



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



# **Guidance for out of specifications veterinary vaccine permit applications**

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## Background

The Australian Pesticides and Veterinary Medicines Authority (APVMA) administers a permit scheme, which allows for the legal use of chemicals under certain conditions. This may include uses that:

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

## Out-of-specification

For the purposes of this document, the term out-of-specification (OOS) includes all test results that fall outside the specifications or acceptance criteria established at the time of registration of the product or during an approval of a permit. The OOS permit evaluation process relates to a specific batch or serial of a vaccine.

An OOS application should normally be lodged as an Item 23 – miscellaneous permit application. However, in some circumstances, an OOS application may be lodged as an emergency permit application - item 22 with appropriate scientific justification. A benefit-risk assessment should be undertaken by the applicant to justify the basis for the release of an OOS batch. This particularly applies where there is a vaccine registered for the same disease/condition already on the market. Applications for releasing OOS batches will only be considered in exceptional circumstances where there is an urgent health and welfare issue and where registered vaccines that are within specification are not expected to meet the market demand. Application made on purely commercial grounds will not be considered.

The time taken for the APVMA to complete an evaluation of an OOS permit application can vary from 2 to 8 months depending on the technical assessment module(s) and the complexities of the data required. Please refer to: <https://www.apvma.gov.au/registrations-and-permits/permits/before-you-apply-permit> for further information on the appropriate modules and time frames. Where there is an urgent request for an OOS batch due to animal health and welfare issues, the APVMA will prioritise this.

This guidance document outlines the data requirements for the assessment of OOS vaccine permit applications. The data requirements for this type of application are product and batch specific. The guidance provides 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 the vaccines.

This guidance covers conventional classes of veterinary vaccines; for example, live/inactivated vaccines, subunit, or toxoids vaccines, live recombinants, and peptide vaccines. For other immunobiologicals, including monoclonal antibodies, applicants are advised to contact the Permits Teams via email [enquiries@apvma.gov.au](mailto:enquiries@apvma.gov.au) before submitting an OOS permit application.

The APVMA may request a formal variation to the registered product rather than consider an OOS application or request a variation as a condition of granting an OOS Permit.

Where a permit is issued, several conditions are imposed to mitigate the potential risks. This includes a condition that the applicant ensures users of the vaccine are aware of its conditions of use. If the intention is not to re-label the product, a letter of advice to customers should accompany each supply.

## **Definition of standards or specifications approved at registration/permit approval**

### **Minimum release titre**

The minimum release titre (Min RT) is the lowest number of viable organisms or lowest antigenic mass/potency permitted at the time of batch release. The Min RT is determined from the stability studies and must be high enough to ensure the product contains at least the end of shelf life titre (EOSLT) or potency at the end of shelf life.

### **Minimum protective dose**

The minimum protective dose (MPD) is the lowest number of viable organisms or lowest antigenic mass/potency that has been shown to produce the claimed effect(s) in the efficacy studies.

### **Maximum release titre**

The maximum release titre (MRT) is the highest number of viable organisms or highest antigenic mass/potency permitted at the time of batch release. This is established through the target animal safety studies.

### **End of shelf life titre**

The end of shelf life titre (EOSLT) is the titre or potency of the product that must be maintained to the end of the shelf life as determined by the stability studies. It should be shown to be equal or greater than the minimum protective dose.

## Extension of batch specific product shelf life

Real time stability data must be provided to support an extension of a batch-specific shelf life of a registered product. The data should include the batch release results. The parameters included in the stability trial should be identical to those used to generate the shelf-life data during registration or permit approval.

The stability study needs to demonstrate that the batch(es) conforms to all the stability specifications for the registered product and is above the EOSLT.

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 or a declaration letter to customers. The permit would indicate the new shelf life subject to the ongoing stability studies as per the registered specifications.

Where sufficient evidence has been provided to support an extension of shelf life, the APVMA may issue a permit extending the shelf life with appropriate conditions.

The risk that potency of a veterinary vaccine batch will fall below the end of shelf-life specification within the duration of the permitted extension is real and should be managed by regular testing of the specific batch in question. The frequency of testing is determined on case-by-case basis, but it is typically 3 to 6 months depending on the characteristics of the product and the quality of data submitted by the applicant. The frequency of re-testing to monitor the stability of the product should be justified. For example, for vaccines stored at  $-196^{\circ}\text{C}$ , a more extended shelf life may be considered owing to the nature of the vial and demonstrated stability of the active constituent.

### Extension of shelf life of a vaccine batch with a registered/approved shelf life of less than 18 months

- Test at EOSLT and at 3 months after EOSLT for a 6 month extension.
- Test every 3 months thereafter for any further extension beyond the 6 months (maximum extension period of 12 months).

### Extension of shelf life of a vaccine batch with a registered shelf life of greater than 18 months and up to 36 months

- Test at EOSLT and at 6 months after EOSLT for a 12 month extension.
- Test every 4 months thereafter for any further extension beyond the 12 months (maximum extension period of 24 months).

### Extension of shelf life of a vaccine with a registered shelf life greater than or equal to 36 months

- Test at EOSLT and at 6 months after EOSLT for a 24 month extension, and every 6 months thereafter for any further extension beyond 24 months (maximum extension period of 36 months).

## Conditions of the permit

Standard conditions apply for an extension of batch specific shelf life as follows, which may be varied as required.

- The product, Batch number XXX must be potency tested at XX monthly intervals and the results must be supplied to the APVMA.
- If the potency test fails during the shelf life period, then the batch must be recalled.
- The applicant should submit a declaration letter for issuing each batch which will be annexed on the permit.

## Extension of shelf life of vaccines products stored in liquid nitrogen or at $-70^{\circ}\text{C}$ and lower temperature where antigens may be stable for a longer time.

Under these conditions, a batch may be allowed an extension of shelf life beyond 36 months past the registered shelf life, on the basis of regression analyses of data demonstrating that they may be expected to remain above the EOSLT over the life of the permit and a commitment to ongoing testing at appropriate intervals; however, a determination will be made on case-by-case basis.

## Reduction of batch-specific product shelf life

This type of application should be submitted where a specific batch returns a titre lower than the Min RT. The applicant will need to provide adequate justification for the proposed reduction in shelf life to ensure the registered EOSLT can be assured.

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

## Potency exceeds maximum batch release specification (approved MRT)

On occasion, during the manufacture of a product, a vaccine organism or antigen may exceed the approved maximum release titre. The applicant should provide adequate justification as to why they consider a batch released under such a scenario will be safe for the target species.

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.

If a pivotal safety study (overdose study) has been submitted and accepted by the APVMA at the time of product registration, a permit may be issued without any additional safety information. However, the applicant must submit that information with the permit application.

However, further safety studies may be required where the titre of the batch is higher than the titres used in pivotal safety studies. In such cases, the vaccine may be administered to a small group of target species of the most sensitive category and monitored for a period of 7–14 days.

Standard conditions for permits exceeding potency above MRT are as follows:

- This batch of *product name* is formulated to contain a higher potency of *antigen name* than the APVMA-registered product. Where possible the product label for the batch should be updated to reflect the revised specification.
- Reports of any adverse experiences associated with the use of the product must be provided to the APVMA's Adverse Experience Reporting Program. Phone: 1800 700 583; Email: [aerp@apvma.gov.au](mailto:aerp@apvma.gov.au).
- 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, efficacy, or trade 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 XXX must not be supplied unless accompanied by this permit.
- Conditions of use:
  - An authorised person may use *product name* with batch numbers XXX as outlined above, accompanied with this permit.
  - An authorised person is responsible for overseeing and checking that the reconstitution of *product name* with batch numbers XXX as outlined above, accompanied with this permit.
  - An authorised person is responsible for increasing the observation period after vaccination *product name* with batch numbers XXX as outlined above, accompanied with this permit.
  - *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 XXX as outlined above may be used as authorised by this permit.

### Resize of a batch outside of registered pack size

Resizing of batches may be required when real time potency assay yields lower doses than expected. For resizing of a batch outside of a registered pack size, the applicant will need to justify the safety and efficacy of the proposed presentation that falls outside the registered pack sizes.



## References

European Medicines Agency (July 2008). [Veterinary International Conference on Harmonization Guideline \(VICH\) GL41](#). Target animal safety: examination of live veterinary vaccines in target animal for absence of reversion to virulence, accessed on 15 August 2020.

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