Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public consultation on Guideline for out of specifications veterinary vaccine permit applications

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Contents

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 vaccine
- are intended for the limited use of an unregistered chemical product (minor use, emergency use or research)
- 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 is commonly lodged as an Item 23 miscellaneous permit application. In some circumstances, an OOS application may be lodged as an emergency permit application (EPA) with appropriate scientific justification. A benefit-risk assessment should be undertaken by the applicant to justify the basis for the release of an out of specification batch. This particularly applies where there is a vaccine registered for the same disease/condition already on the market. Please note, marketing/commercial issues raised due to lack of proper planning by the applicant are not considered valid justification for an EPA.

The time taken for the APVMA to complete an evaluation of a permit application can vary from 2 months to 8 months depending on technical assessment module(s) and the complexities of the data required.

This guideline outlines the technical requirements for the assessment of OOS permit applications. The data requirements for this type of application are product- and batch-specific. The guideline 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 guideline covers conventional classes of veterinary vaccines (live/inactivated vaccines, subunit or toxoids vaccines, live recombinants and peptide vaccines). Specific criteria are indicated for products stored in liquid nitrogen or at –70°C where antigens may be stable for more than 5 years.

OOS permit applications are expected to be rare or occasional. The APVMA may request a formal variation to the registered product should such applications become frequent.

Where a permit is issued, several conditions are imposed. 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 EOSLT or potency at the batch expiry date.

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 in 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 derived or verified from 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 higher than the minimum effective dose to accommodate factors such as assay variation.

Extension of batch-specific product shelf life

Extension of batch-specific product shelf-life application arises where at the end or near the registered/approved shelf-life of the product, the batch returns a titre between the MRT and Min RT. Real time stability data must be provided to support an extension of batch-specific product shelf life. The data should include all batch release information – for example pH and moisture content loss on drying. The conditions of the stability trial should be identical to that used to generate the data used to establish the shelf life of the product on registration.

Stability data supplied in support of the specific batch(es) do 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.

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, where appropriate, the APVMA will accept such data.

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 meeting 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 2 to 6 months depending on the characteristics of the product and the quality of data submitted by the applicant.

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 2 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 EOSL 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°C, where antigens may be stable for greater than 5 years

Viral vaccines stored at –196°C in liquid nitrogen may have shelf lives greater than 5 years. Being entirely sealed in glass, they may not be limited by possible degradation of rubber stoppers and subsequent ingress of moisture or contaminants.

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 but higher than the EOSLT.

A batch of product can fail to achieve the minimum batch release specification (titre or potency) without any specific identifiable cause. 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 multiplies or replicates in the host as part of its mechanism to generate sustained or lifelong immunity.

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, an antigen fraction may exceed the approved maximum release titre. Under the current regulatory requirement such a deviation would require a batch-specific permit.

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. The applicant must submit that information with the permit application.

However, further safety studies will be required where the titre of the batch is higher than the titres used in pivotal safety studies. In such a case, the vaccine should be administered to a small group of target species of the most sensitive category.

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. The *overdose or repeat dose* safety study indicates injection site swelling may (or may not) occur.
- 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
- 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 *XXX* 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.
- 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.

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. An application for a permit is required to release a batch outside of registered pack size.

Generally, there are three such scenarios and the data requirements for each scenario is different.

Scenario 1

Where there is only one dose presentation registered, stability data or additional information will be required to support a new presentation.

Scenario 2

Where the product has multiple pack sizes registered and proposed presentation falls outside the registered presentation, stability data may be required to support such permit. For example, the registered dose presentations are 1000, 2000 (doses) and the proposed dose presentation is 500.

Scenario 3

Where the proposed presentation falls within registered product presentation range, no additional stability data will be required to support the permit application. For example, where the proposed dose presentation is 2500 doses, and the product has these pack sizes registered 500, 1000, 2000, 3000, 4000 (doses), assuming that the product has the same container and closure system used for three or more pack sizes (bracketing), no additional stability data is required.

References

1. 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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3. Veterinary Services Memorandum No. 800.207 (July 2010). General licensing considerations: Target Animal Safety (TAS) studies, accessed on 15 August 2020.