—charges apply for calls made from mobile phones; email: [aerp@apvma.gov.au](mailto:aerp@apvma.gov.au)
- (note) section 161 of the Agvet Code requires a permit holder to provide any relevant information to the APVMA as soon as the holder becomes aware of the information. The Agvet Code provides that information is relevant if it contradicts any information entered in the Record of Permits or shows that the product may not meet the safety criteria, the trade criteria or the efficacy criteria
- (condition of supply) <product name> with a titre or potency above the registered maximum batch release titre or potency and the maximum batch release titre or potency supplied for batch number <xxxx> must not be supplied unless accompanied by this permit
- (condition of use) an authorised person may use <product name> with batch numbers as outlined above, accompanied with this permit
- (condition of use) an authorised person is responsible for overseeing and checking that the reconstitution of <product name> with batch numbers as outlined above, accompanied with this permit
- (condition of use) an authorised person is responsible for increasing the observation period after vaccination <product name> with batch numbers as outlined above, accompanied with this permit

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- (condition of use) <company name> must maintain a record of any reported adverse reaction, including lack of safety or efficacy, resulting from the administration of the product. <Company name> must fully investigate all adverse reactions
  - (condition claims) an authorised person may claim that <product name> with batch number as outlined above may be used as authorised by this permit.

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## 4 RESIZE A BATCH TO A SMALLER THAN REGISTERED PACK SIZE

In this instance, the registered presentation may be an X mL of vaccine to deliver an expected 5 000 doses as registered, but the real-time potency assay of the dispensed and bottled product then proves to be 4 400 doses—which is not the registered 5 000 presentation, nor the registered 2 000 dose presentation. Alternately, perhaps a registered 1 000 dose presentation could be resized to an unregistered 500 dose presentation.

Product quality, safety or stability is not in question; the issue is wholly a resizing of the batch because of the vagaries of manufacture of this type of product.

Industry would expect that this type of application could be managed either as a notification, or within not more than six weeks administration time.

The APVMA will issue a permit indicating the number of single doses per vial to ensure animals will receive the registered dose that is both safe and efficacious.

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## REFERENCES

VICH GL41 *Guideline on target animal safety: examination of live veterinary vaccines in target animal for absence of reversion to virulence*, July 2008.

VICH GL44 *Guideline on target animal safety for veterinary live and inactivated vaccines*, July 2009.

USDA Memo No. 800.207. *General licensing considerations: Target Animal Safety (TAS) studies*, July 2010.

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