Liquid, Frozen or Lyophilized?

Formulation Considerations to Get Your ADC to the Clinic Quickly While Ensuring Commercial Final Product Stability

Wendy Saffell-Clemmer
Director, Research, BPS
October, 2015
About Baxter BioPharma Solutions

We partner with pharmaceutical companies to support their commercialization objectives by providing:

- Scientific expertise
- Sterile manufacturing solutions
- Parenteral delivery systems
- Customized support services
- Diverse experience with a variety of drug categories and parenteral delivery systems
- Worldwide manufacturing capabilities
- Experience with worldwide regulatory agencies
- Quality systems

We provide our clients with confidence of delivery, service and integrity – knowing the work we do is ultimately vital to the patients you serve.
Worldwide Facilities

Expansive Network.

Baxter has manufacturing sites across the globe in support of a diverse portfolio of delivery systems and manufacturing solutions.

**Round Lake, Illinois, USA**

**Best-in-Class Aseptic Solution Manufacturer**

- Manufacturing of ready-to-use IV solutions
- Broader portfolio of manufacturer prepared premixed drugs in the industry
- Decades of experience in parenterals development, manufacturing, and partnering

**Bloomington, Indiana, USA**

**Full-Service, Award-Winning Contract Manufacturing Facility**

- Clinical development through commercial launch
- Lyophilization expertise with our Lyophilization Center of Excellence
- Experience with worldwide regulatory agencies
- Aseptic formulation, filling, and finishing services for:
  - Prefilled Syringes 0.5 mL–20 mL
  - Diluents for Reconstitution
  - Liquid Vials 2 mL–100 mL
  - Lyophilized Vials 2 mL–50 mL
  - Cartridges 1–3 mL

**Halle/Westfalen, Germany**

**World-Class, Dedicated Manufacturer of Cytotoxic and Highly Potent Compounds**

- Dedicated clinical through commercial production with integrated technologies and services
- Equipped with barrier technology
- Qualified cold chain storage: -70°C/-20°C/2–8°C/15–25°C
- Meets FDA, JP, and EU regulatory standards
- Environmental Health and Safety certification is according to ISO 14001
- Aseptic manufacturing of:
  - Vials
  - Lyophilizates 2 mL–100 mL
  - Liquid Vials 2 mL–200 mL
  - Powder filled Vials 6 mL–100 mL
  - Ampoules 1 mL–10 mL
  - Sterile crystallization Polyethylene bags (1kg–10kg)
Purpose of today’s presentation:
- Understand the advantages of a lyophilized formulation for ADC final products
- Describe possible phase 1 clinical presentations: liquid, frozen, or lyophilized
- Regardless of the Phase 1 presentation, what formulation considerations are required to allow for development of a stable lyophilized final product?
- What steps does early phase formulation development require?
- Following success in the clinic, how can the product be further optimized to result in a stable, commercial product?
Formulation Development of Biomolecules

Goal of formulation development is to produce a stable product
Focus of our Bloomington team: Development of Liquid or Lyophilized Products

Core Competencies include:

- Strong understanding of protein physical and chemical stability
- Well equipped to perform a variety of stability-indicating methods for biologics
- Particulate matter and particle identification capabilities

<table>
<thead>
<tr>
<th>Correct Dose</th>
<th>Physical Stability</th>
<th>Chemical Stability</th>
<th>Particulate Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONCENTRATION AS DELIVERED IS AS DESIGNED. MAJOR CONCERNS ARE ABSORPTION ON CONTAINER OR IN PROCESS</td>
<td>FRAGMENTATION, PROTEIN UNFOLDING, AND AGGREGATION WHICH MAY RESULT FROM PROCESS OR INSTABILITY OF THE PROTEIN. CAN RESULT IN PARTICULATE FORMATION</td>
<td>CHEMICAL MODIFICATIONS OF PROTEINS RESULTING FROM FORMULATION, PROCESSING, AND STORAGE CONDITIONS. EXAMPLES ARE DEAMIDATION AND OXIDATION</td>
<td>FREE OF EXTRINSIC (FROM ENVIRONMENT), INSTRINSIC (FROM DEGRADATION OF COMPONENTS OR FORMULATION) AND INHERENT PARTICLES</td>
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Commercial Product Considerations – Liquid or Lyo

**Advantages of Liquid Formulation**
- Ease of use
- Less expensive manufacturing

**Advantages of Lyo Formulation**
- Higher probability of technical success
- Better stability
- Frozen storage not required.

**Disadvantages of Liquid Formulation**
- Formulation may be less stable
- Complicated cold chain management

**Disadvantages of Lyo Formulation**
- More expensive manufacturing
- Specialized capabilities required

Frozen liquid presentations combine the disadvantages or both liquid and lyo formulations.

**In the case of ADCs:**

- The expense of the lyophilization process is minor compared to the overall cost of the product
- Ease of use is not a significant issue
- Use of a lyophilized formulation reduces overall risk of failure during the development process
## Options for Phase 1

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Frozen Liquid</th>
<th>Freeze-Dried</th>
</tr>
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<tbody>
<tr>
<td>• Lower cost of manufacturing and lyo capability not required.</td>
<td>• Lower cost of manufacturing and lyo capability not required.</td>
<td>• Higher manufacturing cost</td>
</tr>
<tr>
<td>• Development of Physical stability issues, particularly, particulates over time is a risk.</td>
<td>• Choice of storage temperature is critical</td>
<td>• Additional development work required, but much of this can be delayed into later stages of development.</td>
</tr>
<tr>
<td></td>
<td>• Complicated distribution</td>
<td>• Highest probability of technical success</td>
</tr>
<tr>
<td></td>
<td>• Depending of formulation, frozen may not be more stable than solution</td>
<td></td>
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### Selection should be made with end in mind:

- Goal is final product with acceptable physical and chemical stability
- Clinical trials should be performed with formulation representative of the final product

An appropriate lyo formulation is always suitable for a frozen solution
The Development Process – Lyophilized Final Product

Formulation Studies
- Biophysical Characterization
- Effect of pH, Ionic Strength, Surfactants Screening Study

Lyo Form Development
- Low Temp Thermal Analysis by DSC
- Freeze-Dry Microscopy
- Trial runs to induce failure during primary drying

Cycle Development
- Primary Drying – Design Space
- Secondary Drying – Effect of Residual Moisture Study
- Confirmation Batch and Long Term Stability

Analytical Method Development

Analytical Support
The Formulation Development Process – Phase 1

- Analytical Method Development

  - Biophysical Characterization
  - Effect of pH, Ionic Strength, Surfactants
  - Excipient Screening Study

Pre-Formulation Studies

Parallel Presentation Studies

- Low Temp Thermal Analysis by DSC
- Freeze-Dry Microscopy
- Production of Development Stability Materials
  - Liquid
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  - Lyo (using conservative cycle)

Analytical Support

Phase 1 Clinical

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Post Phase 1 Lyo Cycle Optimization

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Analytical Support
Freeze-Dry Cycle Introduction

Freezing (Solidification)  Primary Drying (Ice sublimation)  Secondary Drying (Desorption)

- Ambient
- Vacuum

Over 90% water

2-5% water
### ADC and Protein Formulation Components and Their Functions

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<th>Function</th>
<th>Examples</th>
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<td>Isotonicity</td>
<td>NaCl, Mannitol, and Glycine</td>
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<td>Non-ionic surfactant</td>
<td>Inhibit formation of aggregates</td>
<td>Polysorbate 20 or Polysorbate 80</td>
</tr>
<tr>
<td>Buffer</td>
<td>pH Control</td>
<td>Sodium phosphate, potassium phosphate, citrate, histidine, and tris</td>
</tr>
<tr>
<td>Disaccharide</td>
<td>Stabilizer</td>
<td>Sucrose, Trehalose, Maltose, Lactose, Sorbitol</td>
</tr>
<tr>
<td>Crystalizing Excipient</td>
<td>Provide structure to cake</td>
<td>Mannitol or Glycine</td>
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*Common solution buffer components can destabilize Proteins and ADCs when used in a frozen or freeze-dried formulation.*
Customer requested product development and phase 1 clinical manufacturing.

- Customer had performed a preformulation study examining the stability of the naked Mab, testing the addition of sodium chloride or sorbitol to create an isotonic solution.
- The material was provided in a solution of 10 mg/mL ADC
- The goal of the study was to develop a solution formulation using the existing solution with an option of developing a lyophilized formulation, if needed.

Customer’s extensive preformulation work established histidine as a suitable buffer system and buffer screening studies were not repeated.
# The ADC Analytical Tool Box

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Aggregation</th>
<th>Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UV-Vis</td>
<td>• SEC</td>
<td>• iCE</td>
</tr>
<tr>
<td>• Nano-Drop</td>
<td>• DLS</td>
<td>• Peptide Mapping</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fragmentation</th>
<th>Particulates</th>
<th>Compendial</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SDS-PAGE</td>
<td>• MFI</td>
<td>• pH</td>
</tr>
<tr>
<td>• CE-PAGE</td>
<td>• HIAC</td>
<td>• Appearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Antibody Ratio</th>
<th>Linker Stability</th>
<th>Lyo</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DAR-HIC</td>
<td>• Free-Drug by RP-HPLC</td>
<td>• Residual Moisture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recon Time</td>
</tr>
</tbody>
</table>
Buffers and isotonicity modifiers commonly used in solution are not suitable for frozen or freeze-dried formulations:

- Sodium Chloride: Increases osmotic strength during freezing which can influence aggregation and chemical stability.
- Phosphate Buffers: During freezing, one component of the buffer can precipitate, shifting the equilibrium, resulting in a pH shift. The presence of phosphate buffers, such as sodium phosphate, will not always cause a pH shift. There is only a pH shift if one component precipitates.
- More buffer is not better.
Surfactants such as polysorbate 80 protect against formation of aggregates during filtration, filling, freezing and freeze-drying.

- Adherence to the glass vial at the solution interface
- Unfolding at the air/solution interface leading to aggregation
- Unfolding at the ice/solution interface leading to aggregation.

Screening studies for surfactants typically included agitation and freeze-thaw as well as accelerated stability.

The screening study used in this study included evaluation of pH, surfactant and inclusion of sorbitol.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH</th>
<th>Polysorbate 80 Concentration (%)</th>
<th>Sorbitol (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>0</td>
<td>225</td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>5.5</td>
<td>0.02</td>
<td>225</td>
</tr>
<tr>
<td>5</td>
<td>6.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6.0</td>
<td>0</td>
<td>225</td>
</tr>
<tr>
<td>7</td>
<td>6.0</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>6.0</td>
<td>0.02</td>
<td>225</td>
</tr>
<tr>
<td>9</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>6.5</td>
<td>0</td>
<td>225</td>
</tr>
<tr>
<td>11</td>
<td>6.5</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>6.5</td>
<td>0.02</td>
<td>225</td>
</tr>
</tbody>
</table>
In agitation, freeze-thaw and accelerated stability studies, the addition of polysorbate 80 and sorbitol had no effect. The ADC appeared to be more stable at pH of 6 in SEC and iCE testing.
Nonreducing disaccharides are used to stabilize the ADC during the freezing and drying process.

- Common choices are sucrose or trehalose
- Protection during freezing is dependent on the bulk concentration of the sugar and can require up to 5% wt/vol
- Protection during drying depends on the mass ratio between the sugar and the protein, requiring ratios of sugar to protein of 1:1 or greater.

Reducing sugars should be avoided

- Protein degradation via Maillard reaction between the carbonyls of the sugar and free amino groups in the protein.

To stabilize the ADC as a freeze-dried solid, the final product Tg must be well above the storage temperature.

- Sorbitol has a low Tg’ of -43°C
- Sucrose has a Tg’ of -32°C
- Trehalose has a Tg’ of -30°C
Concurrent with sorbitol solution study, formulations containing either sucrose or trehalose were prepared and stored as solutions and as freeze-dried solids.

Solution Samples – 2-8°C and 25°C

Lyo Samples – 25°C and 40°C

Shake and Freeze-thaw

- Formulations prepared at pH 6 exhibited better results on stability than formulations prepared at pH 5.
- No large differences in stability data were observed for samples prepared with sucrose or trehalose with or without polysorbate 80.
- No difference between samples prepared with or without polysorbate 80.
- The formulation candidate chosen for further studies contained sucrose at pH 6 without polysorbate 80.

Based on early stability results, the customer made a decision to pursue a lyophilized formulation.
While the ADC had good chemical and physical stability in a 30 mM Histidine, 225 mM (7.7%) Sucrose formulation, shrinkage of the cake was observed.

Crystallizing excipients such as mannitol and glycine can provide improved cake structure.

- Crystalline bulking agents do not provide protection to the ADC.
- Combinations of amorphous sugars and crystalizing excipients are commonly used to stabilize Mabs and ADCs.

When using mannitol, it is essential to ensure that it is fully crystallized. If mannitol crystallizes post lyophilization, it can release the water associated with it back into the cake, potentially accelerating destabilization of the product.
Cryoprotectants and Bulking Agent Concentration Study

Lyophilized samples were stored at 50°C for 4 weeks, and 25°C and 40°C for 2 months. Samples were tested by SEC, iCE, DLS, and UV.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Histidine (mM)</th>
<th>Sucrose</th>
<th>Mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation 1</td>
<td>30</td>
<td>225 mM (7.7%)</td>
<td>274 mM (5%)</td>
</tr>
<tr>
<td>Formulation 2</td>
<td>30</td>
<td>88 mM (3%)</td>
<td>165 mM (3%)</td>
</tr>
<tr>
<td>Formulation 3</td>
<td>30</td>
<td>160 mM (5.5%)</td>
<td>274 mM (5%)</td>
</tr>
</tbody>
</table>

Percent Main Peak from SEC for Formulations 1, 2, and 3 after Storage at 50°C for 4 Weeks.

Percent Main Peak from iCE for Formulations 1, 2, and 3 after Storage at 50°C for 4 Weeks.
DLS Particle Size Distributions for Formulation 1 as a Solution at T0, After Lyophilization at T0, and After Storage at 25°C and 40°C for 2 Months

DLS data for formulation 1 show that there was a shift in average particle size after lyophilization and growth of large particulates after storage at 40°C and 50°C. Changes were not observed in formulations 2 and 3.

Second Derivative FTIR Spectra for Formulations 1, 2, and 3 After Storage at T0.

Second Derivative FTIR Spectra for Formulations 1, 2, and 3 After Storage at 50°C for 2 Weeks.
Annealing and Crystallization of Mannitol

Formulation 2 was selected for future work:

30 mM Histidine, 88 mM Sucrose (3%), 165 mM Mannitol (3%).

Annealing is a step in the freeze-drying process when the frozen product is warmed to a temperature greater than the Tg’, but not to a temperature to cause melting.

For the selected formulation, DSC was utilized to determine the annealing conditions needed to crystalize the mannitol in the formulation.

XRPD can be used to determine the crystalline state of mannitol in freeze-dried products.

Lack of mannitol crystalization can result in higher than expected moisture content and result in poor stability.
Glass Transition Temperature (Tg’) and Collapse Temperature (Tc)

In non-crystalline frozen systems, the glass transition temperature of the freeze-concentrated solute determines the **collapse temperature** during freeze-drying.

Above Tg’, the freeze concentrated material undergoes viscous flow after the supporting ice structure is gone, resulting in collapse. Below Tg’, the freeze-concentrated material is rigid enough to support its own weight after the ice has sublimed away.

**Freeze- dry microscopy** can be used to screen multiple formulations.
A few microliters is placed on freeze-drying stage and visually monitored during the freezing and primary drying process.

By DSC the Tg’ was between -32°C and -34°C

The Tg’ and Tc of -32°C provides a conservative upper limit of product temperature during primary drying. Edge of failure studies can reduce this upper limit.
The Formulation Development Process – Phase 1

Analytical Method Development

Pre-Formulation Studies
- Biophysical Characterization
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Analytical Support

Phase 1 Clinical
Post Phase 1 Lyo Cycle Optimization

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Analytical Support
What is a Design Space?

A Design Space for Primary Drying represents a Safe Zone of Operation

Defined by Three Factors:

- Equipment Capability
  - Maximum Sublimation Rate Supported by the Freeze-Dryer
- Effect of the Vial
  - Heat Transfer Coefficient for the Vial (Kv)
- Effect of the Product/Formulation
  - Resistance of the Dried Product Layer (Rp)

Results in a minimum time – robust cycle which reduces manufacturing cost
Advantages of Process Design Space

Process Optimization

– Results in a minimum time – robust cycle which reduces manufacturing cost
– Produces consistent pharmaceutically acceptable product
– Provides assurance that the cycle is well within capacity of equipment failure points

Accelerates process development

Includes the edges of failure

Facilitates handling of deviations during production

Design Space Reduces risks in development and in production
**Calculation of Design Space**

**Use equations based on first principles of heat and mass transfer**

\[
\frac{dq}{dt} = K_v A_v (T_s - T_b) \quad \frac{dm}{dt} = A_p (P_i - P_c)/R_p \quad \frac{dq}{dt} = \Delta H_s \frac{dm}{dt}
\]

**Known**

- \(A_v\) = area of the outside of the vial
- \(T_s\) = Shelf temperature
- \(A_p\) = area of the inside of the vial
- \(\Delta H_s\) = Heat of Sublimation of Ice
- \(P_c\) = Chamber Pressure

**Measured**

- \(T_b\) = Product temperature at the bottom of the vial

**Calculated**

- \(\frac{dq}{dt}\) = heat flux
- \(P_i\) = Vapor pressure of ice at the sublimation front

Where \(P_i = 2.698 \times 10^{10}^{-6144.96}/T_b\)

- \(K_v\) = Heat Transfer Coefficient
- \(R_p\) = Product Resistance
Resistance of Dried Product Layer ($R_p$)

$$R_p = A_p(P_i - P_c)/(\frac{dm}{dt})$$

$\frac{dm}{dt} =$ mass flux

$A_p =$ area of the inside of the vial

$P_i =$ Vapor pressure of ice at the sublimation front

$P_c =$ Chamber Pressure

Fill vials with formulated product at the intended fill volume

Place thermocouples in at least three vials

Monitor mass flow rate by TDLAS

Generate Product Temperature ($T_b$) Isotherms

$$\frac{dm}{dt} = A_p[2.698 \times 10^{10} \exp(-6144.96/T_b) - P_c]$$

$R_p$

Use arbitrary Product Temperature $T_b$ and Chamber Pressure $P_c$
Heat Transfer Coefficient of Vial ($K_v$)

$$K_v = \frac{\Delta H_s \, dm/dt}{A_v(T_s - T_b)}$$

$A_v = \text{area of the outside of the vial}$

$T_s = \text{Shelf temperature}$

$T_b = \text{Product temperature at the bottom of the vial}$

$dm/dt = \text{mass flux}$

$\Delta H_s = \text{Heat of Sublimation of Ice}$

Use water filled vials with thermocouples in at least 3.

Carry out cycle at appropriate shelf temperature and at the low end of the pressure range.

Monitor $dm/dt$ using TDLAS, until it stabilizes.

Repeat at multiple pressure points to create table correlating $P_c$ to $dm/dt$.

Generate Shelf Temperature ($T_s$) Isotherms

$$dm/dt = K_v A_v (T_s - T_b)$$

Solve for $dm/dt$ at multiple $P_c$ for the same $T_s$. 

Mass Flow Rate

Pressure
Cycle optimization focused on three objectives

- Determine the effect of residual moisture and optimization of secondary drying conditions
- Improve cycle efficiency by determining the highest acceptable shelf temperature for annealing and primary drying.
- Complete design space
- Produce demonstration batch and place on long term stability for 18 months at 5°C and 25°C, and for 6 months at 40°C

The conditions marked with a circle represent a cycle time of 40 hours. The maximum efficient cycle was 23 hours.

By all test methods, the lyophilized product remained stable at all conditions studied.
Conclusions

Formulation development must be conducted with end in mind. 

Lyo formulations provide the greatest probability of technical success.

- Multipath development – liquid/frozen liquid/lyo can speed time to clinic while minimizing risk
- However, while the optimum lyo formulation is always the optimal frozen solution formulation, the inverse is not true.
- The formulation development considerations are the same for both frozen and lyo and because of this, why not lyophilized?
- Use of an optimal lyophilized formulation in early clinical trials, whether using solution, frozen solution or lyophilized presentation provides the option
  - to move forward with a lyophilized presentation if needed
  - further optimize the lyophilization cycle
  - and provides the best odds for ensuring a stable commercial product

Formulation development must be conducted with end in mind through all phases of development.
Acknowledgments

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Kelly Roby
Nathan Pease
Brendan Mayhugh
Thank You!

For more information:
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or
www.baxterbiopharmasolutions.com