An integrated, science and risk based approach to the development and control of Biotechnology Drug Product

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Where were we in the good old days……

• Setting specifications
  • If you can detect it, you will test it on lot release
  • Your limits will be what you have exposed patients to in the clinic

• Methods

• Risk Management
  • What’s that?

• Container
Where are we now?

- **Setting specifications**
  - Using Quality by Design - Target Product Profiles through lifecycle management
  - Understanding the criticality of quality attributes – setting limits based on risk and process capability

- **Methods**
  - Risk Management
    - Everywhere!

- **Container**
Control strategy integrates all aspects of process and product controls

Input controls (raw materials and components)

In-process testing (IPCs, process monitoring, validation)

Production Process

Procedural controls (facility, equipment and operational controls)

End product testing (specifications, comparability, stability)

Control elements are well coordinated and integrated in effective control strategies
Creating an Effective control strategy links product and process understanding

Product Understanding
- Safety and Efficacy Data
- Criticality Assessment
  - High Criticality Attributes: Quality attribute that must be considered in the overall control strategy
  - Acceptable ranges for quality attributes to ensure drug safety and efficacy
  - Attribute that may not need to be considered in the overall control strategy

Risk based control strategy ensures achievement of CQAs

Process Understanding
- Unit Operation and Operating Parameter Risk Assessment
  - Raw Material Risk Assessment
  - Process Characterization and Unit Operation Design Space
  - QbD Control Strategy Assessment

Control Strategy
- Raw Materials
- Process Controls
- Procedural Controls
- Operating Ranges
- Process Qualification
- Testing
- In process
- Specifications
- Characterization and Comparability
- Stability
- Continuous Process Verification (Commercial Scale)

Note: Figure modified from CMC BWG Case Study
We want to Focus on the End User

By beginning with the end in mind, the result of development should be robust manufacturing drug substance and drug product processes with acceptable control strategies that ensure the performance of the drug product with positive patients’ experiences.
Desired Patient and Clinical Profiles are Captured by the Target Product Profile (TPP)

Potential Elements of a TPP:

- Indication and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Clinical Studies
- Over Dosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- How Supplied/Storage and Handling
- Patient Counselling Information
With Patient Focus The Product should Define the Process

1) Molecule Selections

2) Designs for DS Process, DP Process and Product Presentation

** Patient Profile: TPP **

** DS Process:**
- Cell Bank
- Cell Culture
- Harvest
- Purification
- UF/DF
- Drug Substance

** DP Process:**
- Filtered Formulated Bulk at 20 mg/mL
- 0.22 μm PVDF Filter
- Time Pressure Filling and Stopping
- 20cc or 5cc DP filled vials with stoppers
- Cold Storage at 2-8°C and Transfer

Ensure Molecule Candidate can be formulated to fit Presentations that will meet the TPP
QbD is at its Most Powerful During Molecular Design – Getting it Right From the Start Offers the Biggest Opportunity for Obtaining Desired Drug Product

Sequence binning used to identify antibodies with diversity and desirable attributes

Expression Assessment to achieve high productivity

Viscosity testing for ease of SC delivery at high concentration
# Using Data Establishes the Building Blocks: PQAA, QTPP and Associated Process

## Identifying Attributes

<table>
<thead>
<tr>
<th>Indication and Use</th>
<th>CDR modifications</th>
<th>Oxidation, Deamidation, Isomerization (molecule specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage and Administration</td>
<td>Fc binding regions</td>
<td>Methionine oxidation</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Glycan structure</td>
<td>High mannose variants (IgG class)</td>
</tr>
<tr>
<td>Dosage Forms and Strengths</td>
<td>Fucose modifications (IgG1)</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Other backbone modifications and aggregated forms</td>
<td>Disulfide variants (IgG2, IgG4)</td>
</tr>
<tr>
<td>Safety/Side Effects</td>
<td>Truncated/clipped forms</td>
<td></td>
</tr>
<tr>
<td>Value and Access</td>
<td>Aggregated forms</td>
<td></td>
</tr>
</tbody>
</table>

## Scoring Impact

<table>
<thead>
<tr>
<th>Safety and Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of potency</td>
</tr>
<tr>
<td>• PK and efficacy</td>
</tr>
<tr>
<td>• Efficacy due to ADCC</td>
</tr>
<tr>
<td>• Potency</td>
</tr>
<tr>
<td>• Potency and PK due to missing functional regions</td>
</tr>
<tr>
<td>• Potency and Immunogenicity</td>
</tr>
</tbody>
</table>

## Target Range Levels

| • Low, < 5 % |
| • Low, < 10 % ± 3 % |
| • Low, < 2 % |
| • Depends on criticality |
| • Low, < 2 % |

## QTPP Building Blocks for Developing Processes:

- API
- Exipients
- Container
- Device

## Attribute Focused Process Development
Assessing Product Quality Attributes – the PQAA

- **Purity: product-related**
  - Aggregates
  - CDR Trp
  - C-term lys
  - Deamidation
  - Dimers
  - Fragmentation
  - Free –SH, Cys adducts
  - Glycation
  - HC C-term proline amidation
  - Hydroxyls
  - IgG2 Disulfide Isoforms
  - Met Ox
  - Mutation Misincorp
  - N-term Pyro Glu
  - N-term signal seq variants
  - Stability degradants
  - Thioether
  - Translated Intron
  - Trisulfide

- **Glycosylation**
  - Fucosylation
  - Galactosylation
  - High Mannose
  - Non-consensus Glycosylation
  - Non-glycos HC
  - O-linked glycans
  - Sialic Acid
  - Unusual Fc Glycans

- **Purity: process-related**
  - CHOP
  - Process Reagents
  - Residual host cell DNA
  - Residual Pr A

- **Obligatory properties (General)**
  - Appearance
  - Bioburden
  - Clarity
  - Color
  - Container Volume
  - Endotoxins
  - Excipient Conc
  - HMF/F (lyo only)
  - Osmolality
  - pH
  - Product Conc
  - Sterility
  - Sub-vis particles
  - Vis particles
  - Water (lyo only)

Knowledge is used to guide PQAA process
Product quality risk assessment (PQRA) evaluates overall risk to patient

- Product Quality Risk Assessment
  - Considers all known Product Quality Attributes
  - Includes all steps leading up to administration to the patient

- Risk assessment inputs:
  - Comprehensive understanding of quality attributes [Severity]
  - Understanding of process impact on quality attributes [Occurrence]
  - Testing strategy/method capability [Detection]

\[
\text{Overall Risk} = f(\text{PQA Criticality}, \text{Process Capability}, \text{Testing Strategy})
\]

QbD control strategies focus on risk based control of Product Quality Attributes
Understanding Attributes Whose Levels Change in vivo is the Basis for a Rational Control Strategy

- Deamidation/isomerization Liu et al. *Biologics* 37, 313-322 (2009)
- Trisulfide loss (unpublished)
- Methionine oxidation (unpublished)
Fill-Finish/ Aseptic Process Overview

<table>
<thead>
<tr>
<th>Process Step</th>
<th>DS Thaw</th>
<th>Transfer &amp; Blend</th>
<th>Filtration</th>
<th>Filling</th>
<th>Stoppering</th>
<th>Visual Inspection</th>
</tr>
</thead>
</table>

- **De-bagging**
- **E-beam**
- **De-lid/De-liner**
- **Filling**
- **Fill-Weight Checks**
- **Stoppering**

- **Formulation**
- **Primary Container**
- **Device**
- **Secondary Packaging & Labeling**

Integrated Product Design and Process Development
Parenteral Product Development: A Case for Integrated Process Design

Syringe tub properties
- Dimensions
- Delidding and debagging of tubs
- Mechanical handling: Interactions with robotics
- E-beam decontamination: Shape may impact penetration; Ozone creation may impact PQ

Syringe nest properties
- Dimensions
- Mechanical Handling/Machinability
- Warpage → Stopper position

Syringes in 10x10 nested format

**Fill volume**
- Label Claim
- Fill technology
- Process controls
- Air gap/plunger depth
- Device integration

**Tungsten**
- Levels
- Aggregation

**Si Oil**
- Level & uniformity
- Sub vis-particles
- Aggregation
- Glide force

**Needle shield**
- Leachables
- CCI
- RNS vs nRNS
- Device integration

**Syringe Barrel**
- Glass quality
- Breakage
- Geometry
- Glide force
- Label/ink migration
- Device integration

**Syringe stopper**
- Leachables
- CCI
- Particles
- Device integration

**Plunger depth/Air gap**
- Air Gap - transport, cavitation
- Stopping technology
- Device Integration
- Process controls

**Plunger rod**
- End use
- Differentiation

**Formulation**
- Protein concentration
- Viscosity
- Extrusion force
- Device integration

**Adhesive**
- Leachables
- CCI

**Manufacturing**
- Clinical and commercial mfg. sites drives implementation of the mfg. process and associated control strategy

*Clinical and commercial mfg. sites drives implementation of the mfg. process and associated control strategy

**Parenteral Product Development: A Case for Integrated Process Design**
High concentration formulations offer several benefits and Illustrate one of Several Drug Product Critical Attributes - Viscosity

- Address higher dosage requirements
- Allow for lower injection volumes
  - Subcutaneous delivery through pre-filled syringe
  - Patient’s preference for fewer injections
- Lower cost of goods
  - Reduced shipping and storage costs

- However, high concentration products also present several challenges
  - Formulation stability
  - Analytical considerations
  - Manufacturability: processing, yield, product quality
  - Product delivery
Product viscosity is a key challenge resulting from increased protein concentration

- Product viscosity should be thoroughly characterized \textit{wrt.} Temperature (T), Concentration (C) and pH
- Allowed variations in T, C and pH may contribute to significant variations in viscosity \Rightarrow Process impact

\begin{itemize}
  \item \textbf{mAb1 in buffer C}
  \begin{itemize}
  \item T = 2\textdegree{}C
  \item T = 10\textdegree{}C
  \item T = 25\textdegree{}C
  \end{itemize}

  \begin{itemize}
  \item mAb 1 @ 140 mg/mL in different buffer formulations: A, B, C, D and E
  \end{itemize}
\end{itemize}
High concentration is challenging to both process and product

- High viscosity could be a challenge for process steps (e.g. filtration, fill) and delivery
  - Shear and contact surfaces / interfaces could also impact product quality
- Increased propensity for self-association could impact product quality

**Drug product process & handling steps**
Concentration gradients created during freeze-thaw could destabilize product

Extent of gradient formation is scale specific

<table>
<thead>
<tr>
<th>Top</th>
<th>Protein Conc.</th>
<th>Excipient</th>
<th>Osmo (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95 mg/mL (-40%)</td>
<td></td>
<td>190</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Bottom</th>
<th>Protein Conc.</th>
<th>Osmo (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg/mL (+40%)</td>
<td>520</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Top</th>
<th>Protein Conc.</th>
<th>Osmo (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~80 mg/mL</td>
<td>~160</td>
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</table>

<table>
<thead>
<tr>
<th>Bottom</th>
<th>Protein Conc.</th>
<th>Osmo (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~220 mg/mL</td>
<td>~600</td>
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</table>
Destabilization during freeze-thaw could result in higher sub visible particle count

<table>
<thead>
<tr>
<th>Formulation</th>
<th>HIAC count (cumulative/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2µm</td>
</tr>
<tr>
<td>A</td>
<td>54</td>
</tr>
<tr>
<td>B</td>
<td>15453</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
</tr>
<tr>
<td>D</td>
<td>45</td>
</tr>
</tbody>
</table>
Filler performance can be significantly impacted by product viscosity

Dripping
- Hanging droplet for viscous products
- Optimum change parts (nozzle) and fill parameters (drawback, speed)
- Lower fill speeds $\rightarrow$ Higher cycle time

Shear forces/interfaces
- Amount and duration of shear specific to fill technology
- Time/Pressure filler exerts higher shear
- Air-liquid interfaces also pose challenge

Drying/Nozzle clogging
- Faster drying due to higher concentration
- Minimize “pauses” during fill

Yield/COGs
- Increased line loss
Modelling for Delivery Devices Verified by experimental data helps to estimate impact of viscosity

- High concentration also pose challenge for robust device design
- Extrusion forces can be modeled using Hagen-Poiseuille Equation
  \[
  F_{\text{Total}} = F_{\text{friction}} + \frac{8\pi \mu L_n}{r_n^4} \bar{v} r_b^4
  \]
- Mechanistic modeling allows for estimating impact of product viscosity, needle size, etc on injection time

\[F_{\text{friction}} = 1.5 - 3N\]

<table>
<thead>
<tr>
<th>Viscosity</th>
<th>Injection time (27G Needle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cP</td>
<td>8.2  4.1  2.7  1.6  0.8</td>
</tr>
<tr>
<td>4 cP</td>
<td>16.4 8.2  5.5  3.3  1.6</td>
</tr>
<tr>
<td>6 cP</td>
<td>24.6 12.3 8.2  4.9  2.5</td>
</tr>
<tr>
<td>8 cP</td>
<td>32.8 16.4 10.9 6.6  3.3</td>
</tr>
<tr>
<td>10 cP</td>
<td>41.0 20.5 13.7 8.2  4.1</td>
</tr>
<tr>
<td>15 cP</td>
<td>61.6 30.8 20.5 12.3 6.2</td>
</tr>
<tr>
<td>20 cP</td>
<td>82.1 41.0 27.4 16.4 8.2</td>
</tr>
</tbody>
</table>
Analytical model helps to establish performance over entire operating range

Acceptable Conc. Range

Desired User Range

Viscosity (cP)

- <= 10
- <= 20
- <= 30
- <= 40
- <= 50
- <= 60
- > 60

- 6 sec → 25 N
- 17 N → 9 sec
- 6 sec → 17 N
- 18 sec → 44 N
- 6 sec → 17 N
- 7 sec → 13 N
- 17 N → 4 sec
- 6 sec → 20 N
Product Quality Must be Maintained from the Manufacturing Plant to the Patient
Transport validation is a regulatory expectation and is required for the marketing application

- Provides a high degree of assurance that:
  - Product quality is not impacted by transportation
  - Transport processes function effectively and reproducibly as intended.
Transport Validation consists of two independent work streams

- Shipper Qualification: Demonstrates temperature control (cold chain) in our distribution network functions effectively and reproducibly as intended.
- Product Transport Evaluation: Demonstrates that product can be transported without adverse impact to product quality attributes
Wholesale Distributor Practices

**Larger Orders:** Ship via refrigerated truck in original shipper or carton in rigid totes.

**Smaller Orders:** Utilize insulated shipping containers with gel ice/refrigerant packs. Each Distributor had their own unique insulated tote configurations.

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Product Protection

- Product packed loosely with hard ice packs in large container
- Ice packs locked against wall create isolated product area
- Refrigerated (soft) packs sized to tote between product & ice packs

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Excellent Product Protection

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Specialty Pharmacies Practices

- Specialty pharmacies can have unique insulated packaging configurations & procedures. Product cartons placed in plastic bag, placed into insulated shipper with gel ice packs. Inconsistent use of bubble wrap & corrugated pads. Sharps containers could be added per customer request.

- If the prescribed quantity is less than the supplied multi-pack carton quantity, the vial or syringe can be removed & packaged per their individual procedure. Vials placed in plastic bag or foam inserts. Syringes placed in plastic bag in plastic pill bottles. Individually blistered products remain in the blisters.
Lessons Learned on Drug Product Development

• It is critical to invest in characterization of product quality early in the development continuum and revisit often at key points where redirection can still be achieved in time
• Confirm Agency agreement with MoA that will drive CQA identification early
• Regulators are open to moving away from traditional approaches to process and product controls
• Drug product development in isolation from considering the QTPP and DS development can lead to late stage issues
• Devices are becoming an integral part of DP development and have to be considered during molecule selection and formulation development
• Getting drug product to patients involves the development of a cold chain process that is essential if all the work carried out during product development is going to be successful