Veterinary Vaccines in EU: Stability regulatory framework

Examples of stability assessments and definitions of release and end of shelf-life specifications

IFAH-Europe Biologicals Working Party

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Stability regulatory framework

- Ph. Eur. 04/2013:0062 – Vaccines for Veterinary Use
- EMA/CVMP/IWP/206555/2010 - Guideline on requirements for the production and control of immunological veterinary medicinal products (superseding GRLMV and GRIMV)
- VICH GL17: Stability testing of biotechnological/biological veterinary medicinal products

Ph. Eur. 04/2013:0062 – Vaccines for Veterinary Use:

2-2-6. Stability

- Evidence of stability is obtained to justify the proposed period of validity. This evidence takes the form of the results of virus titrations, bacterial counts or potency tests carried out at regular intervals until 3 months beyond the end of the shelf life on not fewer than 3 representative consecutive batches of vaccine kept under recommended storage conditions together with results from studies of moisture content (for freeze-dried products), physical tests on the adjuvant, chemical tests on substances such as the adjuvant constituents and preservatives, and pH, as appropriate.
Stability regulatory framework

Ph. Eur. 0062 Vaccines for Veterinary Use:

- At least 3 batches → - representative, - consecutive
- Regular intervals, up to 3 months beyond intended shelf life
- Parameters:
  - Titration/bacterial count/potency
  - Residual moisture (freeze-dried vaccines)
  - Physico-chemical tests:
    - viscosity, pH, adjuvant/preservative content, .....
Stability regulatory framework

- Dir 2001/82/EC consolidated:

G. STABILITY TESTS

- A description shall be given of the tests undertaken to support the shelf life proposed by the applicant. These tests shall always be real-time studies; they shall be carried out on a sufficient number of batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physicochemical stability tests.

- The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions.
Stability regulatory framework

Dir 2001/82/EC consolidated:

- At least 3 batches → - representative, - consecutive
- **Real time**, regular intervals, up to 3 months beyond intended shelf life
- **Parameters**:
  - Titration/bacterial count/potency
  - Residual moisture (freeze-dried vaccines)
  - Physico-chemical tests:
    - viscosity, pH, adjuvant/preservative content, .....
- Results should justify shelf life
4. STABILITY TESTS

- Stability testing shall be carried out as specified in the Directive 2001/82/EC and in the European Pharmacopoeia monograph 0062 Vaccines for Veterinary Use on not fewer than 3 representative consecutive batches. The three consecutive production runs may be carried out on a pilot scale, providing this mimics the full-scale production described in the application. The sterility of the vaccine has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test for container/closure integrity). Where bulk material is to be stored before formulation and final manufacturing, stability data should be provided.
Stability regulatory framework

Dir 2001/82/EC consolidated:

- At least 3 batches → - representative, - consecutive, - Pilot scale
- Real time, regular intervals, up to 3 months beyond intended shelf life
- Parameters:
  - Titration/bacterial count/potency
  - Residual moisture (freeze-dried vaccines)
  - Physico-chemical tests: viscosity, pH, adjuvant/preservative content, .....
  - Sterility at end of shelf life
- Results should justify shelf life
VICH GL 17 Stability testing of biotechnological/biological VMPs

- This document does not cover...conventional vaccines...

- **C Drug product (finished product) 4.3**: Stability information should be provided on at least three batches of finished product representative of that which be used at manufacturing scale.

- **VII. Testing frequency (8)**: for products with expected shelf-lives of greater than one year, the studies should be conducted every three months during the first year of storage, every six months during the second year, and annually thereafter.
VICH GL 17 Stability testing:

- **At least 3 batches** → - representative, - consecutive, - Pilot scale

- **Real time, regular intervals**, 3 months (1\textsuperscript{st} year) 6 months (2\textsuperscript{nd} year) annually; up to 3 months beyond intended shelf life

- **Parameters:**
  - Titration/bacterial count/potency
  - Residual moisture (freeze-dried vaccines)
  - Physico-chemical tests:
    - viscosity, pH, adjuvant/preservative content, ..... 
  - Sterility at end of shelf life

- **Results should justify shelf life**
In current EU requirements:

- Give several (non compulsory) advices ...
- No prescribed ways (except number of batches, frequency, nature of tests)
- No recommended statistical tools but should best suit data
- Outcomes of results analysis as well as the required additional 3-month period beyond the specified target for expiry definition should be considered when defining specifications

Easy/straightforward consideration for live vaccines,

Less descriptive for inactivated products (possibly easier since “assay of biological activity” was replaced by “A quantification of the active substance” in updated Dir 2001/82/EC i.e Dir 2009/9/EC)

- (live vaccines) For routine testing it must be demonstrated for each batch that the titre or count at release is such that at the end of the period of validity, in the light of stability studies, the vaccine, stored in the recommended conditions, will contain not less than the minimum acceptable virus titre or bacterial count determined during development studies.

Technical guide for the elaboration and use of monographs for immunological veterinary medicinal products (PhEur): batch potency test

- For live vaccines, a test for virus titre or bacterial count is required by the relevant specific monographs and the general monograph and it is expected that the point will be addressed through setting a suitable acceptance criterion for this test. To this end:

  - during the development studies the minimum acceptable viral titre or bacterial count must be established, based on that in the batch(es) of vaccine used in the Potency test or other efficacy studies, the loss observed during the stability studies should be added to this value to ensure that the content will be not less than the minimum acceptable titre or count at the end of the shelf-life,

  - each batch must then be shown to contain, at release, not less than this calculated titre or count.
From stability to specifications

Ph. Eur. and its technical guide:

- Minimum titer
- Stability losses

- Release = minimum titer + losses

Ensure end of shelf life titer is not less than minimum titer
Basis of Titer Specifications

- EU regulatory expectations are defined by several key Directives, Guidelines, and Monographs spanning two decades:

  - **Directive 2001/82/EC (as amended)** – On the Community Code Relating to Veterinary Medicinal Products
  
  - **European Pharmacopoeia 04/2013:0062** – Vaccines for Veterinary Use.
  
  - **EMA/CVMP/IWP/582970/2009** – Reflection paper on control of the active substance in the finished product for immunological veterinary medicinal products (IVMPs).
  
  - **EMA/CVMP/552/02-CONSULTATION** – EU Requirements for Batches with Maximum and Minimum Titre or Batch Potency for Developmental Safety and Efficacy Studies.
  
  - **CVMP/IWP/038/97-FINAL** – Position Paper on Batch Potency Testing of Immunological Veterinary Medicinal Products.
Basis of Titer/Potency Specifications

- Present in Directive 2001/82/EC, 3. Batch titre or potency
  - A quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre **to ensure its safety and efficacy**.

- Titer specifications are driven by data generated during efficacy/safety, assay development, and stability trials.

- Specifications are described in the marketing authorization application and supporting product dossier submission.

- Best described by Ph. Eur. 0062 – Vaccines for Vet Use:
  - “For live vaccines, the minimum acceptable virus titre or bacterial count that gives satisfactory results in the potency test and other efficacy studies is established during development.”
Basis of Titer/Potency Specifications

- Also defined by EMA/CVMP/IWP/582970/2009 – Reflection paper on control of the active substance in the finished product for immunological veterinary medicinal products (IVMPs):

  - “Directive 2001/82/EC as amended requires that a control of the batch titre or potency is carried out on the finished product. It states that a quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre to ensure safety and efficacy.”

  - “It should be noted that, while the general aim is to ensure that each batch of vaccine will be equally efficacious, the required test is part of the quality control of the finished product intended to confirm consistency of production and that each batch is formulated equivalent to batches that have been demonstrated to be efficacious.”
• Directive 2001/82/EC (as amended 2009/9/EC)

• PART 3: SAFETY TESTS, A. INTRODUCTION AND GENERAL REQUIREMENTS
  – In the case of an immunological veterinary medicinal products containing a live organism, the dose to be used in the laboratory tests described in Sections B.1 and B.2 shall be the quantity of the product containing the maximum titre. If necessary the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

• PART 4: EFFICACY TESTS, CHAPTER II, B. Laboratory trials
  – For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.
Basis of Titer/Potency Specifications

- In a more pragmatic way

- SAFETY
  - Live: the maximum titer is defined as $1/10$ of the titer used in the highest overdose safety study
  - Inactivated: the maximum potency is defined as the (equivalent of) the maximum antigen content used in the safety study

- EFFICACY
  - Live: the minimum titer is defined as the lowest titer that induced full efficacy
  - Inactivated: the minimum potency is defined as the (equivalent of) the lowest antigen content that induced full efficacy
Results/content considered for a product to be:

- efficacious (not too low content),
- safe (not too high content)
- But economically viable (not too high content)
- but stable (not too low content)

- Still having a good Benefit/Risk

Right balance is key in defining the best compromise product
Specifications in short

3 batches, regular testing (0, 3, 6, 9, 12, 15, 21, 27, 39)
Potency/titre, physico-chemical parameters, residual humidity
Bacterial/fungal sterility (0, end)
End of shelf life +3 months: potency **not less than** minimum efficacy limit
Basis of Live Titre Specifications

- Defining requirements for setting potency specifications:
  - A product’s **minimum acceptable virus titre or bacterial count** is established during the development program.
  - This **minimum acceptable virus titre or bacterial count** is specified in the marketing authorisation and the SPC (basis for leaflet).
  - This **minimum acceptable virus titre or bacterial count** must be present throughout the shelf-life of the product (EOSL value).
  - Evidence of stability must be generated on not fewer than three representative batches to define the stability profile of the product.
  - This stability profile is used to set a **release titre level** that must be met or exceeded for each batch of product released to the market.
  - The addition of overage should not exceed the maximum (safe) titre.

- Two examples help frame the EU Authorities approach to these requirements:
Example 1: Setting Live Titre Specifications

Maximum Titre at Batch Release
(based on safety data; using a validated test)

Minimum Titre at Batch Release (using a validated test)

Loss During Shelf-Life at Recommended Temperature (usually average or worse-case)*

Minimum Efficacy Titre Set in Development (minimum titre required through shelf-life)

* Based on data collected through Shelf-life plus 3 months.
Example 1: Live Titer Specifications

### Basis of Titre at EOSL

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Minimum Efficacy Titre*</th>
<th>Minimum Titre at EOSL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Viral Vaccine - Canine</td>
<td>4.3 log$<em>{10}$ TCID$</em>{50}$/ml</td>
<td>4.3 log$<em>{10}$ TCID$</em>{50}$/ml</td>
</tr>
</tbody>
</table>

### Stability over Shelf-Life + 3 Months

<table>
<thead>
<tr>
<th>Component</th>
<th>Maximum Decrease</th>
<th>Average Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Viral Vaccine - Canine</td>
<td>0.8 log$<em>{10}$ TCID$</em>{50}$/ml</td>
<td>0.5 log$<em>{10}$ TCID$</em>{50}$/ml</td>
</tr>
</tbody>
</table>

### Basis of Titre at Release

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Minimum Titre at EOSL</th>
<th>Minimum Titre at Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Viral Vaccine - Canine</td>
<td>4.3 log$<em>{10}$ TCID$</em>{50}$/ml</td>
<td>5.1 log$<em>{10}$ TCID$</em>{50}$/ml</td>
</tr>
</tbody>
</table>

* Based upon OOI, DOI, and/or MID studies.
Example 2: Setting Live Titer Specifications

Maximum Titre at Batch Release (using a validated test)

Minimum Titre at Batch Release (using a validated test)

Loss During Shelf-Life at Recommended Temperature (average or worse-case)*

Minimum Efficacy Titre Set in Development (minimum titre required though shelf-life)

* Based on data collected through Shelf-life plus 3 months.
# Example 2:
## Live Titer Specifications

### Basis of Titre at EOSL

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Minimum Efficacy Titre*</th>
<th>Minimum Titre at EOSL**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Bacterial Vaccine for Chickens</td>
<td>3.1x10⁶ CFU/ds</td>
<td>5.2x10⁶ CFU/ds</td>
</tr>
</tbody>
</table>

### Stability over Shelf-Life + 3 Months

<table>
<thead>
<tr>
<th>Component</th>
<th>Maximum Decrease</th>
<th>Average Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Bacterial Vaccine for Chickens</td>
<td>4.5x10⁶ CFU/ds</td>
<td>3.0x10⁶ CFU/ds (6 batches)</td>
</tr>
</tbody>
</table>

### Basis of Titre at Release

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Minimum Titre at EOSL</th>
<th>Minimum Titre at Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Bacterial Vaccine for Chickens</td>
<td>5.2x10⁶ CFU/ds</td>
<td>8.2x10⁶ CFU/ds</td>
</tr>
</tbody>
</table>

* Based upon OOI, DOI, and/or MID studies.
** Increased by 2 standard deviations
Basis of Live Titer Specifications

- General requirements are clear but are sometimes assessed differently by different Authorities:
  - Minimum Titre Value:
    - Set based upon OOI, DOI, MID, and/or MAB studies.
    - Also tied to description in product information/SPC.
  - EOSL Titre Value:
    - Most often the average of multiple titrations.
    - Infrequently includes a 2 sd offset value.
  - Stability Assessment:
    - Average titer loss over time versus “worse-case” titer.
    - Linear extrapolation of decay rate versus recognition of higher-order kinetics or two-phase decay.
    - Always consider expected shelf life plus 3 months
Basis of inactivated Potency Specifications

- General requirements are less clear but inferred/deduced/inspired by the existing requirements for live vaccines (especially if tested by ELISA or similar in vitro method).

- Key are:
  - Efficacy studies set minimum potency
  - Safety studies set possible maximum antigen content
  - Target formulation should ensure efficacy not less than pivotal batch at end of shelf life
  - Overage impacts safety

- PhEur 62 “The aim of the batch potency test is to ensure that each batch of vaccine would, if tested, comply with the test described under Potency and Immunogenicity”
Basis of inactivated Potency Specifications

- Exceptions for potency tests in animals, e.g. leptospiroisis vaccines
  - Potency test is not quantitative, various approaches, usually:
    - If all time points, more important the latest ones, are satisfactory the product is stable.
    - Acceptance was observed when some non-compliant results were obtained randomly at intermediate time points

<table>
<thead>
<tr>
<th>Months</th>
<th>Serovar Icterohaemorrhagiae</th>
<th>Serovar Canicola</th>
</tr>
</thead>
<tbody>
<tr>
<td>~T=0</td>
<td>10/10 Satisfactory</td>
<td>10/10 Satisfactory</td>
</tr>
<tr>
<td>~T=12</td>
<td>8/10 Satisfactory</td>
<td>10/10 Satisfactory</td>
</tr>
<tr>
<td>~T=18</td>
<td>10/10 Satisfactory</td>
<td>9/10 Satisfactory</td>
</tr>
<tr>
<td>~T=24</td>
<td>7/10 Unsatisfactory</td>
<td>8/10 Satisfactory</td>
</tr>
<tr>
<td>~T=27</td>
<td>8/10 Satisfactory</td>
<td>8/10 Satisfactory</td>
</tr>
</tbody>
</table>
Conclusions

• **Stability assessment**
  - Is part of normal requirements (test protocol design)
  - Allows knowledge of product during storage
  - No prescribed/pre-defined approach for assessment
  - Contains at least 3-months as safety margin

• **Specifications**
  - Ensure a safe and efficacious product throughout shelf life
  - Use stability data for needed adjustment
  - Ensure consistency with developed product (not less than ...) and during production
Thank You!

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