Packaging of Biotech Drug Products: Challenges and Innovative Solutions

Annalisa Delnevo – Research Pharma
Odra Pinato – SG Lab Analytics

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Stevanato is a worldwide producer of high quality cGMP manufactured solutions for the healthcare industry.

- Privately held multi-national conglomerate (HQ Padova, Italy)
- Vertically integrated manufacturer
- Supports primary & secondary pharma packaging and offers fully integrated turnkey device solutions.
STEVANATO GROUP: THE STRUCTURE
STEVANATO GROUP: MAIN MILESTONES

1949
STEVANATO GROUP

1971
SPAMI Foundation

1993
LATINA PLANT
Alfamatic Acquisition

2005
BRATISLAVA PLANT
Medical Glass Acquisition

2007
OPTREL Acquisition
EZ-FILL SYRINGE
Sterile Department

2008
MONTERREY PLANT Opening

2009
EZ-FILL VIALS & CARTRIDGES
New Sterile Department

2010
MONTERREY PLANT Doubling

2011
ZHANGJIAGANG PLANT
Foundation stone

2012
BEIJING PLANT
Foundation stone

2013
INNOSCAN Acquisition

2014
EZ-FILL SYRINGES
New Sterile Department

2015
INNOSCAN Acquisition

2016
SVM Acquisition

2017
SETE LAGOAS PLANT
Foundation Stone

BALDA Acquisition

2018
MONTERREY PLANT Doubling

2019
ZHANGJIAGANG PLANT
Doubling

2020
INNOSCAN Acquisition
YESTERDAY
PHARMA - PARENTERAL

Glass Primary Packaging Supplier & Engineering Systems and Services

TODAY AND TOMORROW
HEALTHCARE

One-stop solutions for Drug-Delivery Systems
FULLY AUTOMATIC CONTROL MACHINE

1. GLASS TUBE LOADER

2. GLASS PROCESSING

3. AFTERFORMING LINE

4. ANNEALING OVEN

5. COSMETIC CONTROL

6. FINAL PACKING

PRODUCTION LINE

FULLY AUTOMATIC CONTROL MACHINE
**BIOPHARMACEUTICALS: UN-CONVENTIONAL DRUGS**

<table>
<thead>
<tr>
<th></th>
<th>SMALL MOLECULE DRUGS</th>
<th>BIOLOGICAL DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIZE</strong></td>
<td>• Small (single molecule)</td>
<td>Large (mixture of related molecules)</td>
</tr>
<tr>
<td></td>
<td>Low molecular weight</td>
<td>High molecular weight</td>
</tr>
<tr>
<td><strong>STRUCTURE</strong></td>
<td>Simple, well defined, independent of manufacturing process</td>
<td>Complex (heterogeneous), defined by the exact manufacturing process</td>
</tr>
<tr>
<td><strong>MODIFICATION</strong></td>
<td>Well defined</td>
<td>Many options</td>
</tr>
<tr>
<td></td>
<td>• Produced by chemical synthesis</td>
<td>• Produced in living cell culture;</td>
</tr>
<tr>
<td></td>
<td>• Predictable chemical process</td>
<td>• Difficult to control from starting material to final API;</td>
</tr>
<tr>
<td></td>
<td>• Identical copy can be made</td>
<td>• Impossible to ensure identical copy</td>
</tr>
<tr>
<td><strong>MANUFACTURING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHARACTERISATION</strong></td>
<td>Easy to characterize</td>
<td>Cannot be characterized completely the molecular composition and heterogeneity</td>
</tr>
<tr>
<td><strong>STABILITY</strong></td>
<td>Stable</td>
<td>Unstable, sensitive to external conditions</td>
</tr>
<tr>
<td><strong>IMMUNOGENICITY</strong></td>
<td>Mostly non-immunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>

**Acetylsalicylic acid**

**mAb**
Protein *Structure–Activity* relationship is a milestone of biopharmaceutics;

- Needs to **ensure** and **maintain** the **stability** of these complex molecules:
  - Exposition to a variety of **interfaces** throughout the **DP life cycle** → during transportation and storage, up to the delivery to the **patients**;

- **Primary packaging** is definitely considered one of the **interface systems** that deeply contributes to the biopharmaceutical **stability, safety** and **efficacy**.

Compatibility of Container Closure System (CCS) with respect to the drug product should be carefully assessed and investigated
As noted by FDA's Container Closure Systems guidance:

Every packaging system should be shown to be suitable for its intended use:

1. Protect the dosage form;
2. Compatible with the dosage form;
3. Be composed of materials that are considered safe for use and the route of administration;
4. If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to function properly.

CONTAINER CLOSURE SYSTEM SUITABILITY ASSESSMENT

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROL'S DOCUMENTATION

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OUR GLASS PRODUCT PORTFOLIO

Non sterile Container

Ampoules  Vials  Syringes  Cartridges  Special product

Ready to Use Vials  Ready to Use Syringes  Ready to Use Cartridges

Different complexity rate of the container closure system
**Container Closure System: Vials vs Syringes**

**VIAL**

- Stopper elastomer (rubber optionally coated)
- Borosilicate glass (optionally coated)

**Pre-Fillable Syringe**

- Plunger elastomer (rubber)
- Needle shield (rubber)
- Stainless-steel needle
- UV-cured adhesive (syringe cone)
- Borosilicate glass coated with silicone oil
- Rod
- Syringe cone
Pharmaceutical Biotechnology

Silicone Oil Microdroplets Can Induce Antibody Responses Against Recombinant Murine Growth Hormone in Mice
Carly Freagle Chisholm 1, Abby E. Baker 1, Kaitlin R. Soucie 1, Raul M. Torres 2, John F. Carpenter 3, Theodore W. Randolph 4

1 Department of Chemical and Biological Engineering, University of Colorado, Boulder, Colorado 80309
2 Department of Immunology & Microbiology, University of Colorado School of Medicine, Aurora, Colorado 80045
3 Department of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045

Silicone Oil Induced Aggregation of Proteins
LAToya S. Jones, ALlYN Kaufmann, C. Russell Middaugh
Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas 66047-37

The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes
Kathia Boven, Scott Stryker, John Knight, Adrian Thomas, Marc van Regenmortel, David M. Kemeny, David Power, Jerome Rossert, and Nicole Casadevall

Johnson and Johnson, Pharmaceutical Research and Development, L.L.C, Raritan, New Jersey, Centre National de la Recherche Scientifique, Ecole Supérieure de Biotechnologie de Strasbourg, France; Department of Microbiology, National University of Singapore, Singapore; Kidney Laboratory, Austin Research Institute, Austin, Australia; Service de Néphrologie, Hôpital Tenon, Paris, France; and Service d'Haematologie Biologique, Hôpital Hôtel-Dieu, Paris, France

Biophysical Comparability of the Same Protein from Different Manufacturers: A Case Study using Epoetin Alfa from Epogen® and Eprex®
SONGpon Deechongkit 1, Kenneth H. AOkl 2, Sungae S. Park 1, Bruce A. Kerwin 1
1Department of Pharmaceutics, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320
2Department of Protein Science, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320

Precipitation of a Monoclonal Antibody by Soluble Tungsten
Jared S. Bee 1, Stephanie A. Nelson 1, Erwin Freund 2, John F. Carpenter 3, Theodore W. Randolph 1
1Department of Chemical and Biological Engineering, University of Colorado, Boulder, Colorado 80309
2Drug Product & Device Development, Amgen Inc., Thousand Oaks, California 91320
3Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center, Denver, Colorado 80220

Aggregation of a Monoclonal Antibody Induced by Adsorption to Stainless Steel
Jared S. Bee 1, Michelle Davis 1, Erwin Freund 2, John F. Carpenter 3, Theodore W. Randolph 1
1Department of Chemical and Biological Engineering, University of Colorado, Boulder, Colorado 80309; Room: ECCH 111, Campus Box 0424, 1111 Engineering Dr, Boulder, Colorado 80309-0424; telephone: 303-492-4776; fax: 303-492-4341; e-mail: theodore.randolph@colorado.edu
2Drug Product & Device Development, Amgen, Inc., Thousand Oaks, California
3Department of Pharmaceutical Sciences, University of Colorado, Aurora, Colorado

Clouding and Deactivation of Clear (Regular) Human Insulin: Association With Silicone Oil From Disposable Syringes?
In November 1984, a patient complained to me that his requirements for regular human insulin before meals and for the correction of elevated blood glucose were progressively increasing. I examined the vial that he carried in a shoulder bag and observed the contents to be cloudy. Because

Biophysical Comparability of the Same Protein from Different Manufacturers: A Case Study using Epoetin Alfa from Epogen® and Eprex®
PROTEIN STABILITY ENEMIES IN CONTAINER CLOSURE SYSTEM

Absorption at Contact Surfaces: Liquid/Solid & Liquid/Air
Reaction/binding with Leachables from CCS components

- Chemical modification (oxidation, deamidation)
- Physical modification (aggregation, precipitation, particles, etc)
- Loss/reduction of potency
- Immunogenicity

Stability, Safety and Efficacy are not guaranteed!
**LEACHABLES FROM CCS COMPONENTS**

**EXTRACTABLES CAN migrate in the DP:**
Organic & Inorganic chemical entities that can be released from packaging system into a DP under laboratory condition may accelerate or exaggerate the normal condition of storage and use.

**LEACHABLES DO migrate in the DP:**
Organic & Inorganic chemical entities that migrate from packaging system into a DP under normal condition of storage and use or during accelerated stability studies.

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**Reaction(binding) with Leachables from CCS components**

Mechanisms of protein aggregation, particles formation and protein damage:

- **Leaching of Silicone oil droplets;**
- **Leachables from CCS components** (glass, plastic, rubber, stainless steel, tungsten, adhesive etc.)
**Leaching of Silicone Oil Droplets: CCS vs. Protein Incompatibility**

- **Syringe** and **Cartridge** barrels are **coated** with **silicone oil**:
  - to facilitate smooth movement of plunger;

- **Silicone oil treatment** can lead to droplets of silicone oil suspended in DP;

- **Protein adsorption** to wall and droplet can result in particles with **aggregated** protein.

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<table>
<thead>
<tr>
<th>Needle shield (rubber)</th>
<th>Plunger elastomer (rubber)</th>
<th>Rod</th>
</tr>
</thead>
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<td>Stainless-steel needle</td>
<td>UV-cured adhesive (syringe cone)</td>
<td>Borosilicate glass coated with silicone oil</td>
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![Diagram of syringe and cartridge assembly with silicone oil treatment](image)
Lysozyme Formulations (pH 7.5, phosphate buffer) → Spiked with Silicone Oil

- High Silicone Oil Concentration
- Low Silicone Oil Concentration

0 hr

72 hr
During the period of 1998 to 2002, there was an increase in the incidence of antibody-positive pure red cell aplasia (PRCA) in patients receiving subcutaneous administration of EPREX (epoietin alfa).

The aqueous formulation containing polysorbate 80, introduced in 1998, facilitated the leaching of small-molecule, aromatic compounds from the uncoated rubber syringe plunger.

Interaction between the extractables from the elastomeric syringe plunger and the drug product formulation caused the adverse event of pure red cell aplasia in certain patients.

The resolution for this issue was a move to a barrier-coated plunger to minimize migration of extractables into the drug product.
CONTAINER CLOSURE SYSTEM: OUR APPROACH

HELP CUSTOMER

to understand containers interaction with

drug

CONTAINER QUALITY MONITORING
Set analytical methods to measure what is critical for container functionality

360°

DESIGN THE RIGHT CONTAINER
Take care about biotech drug & Pharma needs

MANUFACTURING
Transform needs in product with the right process:
i.e. low-Tungsten, Silicone, EZ-Fill, …
CONTAINER CLOSURE SYSTEM: OUR APPROACH

HELP CUSTOMER
to improve a drug delivery device

QUALITY MONITORING
Measure and check the critical to quality parameters

MANUFACTURING
Transform needs in product with the complete set of competences available in Stevanato Group

DESIGN THE RIGHT DRUG DELIVERY SYSTEM
Take care about delivery system specifications

360°
OUR CONTRIBUTION TODAY …

The next Value for Biotech products → NEW COATING GENERATION

NEW COATING GOALS:
- Particles reduction
- Reduced E&L
**Methodology Description**

1. Fill the syringes with 1.3mL of filtered (0.22µm) and distilled water
2. Cap the syringes with aluminum foil
3. Put the syringes inside the autoclave (1h at 121°C)
4. Analyze the extracts with the MFI 5200 series

**Comments**

- All the three Types of syringes are inside the USP788 requirements
- Significant particles reduction for the Alba syringes
- Alba solution answers to the requirements of low particles making the syringe compliant with USP789

*Test method development and analysis by SGLab*
## Alba syringes - Coating layer and distribution

### Methodology Description*

1. Empty the syringes
2. Analyze the syringes by Rapid Layer Explorer

### Comments

homogeneous coating distribution for Alba syringes

### Syringes siliconized with a not optimized process

<table>
<thead>
<tr>
<th>Methodology Description*</th>
<th>Syringes siliconized with a not optimized process</th>
<th>Biotech syringes</th>
<th>Alba syringes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Empty the syringes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Analyze the syringes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analysis by SGLab
**Methodology Description**

1. Empty the syringes
2. Analyze the syringes by Rap-id Layer Explorer

**Comments**

homogeneous coating distribution for Alba syringes guaranteeing the same thickness along the entire surface

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<table>
<thead>
<tr>
<th>Thickness (nm)</th>
<th>Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

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*Analysis by SGLab
Drug primary packaging is not a background decision to take just before the market launch:

the rationalized selection of the proper container closures system can make the difference in terms of drug stability, safety and efficacy.

Drug delivery is fundamental feature to take care:

the best drug with poor delivery will result, in the best case, in inefficacy of therapy.
Thanks for your attention

annalisa.delnevo@stevanatogroup.com
odra.pinato@stevanatogroup.com

www.stevanatogroup.com