Evolution of Veterinary Vaccines – An Industry Perspective on Consistency

September 2015
Introduction

• The world of veterinary vaccines has changed significantly over the years:
Introduction

• Industry’s approach to veterinary vaccine development has evolved significantly in concert with this change.

• This “evolution” has been driven by a number of factors:
  – Globalization of disease risks and needed responses.
  – Better understanding of disease control needs/objectives.
  – Better diagnostic capabilities and understanding of incidence.
  – Greater clarity regarding pathogenesis/virulence factors.
  – Higher customer expectations for vaccine efficacy and safety.
  – Recognition of “benefit/risk” approach to vaccine approval.
  – Evolving global regulatory environment and increasing Authority expectations.
Introduction

• Veterinary vaccine manufacturing, testing, and quality assurance has also evolved during this timeframe.
• This evolution has been driven by a different set of factors:
  – Need to better industrialize processes to meet global needs.
  – Need to adapt processes to meet economic/regulatory realities.
  – Need to better understand processes to define “control points”.
  – Need to qualify processes to demonstrate quality/consistency.
  – Need to test final products to confirm proper production.
  – Need to review the batch “package” to confirm “release-ability”.
  – Need to monitor product performance in the field to reconfirm benefit/risk and “fine tune” product information.
Gaining a Balance Between Development and Manufacturing

**Development Drivers**
- Pursue unmet medical needs.
- Allow product differentiation.
- Justify favourable “benefit-risk”.
- Develop with “speed to market” approach.
- Provide range of solutions to meet individual customer needs.

**Manufacturing Drivers**
- Rugged processes.
- Compatible technologies/assets.
- Predictable processes/costs.
- Process scale-up/yield improvements.
- Easily introduce new technology.
- Flexible process definitions.
Applications of Consistency

• Consistency Principles most-often linked with:
  – Reduction in use of animals for product testing/release.
  – Efforts to improve batch consistency and avoid scrap.

• To be truly transforming, we need to use the consistency approach also drive and reward vaccine evolution/revolution:
  – Improve batch-related root-cause investigations/resolutions.
  – Support continuous improvement initiatives/approvals.
  – Facilitate starting material assessments and replacements.
  – Adjust/optimise antigen production parameters.
  – Confirm proper finished product assembly/blending.

• Share two examples where in-process understanding and consistency concepts offers multiple benefits.
Applications of Consistency

• Adjustment of Antigen Production Parameters:
  – Better control over antigen production is critical to control product performance in terms of quality, efficacy, safety.
  – Improved technology and analytical methods take some of the “mystery” out of antigen manufacturing.
  – Proper process monitoring and data analysis help establish process understanding and support efficient change management:
    • Improved control of cell growth and “target antigen” expression.
    • Improved control over “chemical” processes such as inactivation reactions, conjugation reactions, etc.
Applications of Consistency

• Example - Conjugation Kinetics/Endpoints:
  – Conjugation reactions use reactions that are stoichiometric in nature, but are influenced by a number of inter-related factors:
    • Batch-to-batch variability of carrier and hapten molecules.
    • Molar excesses of key chemicals used in conjugation reaction.
    • Reaction conditions used during process (temperature, pH, etc.)
  – Variability in conjugation efficiency raises questions regarding “potency” and often drives development of immunological methods for product release.
  – Proper process control and data collection allows a manufacturer to fine-tune process using control points within the “potent” range and transition away from variable conjugates (and animal testing).
Applications of Consistency

Conjugation Kinetics/Endpoints:
– Understanding the Chemistry:

Carrier + Hapten → Conjugate
Applications of Consistency

Conjugation Kinetics/Endpoints:
– Understanding the Impact on Immunogenicity:

![Graph showing the effect of conjugation efficiency on immunogenicity. The x-axis represents conjugation efficiency, and the y-axis represents Log2 GMT (U/ml). The graph includes lines for alternate animal potency, batch potency - target animal, and target animal threshold.](image-url)
Applications of Consistency

Conjugation Kinetics/Endpoints:
– Understanding the Process:

<table>
<thead>
<tr>
<th>Conjugate Batch Number</th>
<th>Conjugation Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.2</td>
</tr>
<tr>
<td>2</td>
<td>7.6</td>
</tr>
<tr>
<td>3</td>
<td>7.2</td>
</tr>
<tr>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
</tr>
<tr>
<td>6</td>
<td>8.2</td>
</tr>
<tr>
<td>7</td>
<td>7.0</td>
</tr>
<tr>
<td>8</td>
<td>8.2</td>
</tr>
<tr>
<td>9</td>
<td>7.4</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
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<td>11</td>
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<td>12</td>
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<td>20</td>
<td>8.4</td>
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<tr>
<td>21</td>
<td>7.5</td>
</tr>
<tr>
<td>22</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Average (n=22)</strong></td>
<td><strong>7.9</strong></td>
</tr>
</tbody>
</table>
Applications of Consistency

Conjugation Kinetics/Endpoints:

– Understanding the Impact on Batch Release:

– Range then allows further process improvements over time and justifies more-timely variation assessment and approval.
Applications of Consistency

• Finished Product Formulation Process:
  – Better control over component addition/blending is critical to product performance in terms of quality, efficacy, safety.
  – Especially important for newer “complex” formulations:
    • Products containing closely-related organisms (e.g. HPS serovars, IBV strains, etc.).
    • Products containing multiple, interacting adjuvant components.
  – Process monitoring and data analysis help support batch release without need to routinely test complex final product:
    • Reduces the complexity of final product analytical method development.
    • Reduces the complexity of final product specifications and release.
Applications of Consistency

• Example – Final Formulation Blending:
  – Influenced by a number of inter-related factors:
    – Nature of formulation and energy input needs.
    – Mechanical issues (i.e. capabilities/capacity of equipment).
    – Formulation issues (i.e. blend-ability of components).
    – Conditions used during process (temperature, pH, etc.)
  – Variability in blending efficiency raises questions regarding proper assembly and can drive development of immunological methods for product release.
  – Proper process understanding and demonstration of “consistency” allow a manufacturer to fine-tune process, demonstrate control points within the “proper” range and transition away from variable formulations and excessive finished product testing.
Applications of Consistency

Blending Endpoints:
– Understanding the Assembly/Blending Process:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Addition and dissolution of Component A in WFI</td>
</tr>
<tr>
<td>2</td>
<td>Mixing for x minutes to ensure complete dissolution</td>
</tr>
<tr>
<td>3</td>
<td>pH adjustment from y to z</td>
</tr>
<tr>
<td>4</td>
<td>Mixing for x minutes after pH adjustment</td>
</tr>
<tr>
<td>5</td>
<td>Dilution with antigen and WFI up to final volume</td>
</tr>
<tr>
<td>6</td>
<td>Mixing for x minutes to ensure homogeneity</td>
</tr>
</tbody>
</table>
Applications of Consistency

Blending Endpoints:
– Understanding the impact:

Formulation Profile Over Time
Applications of Consistency

Blending Endpoints:

– Understanding the Impact on Batch Release:

– Demonstration of consistent formulation using in-process tools removes long-term need for finished product testing.
Conclusion

• There have been many key advances in the veterinary vaccine quality movement:
  – Use of “designed for purpose” facilities and equipment (GMP).
  – Implementation of master seed/master cell stock principles.
  – Qualification of starting material quality/purity/consistency.
  – Control of organism growth (and “active ingredient” expression).
  – Understand antigen input (versus “titer before inactivation”).
  – Improved batch blending, processing, and filling.
  – Increased demand on test development and validation.
  – Recognition of animal test drawbacks:
    • Animal welfare concerns.
    • Test reliability and impact on product performance.
• We must continue to evolve to meet the demands of the globe.
Conclusions

• Driving “consistency” philosophy (from an industry perspective):
  – Ensure commercial batches are comparable to clinical materials demonstrated as safe and effective.
  – Allow development programs to focus on “areas of technical risk”.
  – Improve availability of process analytical tools that offer the ability to design consistent processes versus “test into compliance”.
  – Utilise GMP trend analyses and post-marketing surveillance as additional tools to “fine-tune process/product information.
  – Ensure lessons learned from one development program extend to subsequent programs (and reduce development burden).
“Nothing endures but change”
QUESTIONS?