The Function and Criticality of Excipients in Biologic Drug Products

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ExcipientFest
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Disclaimer

\textit{The views and opinions presented herein represent those of the author only and do not represent the views and opinions of Bristol-Myers Squibb.}
Outline

Biotechnology Drugs
Quality Attributes
Function of Commonly Used Excipients
Critical Elements to Select Excipients
◆ and ways of managing them
Summary

Biotechnology Drugs

“Well-characterised proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology.

Generation and submission of stability data for products such as
◆ Cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors)
◆ Erythropoietins
◆ Plasminogen activators
◆ Blood plasma factors
◆ Growth hormones and growth factors
◆ Insulins
◆ Monoclonal antibodies
◆ Vaccines consisting of well-characterised proteins or polypeptides.”
### Biotechnology Drugs

**Proteins/antibodies are the most common molecule types**

**Poor stability and/or absorption via non-injection routes**

**IV and SC are the most common routes of administration routes**

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**Pharmaceutical Development**

- Excipient selection is based on expected function
- Critical elements in excipients should be considered to develop DP’s of desired quality
- Excipient composition can impact CQA’s of DP’s

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**Defining the QTPP**

**Identifying potential CQA’s of the DP**

**Determining CQA’s of DS and excipients, selecting type and amount of excipients = Quality**

**Selecting an appropriate manufacturing process**

**Defining a control strategy**
DP Quality Attributes

Potential Chemical and Biophysical Degradations

<table>
<thead>
<tr>
<th>Degradation</th>
<th>Causes</th>
<th>Possible Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-covalent aggregation</td>
<td>Structural changes, colloidal stability, heat and other physical stress, solubility crystallization during freezing</td>
<td>pH, buffer salt, ionic additives, protein concentration, improving zeta-potential purity</td>
</tr>
<tr>
<td>Covalent aggregation</td>
<td>Disulfide rearrangement</td>
<td>pH, prevent aggregation</td>
</tr>
<tr>
<td>Decomposition</td>
<td>pH ~ 5</td>
<td>pH, magnesium chloride</td>
</tr>
<tr>
<td>Deterioration</td>
<td>pH<del>5 and pH</del>6</td>
<td>pH, degradation of metals, purity</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Free radicals, reactive oxygen, metals, impurities, hydrogen peroxide</td>
<td>pH, free-radical and reactive oxygen scavengers, metal chelation</td>
</tr>
<tr>
<td>Surface denaturation</td>
<td>Low antibody concentration, binding to surfaces, hydrophobicity</td>
<td>Surfactants, protein concentration, pH</td>
</tr>
</tbody>
</table>

➢ Selection of excipients should consider colloidal, conformational and chemical stability


Function of Excipients in Biologics DP

Vehicle  Chelating agents
Buffers/pH modifiers  Antioxidants
Bulking agents  Antimicrobial preservatives
Tonicity agents  Biodegradable polymers
Viscosity modifiers  Liposome forming agents
Surfactants

USP <1059> Excipient Performance

Under Revision (in alignment with USP <1151> Pharmaceutical Dosage Forms)
Commonly Used Buffers

Buffer selection based on pH of maximum biologics stability
→ Mixture of different forms to achieve target pH ←
Levels of tens of mM

Approximate pH ranges

- Acetate
- Citrate
- Succinate
- Histidine
- Phosphate
- Tris
- Photosensitive

Reports of pain upon injection
Saturation of dibasic salt at low temperature


Viscosity Modifiers, Bulking and Tonicity Agents

Multi-Functionality

- Lyoprotection
- Cake-forming
- Viscosity Modifiers
  - Isotonicity
- Stabilizer
  - Glassy Matrices
  - Charge Distribution
  - Preferential Exclusion
  - Direct Binding
- Bulking
  - Sucrose
  - Trehalose
  - Mannitol
  - Sorbitol
  - Mannitol
- Tonicity
  - Levels of mid hundreds mM
  - Levels of tens to low hundreds mM

Chelating Agents and Antioxidants

To mitigate oxidative processes

**Antioxidants**
- Free Radicals (R·); Reactive Oxygen Species (ROS)
- Preferential (sacrificial) oxidation – lower redox potential
- Amino acids (i.e. methionine, cysteine, tryptophan, etc.)
- Low mM levels (~0.01-1.0%)

**Chelating Agents**
- Metal-catalyzed oxidation
- Complexation
- EDTA salts, DTPA, etc.
- μM levels (~0.01-0.20%)
- Antioxidant synergists

\[
\text{RH} \rightarrow \text{R·} + \text{O}_2 \rightarrow \text{ROO·} + \text{RH} \rightarrow \text{R·} + \text{ROOH}
\]


Surfactants

To mitigate biophysical destabilization

Interface-induced aggregation/particle formation
- Direct protein-surfactant interaction
  - Hydrophobic patches, cavities in tertiary structure
  - Van der Waals interactions and Hydrogen bonding

Competitive interfacial adsorption
- Solid-liquid (containers/membranes, ice-water during freezing/thawing)
- Liquid-liquid (silicone oil in prefilled syringes)
- Liquid-gas (air-water)

Predominant non-ionic surfactants
- Polysorbates 20 and 80 (0.001-0.1%) and Poloxamer 188 (~1%)

Critical Elements

Excipients for Biologics Drug Products

Excipients Introduction in Manufacturing

★ Excipient introduction

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Large molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>API Synthesis</td>
<td>DS Upstream (Fermentation)</td>
</tr>
<tr>
<td>API Purification</td>
<td>DS Downstream (Purification)★</td>
</tr>
<tr>
<td>★ DP Manufacturing</td>
<td>★ DP Manufacturing</td>
</tr>
</tbody>
</table>

★ Excipient introduction in last stage of DS manufacturing requires significant collaboration and alignment cross-functionally.
Multi-Applicability of Chemicals

Same chemical may be used as raw material and excipient

- Quality: compendial requirements
- Supply Chain: multiple SKU’s


Criticality of Excipients in Biologics DP

- ISO
- NSF/IPEC/ANSI
- IPEC-PQG
- Excipact
- ICH Q7

- USP/EP/JP
- ChP

- USP <85>
  Bacterial Endotoxin Limit

- Composition
- Impurities
GMP Requirements

Risk Assessment based on material usage and supplier’s quality

- Direct relationship with manufacturers is paramount

I. GMP principles for excipients under pharmaceutical quality system

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<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td>1. Establishment and implementation of an effective Pharmaceutical Quality system</td>
<td>1.2, 1.4</td>
<td>4.3, 4.4</td>
<td>4.1, 4.2.2</td>
<td>✓</td>
<td>4.1</td>
<td>1.1, 1.2</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>2. Sufficient competent and appropriately qualified personnel</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>3. Defined job descriptions for managerial and supervisory staff</td>
<td></td>
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</tbody>
</table>

IPEC EUROPE ‘HOW-TO’ DOCUMENT Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (OJ 2015/C 95/02)

Multi-Compendial Requirements

- USP/NF monographs represent minimum requirements for an excipient that is used in FDA approved drug products

Global DP supply
- USP/NF, EP and JP
- 2015 ChP publication
- Polysorbate 80
- Change in fatty acids composition: ≥ 98% oleic acid
- Compliance: 3-5 years for marketed products
- Re-evaluation of supply landscape

NF/EP/JP

<table>
<thead>
<tr>
<th>Name</th>
<th>Acceptance Criteria, NMT (%)</th>
<th>Acceptance Criteria, NLT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myristic acid</td>
<td>5.0</td>
<td>—</td>
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<tr>
<td>Palmitic acid</td>
<td>16.0</td>
<td>—</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>8.0</td>
<td>—</td>
</tr>
<tr>
<td>Stearic acid</td>
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<tr>
<td>Oleic acid</td>
<td>18.0</td>
<td>—</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>18.0</td>
<td>—</td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>6.0</td>
<td>—</td>
</tr>
</tbody>
</table>
Endotoxin Assessment

Endotoxin Limit = K/M

- K = 5 USP-EU/kg of body weight*
- M = maximum injectable hourly dose
  - Drug Product: 5 EU/kg in a single hour

Stack-up analysis (contributions)

- Packaging components, excipients, infusion solutions, etc.
- Control Strategy: specifications

USP/FDA direction:

- “Such that the requirement under the relevant dosage form monograph(s) in which (the API/excipient) is used can be met.”

* For any route of administration other than intrathecal (K = 0.2 USP-EU/kg of body weight)

Beta-Glucans in Sucrose

D-glucose monomers linked by (1–3) beta-glycosidic bonds – 1,6 glycosidic branches

Potential immunostimulatory properties

- As endotoxins: large polysaccharides → inflammatory response

Contamination of a biotherapeutic solution

- Levels: final product > original formulation buffer/sucrose solution
- Source: cellulose-based filters and sucrose-containing solutions
- Co-concentration with protein during DSP
- Successful removal with nylon-based filter

Literature review: IV total dose < 500 ng not a safety concern
Nanoparticulate Impurities (NPI) in Sucrose

- Mistakenly interpreted as protein aggregates
- NPI disappeared after ultrafiltration (0.02 μm)
- Characterization: ash/dextran residues

“To ensure effectiveness (of proposed ultrafiltration by suppliers), however, it would then require monographs to include a test for nanoparticulate impurities in pharmaceutical-grade sugar products.”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Trastuzumab</th>
<th>Rituximab</th>
<th>Infliximab</th>
<th>Cetuximab</th>
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</thead>
<tbody>
<tr>
<td>Visable particles</td>
<td>Visual inspection</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Turbidity</td>
<td>Visual inspection</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>μm-particles</td>
<td>HPA</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>nm-particles</td>
<td>DLS</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>NPI species</td>
<td>SEC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Protein recovery</td>
<td>SEC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Conformational flexibility</td>
<td>HSD</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Charge variants</td>
<td>cDF</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sum of &lt; 1</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

NPI impact to mAbs

12-Tricosanone in Polysorbate (PS) 80

Visible particles observed in mAb solutions containing specific lots of PS80
- Similar Free Fatty Acid (FFA) profiles across lots
  - FFA’s are known to be formed from polysorbates due to presence of residual lipases in DS
- Identification (FT-IR and GC-MS):
  - 12-tricosanone
    - Synthesis requires harsh conditions not present in PS synthesis nor during DP mfg or storage
    - Commonly found in fat soluble scents/flavors in plants
    - Expected source of impurity: raw material for PS synthesis
    - May also be relevant to PS20
Managing Critical Elements

Qualification of Excipients for Use in Pharmaceuticals

Criticality

Supplier

Commercial

R&D

Regulatory

Clinical

Quality

Clinical Supply

Compendial Affairs

MR & S&T

Procurement

Mfg sites

Close collaboration with suppliers

Volume or Value

Plasma Lyte A:
- Sodium Chloride, Sodium Gluconate, Sodium Acetate Trihydrate, Potassium Chloride, Magnesium Chloride

Dextrose/Sodium Chloride

Human Serum Albumin (25% HSA)
- Sodium, Potassium, N-acetyl-DL-tryptophan, Caprylic Acid

Dextran 40
- LMD in dextrose or Sodium Chloride
- Dimethyl Sulfoxide (DMSO)

Credit: Novartis; DailyMed
Summary

- Most biologics are delivered via injection
- Excipient selection is based on expected function
  - Parenteral delivery of biologics: some excipients present multi-functionality
- Consider critical elements in excipients to develop drug products of desired quality
  - Managing critical elements is vital for the end user
  - Excipient grades of greater aggregated value help to offset risks

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Questions?