A-VAX: Applying Quality by Design to Vaccines

Timothy Schofield
MedImmune (representing VWG)
CASSS Bay Area Discussion Group
San Francisco, CA
June 11, 2015
Some vaccines realities

- **Prophylactic use in healthy populations, mostly children**
  - High level of emphasis on quality
  - Concerns about vaccines safety

- **Vaccines shortages**
  - Robust manufacturing

- **Immense worldwide public health impact**
  - Demand and cost

- **Much lower profit margin compared to small and large molecules**
  - Efficient development and ROI

- **Vaccine development has been happening for 100+ years**
  - Tolerance to changing paradigms

- **Analytical opportunities more scarce than other molecules**
  - “The process is the product”

- **Vaccines are typically less stable than drugs and large molecules**
  - Importance of formulation and control strategy
What do vaccines need?

Better understanding

Break old paradigms – modernize development

Reliable supply to meet public health need

Benefit to public health – “herd effect”
CMC-VWG: Background
Why Group Was Formed

Over 70 people in five companies contributed to the Case Study, during the course of more than a year.

Goal #1

- Establish a **common platform** that can be used to stimulate discussion related to…
  - Risk-based approaches to vaccine development
  - Leveraging science to gain process understanding
  - Continual improvement
  - Strategic control of vaccine manufacturing

  ...**between industry and regulatory agencies** (FDA, EMA, PMDA, Health Canada, etc.)

**Potential Benefit:**
Understand QbD and Its Application

- Define a **vision that will help promote the concepts** and benefits of QbD
- **Expedite development and regulatory review**

Goal #2

- Develop **realistic examples** (that challenge traditional thinking) to better illustrate how QbD can be applied within the development space and overall Product Quality System
- **Highlight and/or develop tools, frameworks**, etc., to enable ICH Q8, Q9, Q10, & Q11 implementation strategies
- **Link key benefits with the strategies illustrated** within the case study

**Potential Benefit:**
Highlight Value

- **Better understanding of product, process**, and different implementation tools and approaches to consider
- **Robust and consistent processes** with clear understanding of impact of future process changes
- **Cost/Benefit analysis framework** to help further promote QbD to senior management
A-VAX innovations

• The A-VAX case study built upon the principles illustrated in A-Mab, together with some innovations

• Innovations included:
  ▪ The importance of potency as a measure of vaccine quality
  ▪ The use of manufacturing modeling to inform clinical development
  ▪ A chapter on implementation (ROI) as a tool to justify the value of QbD in vaccine development
Case Study Outline

I. Introduction

II. TPP / CQA / Risk Assessment

III. Control Strategy

IV. Process Development
   I. Introduction & Overview
   II. Upstream
   III. Downstream
   IV. Drug Product

V. Regulatory

VI. Implementation
TPP/CQA / Risk Assessment

• **Goals:**
  - Set up model vaccine product for case study
  - Establish a Target Product Profile based on clinical and commercial requirements, and process/product knowledge
  - Use a risk tool to identify and triage Critical Quality Attributes that reflect production of a vaccine, consistently delivering the Target Product Profile and desired immunogenic effect
TPP / CQA / Risk Assessment

Objectives & Overview

• Premise is that QbD can be used for vaccines on the basis of scientific & technical understanding of the product & process
  ▪ Applicable to most vaccines
  ▪ Leverage prior knowledge to assess QAs
  ▪ Emphasized the Risk ‘Tool’

• Demonstrate how perceived challenges to using QbD to develop vaccines can be overcome
  ▪ Criticality is a continuum (relevant control strategy has been included)
  ▪ Process Performance vs. Clinical Performance
  ▪ Vaccine science is less ‘mature’ than for mAbs

• Disease definition and MOA
  ▪ Infection with the fictional bacteria *X. horrificus* causes the rapid-onset, short-lived illness cooties, and generally occurs in children & young people
  ▪ *X. horrificus* anticapsular polysaccharide (Ps) antibody levels correlate with significantly reduced incidence of invasive *X. horrificus* infections
Severity = Impact × Uncertainty

‘Iterative triage’ means to adjust scoring as new information is learned (provide rationale)

‘Iterative triage’ of all CQAs, with particular scrutiny around QAs with scores near the cut-off

Includes severity scores for key process ‘intermediates’ (Ps & VLP), DS (Ps-VLPs) & DP (formulated Ps-VLPs)
TPP / CQA / Risk Assessment
A-VAX Profile & Key Assumptions

• A-VAX is a pentavalent vaccine containing the capsular Ps of *X. horrificus* serotypes 1, 2, 3, 4 & 5 individually linked to a recombinant, non-infectious virus-like particle (VLP), and adjuvanted with an aluminum salt
  - 3 doses (containing 5 mcg each of Ps 1-4 & 50 mcg Ps 5; adsorbed to 300 mcg aluminum adjuvant as Ps-VLPs) administered via pediatric vaccine schedule
  - Assume clinical program has finished Phase 2

• Complex multi-component process

\[
\begin{align*}
X. \text{ horrificus } \text{serotype} & \rightarrow \text{bacterial fermentation of Ps’s} \\
E. \text{ coli} & \rightarrow \text{recombinant VLP (20- to 50-nm particles)} \\
\text{Ps}_{15} & \rightarrow *\text{Ps}_{15} + \text{VLP} \rightarrow \text{Ps-VLP (multi-site conjugation chemistry)} \\
\text{Ps-VLP conjugates purified (DS) & alum formulated (DP)}
\end{align*}
\]

• Levels of free VLP, free Ps & extent of conjugation must be controlled
  - Free (unconjugated) Ps do not illicit an immune response
  - VLP alone can interfere with the immune response generated by the Ps-VLP conjugate
Reclassification of Quality Attributes

New knowledge gained through lifecycle may result in reclassification of quality attributes (in either direction) and subsequent modification to process control strategy

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Test Method</th>
<th>Impact</th>
<th>Uncertainty</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Risk Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completeness of Adsorption to Al</td>
<td>mAb-based ELISA (adsorbed)</td>
<td>25</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>Post Phase 1 Risk Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completeness of Adsorption to Al</td>
<td>mAb-based ELISA (adsorbed)</td>
<td>25</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>Post Phase 3 / Registration Risk Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completeness of Adsorption to Al</td>
<td>mAb-based ELISA (adsorbed)</td>
<td>8</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Risk Analysis Category</th>
<th>Process Component</th>
<th>Serotype</th>
<th>Test</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Potential CQA</td>
<td>DP</td>
<td>All</td>
<td>Release</td>
<td>&gt;80% based on literature</td>
</tr>
<tr>
<td>Post P1</td>
<td>CQA</td>
<td>DP</td>
<td>All, Type 4 Worst Case</td>
<td>Release Characterization</td>
<td>&gt;80% based on literature and no trends associated with clinical experience from 85-99%</td>
</tr>
<tr>
<td>Licensure</td>
<td>Less Critical QA</td>
<td>DP</td>
<td>All</td>
<td>Process Monitoring Characterization</td>
<td>In-House Control Limits based on Process Capability</td>
</tr>
</tbody>
</table>
CQA and Control Strategy 'Decision Tree'

Attribute

Prior Knowledge

Not Relevant

Performance Attribute

Key Performance Attribute

No Monitoring or In-House Monitoring

+Info

Development Experience

Severity

Critical Quality Attribute

Release Specification

Less Critical Quality Attribute

No Release Specification

No Monitoring or In-House Monitoring

CMC-VWG
Control Strategy

Goals:

• Propose a scientific approach based on product and process knowledge to provide quality to the vaccinee

• Ensure production of a vaccine with good process capability and therefore continuous supply to the customer
Scientific approach to a control strategy

- **Iterative scientific and risk-based approaches to establishing**
  - Final CQAs
  - Final process performance attributes and CPPs
  - Analytical and process control strategies developed considering prior knowledge, compendia, in vivo models, clinical experience, and process capability

- **Modeling and simulation**
  - Design Space determined from intersection of the process model and process requirements (specifications)
  - Mathematical modeling used together with simulations to determine predictive probabilities of meeting specifications
  - Manufacturing modeling to inform clinical development
Scientific approach to analytical control strategy

Given the complexity of A-VAX, potency is an important marker of clinical effectiveness

A vision for analytical control helps inform product and clinical development

- Scientifically justified minimum and maximum requirements
- Release limits determined to ensure that potency meets its requirements throughout shelf-life
- Alert limits and associated rules to monitor and manage manufacture
Scientific approach to analytical control strategy

- **The predicted potency range (max to min)** is calculated to guide manufacture of clinical lots to be used in Phase III clinical studies
  - Using stability, potency assay variability, variability from a model vaccine and a process capability index to dial in a desired P(OOS)
  - P(OOS) set small to account for multiplicity of testing 5 serotypes

- **The clinical lots were manufactured (diluted) from a common conjugated DS bulk to preserve the planned range in potencies**
  - Dilution preserves the potency range required for appropriate commercial process capability

- **An enhanced potency assay design and analysis was utilized to ensure an accurate assessment of the clinical materials**
  - Batches tested together with a suitable number of replicates to minimize uncertainty

\[
P(OOS_{overall}) = 1 - (1 - 0.01)^5 = 0.05
\]
Comparison of approaches to achieve the minimum requirement at end of shelf-life

- **Dilution to minimum dose**
  - Pro – easy to target
  - Con – not representative of “degraded” product

- **Aged at labeled storage temperature**
  - Pro – representative of aged vaccine
  - Cons – difficult to target and/or long time to achieve desired expiry potency

- **Accelerated aging to target**
  - Pro – able to target within a feasible time
  - Con – accelerated aging may be non-representative of naturally degraded vaccine
Accelerated aging facilitates targeting and yields a precise estimate of potency

- Use interim accelerated stability data to forecast “pull time”

- Stability data can be combined with release data to obtain a more precise estimate of potency of the aged material (with confidence)
Stability data for a clinical lot can be used to estimate potencies that subjects received

- Vaccine potency decreases over the course of a clinical study
- The release potency of a clinical lot is not what subjects received
- Statistical modeling of clinical stability data can be used to estimate potencies that individual subjects received
- The individual potencies can be used to model the clinical kinetics

... and thereby the minimum potency requirement
Process Development

INTRODUCTION AND OVERVIEW
UPSTREAM PROCESS “DRILL DOWN”
DOWNSTREAM PROCESS “DRILL DOWN”
DRUG PRODUCT “DRILL DOWN”
Introduction

• The Process Development section of the case study was divided into Upstream, Downstream and Drug Product sections to help illustrate how QbD could be applied across all operations

• Among these sections the teams were able to illustrate a number of concepts including
  - **Prior Knowledge**: Use of prior knowledge to justify key development and post-licensure decisions
  - **Risk Assessment**: Identify steps and parameters that will be examined closely during development
  - **Design Space**: Use of Multivariate models to define the design space and demonstrate process understanding
  - **Scale-Up**: Use of models to verify applicability of scale down results
  - **Continuous Improvement**: Based on continuous process verification and movement within design space to enhance process performance and understanding
Upstream Team Explored the Fermentations Expressing the Polysaccharide and Virus-Like Particle

<table>
<thead>
<tr>
<th>Unit Operations To Be Explored</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial seed expansion, fermentation, inactivation (PS)</td>
<td>Demonstrate interactions between upstream parameters and polysaccharide structural attributes</td>
</tr>
<tr>
<td>Ecoli fermentation, harvest (VLP)</td>
<td>Impact of process on VLP aggregation and/or downstream process performance</td>
</tr>
</tbody>
</table>

**Bacterial fermentation risk assessment**

**Polysaccharide**
- Cell Thawing: Cell Bank
- Cell Expansion: Shake Flask
- Multiple Shake Flasks
- Seed Bioreactor
- Production Bioreactor
- Phenol Inactivation

**To purification**
Downstream Team Explored the Polysaccharide Extraction and PS-VLP Conjugation Steps

<table>
<thead>
<tr>
<th>Unit Operations To Be Explored</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide Extraction</td>
<td>Prior knowledge, use of biologic raw material, requires additional processing to determine outcome</td>
</tr>
<tr>
<td>VLP Freezing</td>
<td>Impacting VLP aggregation</td>
</tr>
<tr>
<td>PS-VLP conjugation</td>
<td>Important step, determines drug substance properties</td>
</tr>
</tbody>
</table>

**Polysaccharide**

*From fermentation*

- Extraction (enzymatic)
- Depth Filtration
- Precipitation
- AEX Column
- UF/DF
- Drying / Freezing
- Bulk PS

*Design space*

- Simulations from DOE showing proportion of results meeting specifications
- Simulated design space (green) is significantly larger than tabulated design space (rectangles)
Site to Site Change Proposed

Post Licensure Change

• Goal:
  - To achieve successful site-to-site transfer of lyophilized product utilizing prior knowledge and design space understanding

• How Achieved
  - Compared Equipment Design Specifications and Performance
  - Compare design space of the two lyophilization cabinets at the respective sites
  - Developed a comparability protocol to determine the expected level of process and regulatory requirements
Regulatory
Regulatory

• **Goals:**
  - Explore the application of QbD concepts to the content of regulatory filings
  - Review the strategies offered in the other sections of the case study & give guidance on how best to illustrate these strategies in various types of regulatory filings

• **Key highlights:**
  - Hybrid filings
  - Prior knowledge
Regulatory Key Highlights - Hybrid filings

• Industry likely to implement QbD for vaccines on certain process steps; it is rarely possible to explore every process step applying an enhanced development approach.
  - Targeted QbD application
  - Hybrid regulatory filings

• Implementation of QbD for vaccines may focus on areas where the enhanced approach might provide additional process knowledge that could be useful over the product lifecycle in view of anticipated post-licensure changes; eg equipment changes, raw mat changes, process changes (scale-up), site changes …

• Hybrid submissions are a natural extension of current practice
Prior Knowledge

• Use of prior knowledge is presented throughout the case study.
  - e.g., replacement of an enzyme purified from bacterium with a recombinant source.

The extraction and clarification steps are performed at reference conditions and at the eight extremes of the bacterium design space with the new enzyme.

The responses meet the acceptance criteria: Extraction yields are in the ranges from the DOE performed on the original source, and all the extracts are filterable.
Implementation
Considerations for QbD Implementation

• Current barriers to QbD are perceived costs and the uncertain regulatory response versus the Traditional Approach

• When dealing with uncertainty, the best strategy is to build knowledge and utilize that knowledge to communicate a clear proposal
  – Gather relevant data
  – Develop Information
  – Evaluate risk based on the information
  – Engage/don’t engage in QbD approaches according to risk/benefit

• In addition industry should communicate frequently with the agency to reach a common understanding of QbD content appropriate to achieve the desired goals
Implementation

• **Goals:**
  - Present potential value drivers and evaluation tools to communicate a business case for application of the Enhanced Approach
  - Demonstrate that a risk-based application of the Enhanced Approach to vaccine process development can *reduce investment over the product lifecycle* and *improve the probability of success* before substantial resource investments have been made
  - Stakeholders are the manufacturer, regulatory authorities and customers

• **Risk/benefit approach:**
  - Defined in terms of the organization’s “Ability to Predict”:
    - Safety & Effectiveness
    - Availability (Robustness)
    - Cost Effectiveness
Implementation Return on Investment (ROI) Metrics

ROI factor is **Greater** than 1
- Increasing Benefit
- Enhanced Approach Supported

ROI factor is **Equal** to 1
- Likely to Break Even for Enhanced Approach
- Benefit and Costs Balance

ROI factor is **Less** Than 1
- Complexity & Cost does not provide additional value from the Enhanced Approach
- Consider alternative control strategies

<table>
<thead>
<tr>
<th>Benefit Factor</th>
<th>25</th>
<th>20</th>
<th>15</th>
<th>10</th>
<th>5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation Factor</td>
<td>5</td>
<td>2.5</td>
<td>2</td>
<td>1.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.67</td>
<td>1.33</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>0.75</td>
<td>0.75</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.67</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.67</td>
<td>0.25</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Increasing Cost and Implementation Difficulty
Next Steps

• Case study currently published on the ISPE website (www.ispe.org)

• Opportunity for further detailed discussions and workshops

• Realization of QbD paradigms in submissions is dependent upon:
  - Complexity of vaccine
  - Agency acceptance of approaches to manufacturing flexibility
# CMC-VWG Participants

<table>
<thead>
<tr>
<th>GSK</th>
<th>MedImmune</th>
<th>Merck</th>
<th>Pfizer</th>
<th>Sanofi Pasteur</th>
<th>Facilitators (PwC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annick Vandercammen</td>
<td>Nancy Cauwenberghs</td>
<td>Bob Ferris</td>
<td>Beth Junker</td>
<td>Amit Banerjee</td>
<td>Carole Ghiglieri</td>
</tr>
<tr>
<td>Vivian La Bras</td>
<td>Ouzama Nicholson</td>
<td>Harry Yang</td>
<td>Dave Maraldo</td>
<td>Basav Ghosh</td>
<td>Christian Klock</td>
</tr>
<tr>
<td>Benoit Champluvier</td>
<td></td>
<td>John Finkbohner</td>
<td>Dicky Abraham</td>
<td>Greg Steeno</td>
<td>Dave Jaipersad</td>
</tr>
<tr>
<td>Benoit Slegers</td>
<td>Roland Mainil</td>
<td>Jonathan Liu</td>
<td>Jeff Blue</td>
<td>Lakshmi Khandke</td>
<td>Earl Zablackis</td>
</tr>
<tr>
<td>Catherine Vigano-Wolff</td>
<td>Sandrine Dessoy</td>
<td>Mark Schenerman</td>
<td>Jim Warren</td>
<td>Leslie Bloom</td>
<td>Guillermo Albanesi</td>
</tr>
<tr>
<td>Cecile Ponsar</td>
<td>Tim Schofield (ex-GSK; now with MedImmune)</td>
<td>Mark Thompson</td>
<td>Joseph Schaller</td>
<td>Lynn Phelan</td>
<td>Pierre Chouven</td>
</tr>
<tr>
<td>David Le-Tallec</td>
<td>Michael Washabaugh</td>
<td>Mark Mikola</td>
<td>Mark Ruppen</td>
<td>Randy Halstead</td>
<td></td>
</tr>
<tr>
<td>Gabriel Caliaro</td>
<td>Ranjit Deshmukh</td>
<td>Mary Retzlaff</td>
<td>Paul Rohlfing</td>
<td>Regis Gervier</td>
<td></td>
</tr>
<tr>
<td>Jean-Francois Chaubard</td>
<td></td>
<td>Mike Kosinski</td>
<td>Robert Repetto</td>
<td>Velupillai Puvanesarajah</td>
<td></td>
</tr>
<tr>
<td>Linda Kramer</td>
<td></td>
<td>Nilesh Mehta</td>
<td>Roberto Rodriguez</td>
<td>Victor Awafo</td>
<td></td>
</tr>
<tr>
<td>Marie Parker</td>
<td></td>
<td>Rachel Thornton</td>
<td>Sandeep Nema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael Schwartz</td>
<td></td>
<td></td>
<td>Robert Sitrin</td>
<td>Tara Lorenz</td>
<td></td>
</tr>
</tbody>
</table>
Thank you!

Questions?