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Packaging Components & Biopharmaceuticals

Quality aspects from an industry perspective

Hanns-Christian Mahler | Lonza AG

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Forward-Looking Statements

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Certain matters discussed in this presentation may constitute forward-looking statements. These statements are based on current expectations and estimates of Lonza Group Ltd, although Lonza Group Ltd can give no assurance that these expectations and estimates will be achieved. Investors are cautioned that all forward-looking statements involve risks and uncertainty and are qualified in their entirety. The actual results may differ materially in the future from the forward-looking statements included in this presentation due to various factors. Furthermore, except as otherwise required by law, Lonza Group Ltd disclaims any intention or obligation to update the statements contained in this presentation.

Parenteral Preparations of Biotech Drugs

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- "Biologics" are increasingly developed and commercialized
  - Antibodies
  - New Format biologics (bispecifics, fusion proteins)
  - Conjugates
  - Viral Therapy
  - Cell Therapy
  - Other
- Proteins are often rather fragile molecules and can degrade easily
  - Storage typically refridgerated, sometimes frozen
  - Chemical Degradation (e.g., Deamidation, Oxidation)
  - Physical Degradation (e.g., Adsorption, Aggregation, Particle formation

Legal Definitions & Requirements

Parenteral Preparations in Ph.Eur.

- Parenteral Preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body (Ph.Eur.)
- (Some) Requirements
  - Sterility (incl CCI* and Preservative efficacy in multidose)
  - Compliant with endotoxin limits
  - Practically free from (visible) particles. (cf. 2.9.20)
  - Compliant with the test „sub-visible particles“ (cf. 2.9.19)
  - Content of (critical) excipients
  - Homogeneity (Batch definitions)
  - Testing for clarity, color, pH, osmolality
  - Content, Identity, Purity, Bioactivity, Stability
- Monoclonal Antibodies for human use
  - Appearance. (…), without visible particles, unless otherwise authorized or justified.

Parenteral preparations EUROPEAN PHARMACOPOEIA 5.2

After dissolution, they comply with the requirements for syrups.

TESTS

Uniformity of dosage units. Single-dose powders and granules for syrups comply with the test for uniformity of dosage units (2.9.40) or, where justified and authorised, with the tests for uniformity of content and/or uniformity of mass shown below. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content (2.9.6). Unless otherwise prescribed or justified and authorised, single-dose powders and granules for syrups with a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with test B for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to these substances that correspond to the above conditions.

Uniformity of mass (2.9.5). Single-dose powders and granules for syrups comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

Dosage forms

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PARENTERAL PREPARATIONS

Parenteralia

The requirements of this monograph do not necessarily apply to products derived from human blood, to immunological preparations, or radiopharmaceutical preparations. Special requirements may apply to preparations for veterinary use depending on the species of animal for which the preparation is intended.

DEFINITION

Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body.

Parenteral preparations may require the use of excipients, for example to make the preparation isotonic with respect to blood, to adjust the pH, to increase solubility, to prevent deterioration of the active substances or to provide adequate antimicrobial properties, but not to adversely affect the intended medicinal action of the preparation or, at the concentrations used, to cause toxicity or undue local irritation.

Containers for parenteral preparations are made as far as possible from materials that are sufficiently transparent to permit the visual inspection of the contents, except for implants and in other justified and authorised cases.

Where applicable, the containers for parenteral preparations comply with the requirements for *Materials used for the manufacture of containers* (3.1 and subsections) and *Containers* (3.2 and subsections).

Parenteral preparations are supplied in glass containers (3.2.1) or in other containers such as plastic containers (3.2.2, 3.2.2.1 and 3.2.9) and prefilled syringes. The tightness of the container is ensured by suitable means. Closures ensure a good seal, prevent the access of micro-organisms and other contaminants and usually permit the withdrawal of a part or the whole of the contents without removal of the closure. The plastic materials or elastomers (3.2.9) used to manufacture the closures are sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures for multidose containers are sufficiently elastic to ensure that the puncture is resealed when the needle is withdrawn.

Several categories of parenteral preparations may be distinguished:
- injections,
- infusions,
- concentrates for injections or infusions,
- powders for injections or infusions,
- gels for injections,
- implants.

PRODUCTION

During the development of a parenteral preparation, the formulation for which contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided under *Efficacy of antimicrobial preservation* (5.1.3).

Parenteral preparations are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms. Recommendations on this aspect are provided in the text on *Methods of preparation of sterile products* (5.1.1).

Water used in the manufacture of parenteral preparations complies with the requirements of water for injections in bulk stated in the monograph on *Water for injections* (0169).

TESTS

Particulate contamination: sub-visible particles (2.9.19). For preparations for human use, solutions for infusion or solutions for injection comply with the test.

In the case of preparations for subcutaneous or intramuscular injection, higher limits may be appropriate. Radiopharmaceutical preparations are exempt from these requirements. Preparations for which the label states that the product is to be used with a final filter are exempt from these requirements, providing it has been demonstrated that the filter delivers a solution that complies with the test.

For preparations for veterinary use, when supplied in containers with a nominal content of more than 100 ml and when the content is equivalent to a dose of more than 1.4 ml per kilogram of body mass, solutions for infusion or solutions for injection comply with the test for particulate contamination: sub-visible particles.

Sterility (2.6.1). Parenteral preparations comply with the test for sterility.

STORAGE

In a sterile, airtight, tamper-proof container.

LABELLING

The label states:
- the name and concentration of any added antimicrobial preservative,
- where applicable, that the solution is to be used in conjunction with a final filter,
- where applicable, that the preparation is free from bacterial endotoxins or that it is apyrogenic.

3144 *See the information section on general monographs (cover pages)*

** Container Closure Integrity*

Pharmacopeial requirements related to Particulates

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	Sub-visible Particles (SVPs)	Visible Particles
Ph. Eur.	NMT 6000 ≥10 um / container NMT 600 ≥25 um / container*	„…practically free of visible particles“ (*Parenteral Preparations*) „…without visible particles, unless otherwise justified and authorised“ (*MABs for human use*)
USP	Ophthalmic Products per USP 789: NMT 50 ≥10 um / container NMT 5 ≥25 um / container*	„…essentially free of visible particles“ (USP 790 & 1790: concept of AQL and definition of X units with particles in Y tested)

NB. Definitions are based on historic data and product knowledge and based on extrinsic particulates.

A Successful Parenteral Product depends on how well the interplay of its components are understood

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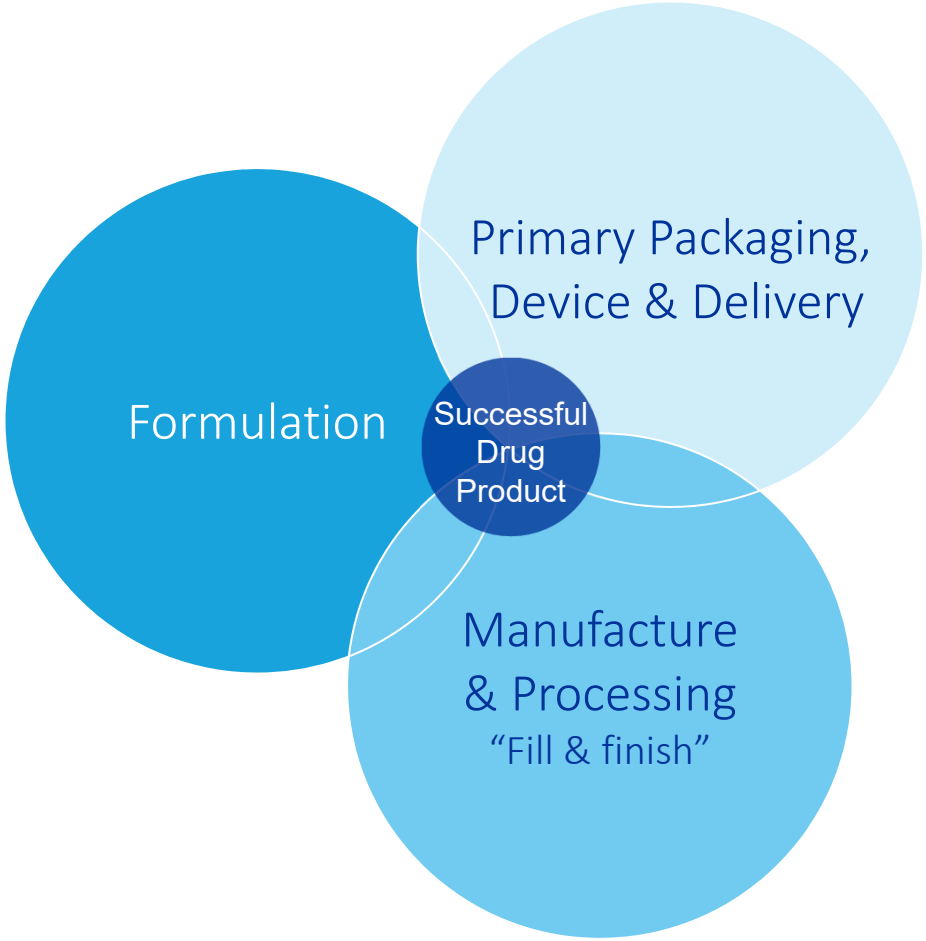

What Quality Attributes to Consider?

The Interface of Packaging & Biologics

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Attribute	During manufacture	During storage	During shipment	Until point of use (possibly beyond)
Sterility	**Aseptic Manufacture,** **Design/choice of CCS** (dimensional fits, CCI, manufacturability), **Design of Process**, e.g. Impact of Critical Process Unit ops (e.g. Capping) on CCI, **Contact Materials assessment** (sterility/bioburden, etc) **Sterility testing, Functionality testing**	Sterility/CCI ensurance by appropriate **CCS and Process Design** (see above)	**Simulated shipment** testing (impact on **CCI** & **Functionality**)	**Stopper resealing**, Assessing **Microbiological Quality after opening**. "Pharmacy manuals" and User **Trainings**.

1. Sterility
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Are the chosen Primary Packaging components "sterile" at the point of use (aseptic manufacture/F&F)?

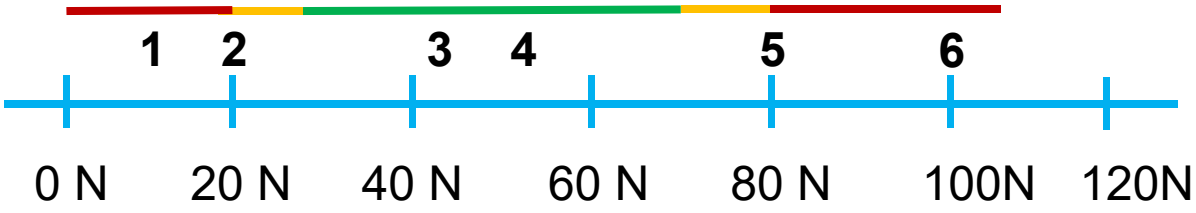
- (Washing, Depyrogenization) Sterilization of Primary Packaging Components
- For "RTU" CCS: ensure of Sterility until point of use, incl.
  - *Sterilization process ensurance (euipment qualification, process validation) (e.g., e-beam)*
  - *Sterility maintenance during shipment*
  - *Sterility ensurance during receipt, storage and until point of use (during DP manufacture)*

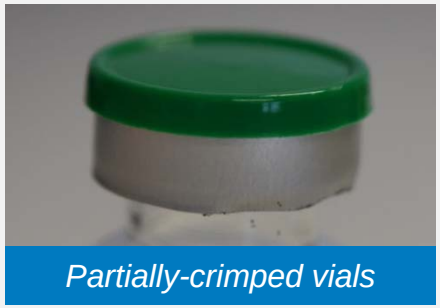
Is the Chosen Primary Packaging (CCS) and the DP Manufacturing Process ensuring sufficient "Tightness"?

- Sterility maintenance
- Gas tightness (as required)
- Within expected variability of the CCS Components and Process parameters, e.g.
  - *Vials (Dimensions)*
  - *Stopper (Dimensions, Rigidity/Flexibility)*
  - *Cap (Dimensions)*
  - *Capping Process Parameters (Seal quality and force)*
- Under storage , shipment & use conditions (intended storage, accelerated and "accidential" storage),
  e.g. could be at 2-8°C vs ambient vs 40°C vs freezing vs shaking
- Known challenges
  - *CCI in "worst case" combinations (e.g., smallest stopper in largest vial and lowest capping pressure)*
  - *CCI in frozen state*
  - *Shipment and CCI (e.g., plunger rod movements), e.g. depends on air bubble size, fill volume, lubrication etc.*

1. Sterility
Seal Quality and CCI

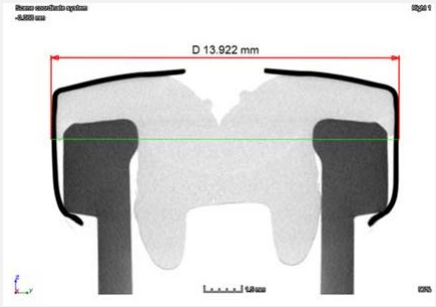
- Capping (crimping, sealing) is a critical unit op for seal quality and CCI
- Seal quality can be assessed via
  - Visual Inspection
  - CCI with differently crimped vials (bracketing)
  - RSF testing with different crimped vials (bracketing)





Partially-crimped vials

Dimpling



2. Particles
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Particles coming from Primary Packaging Components

- Particles from disposable material may enter the product solution and contribute to particulate load (pre-filtration)
- If a product cannot be final filtered, this may render a final product non-compliant
- Sources: stoppers, vials
- Washing may be (some level) of mitigation
- Particulates from components add to the "general load" of particulates in product and may lead to Failure of the
  final DP Specifications and requirements
- Particulates may –or in many cases may not- trigger Protein Instability (e.g., aggregation

Leaching from CCS Components

Glass vials can leach ions(e.g. metal ions such as Al, As, Ba, Fe) into solution. These metal ions are added in glass to impart physical and chemical properties.
Potential impact: "Particles/precipitation" (with formulation components) and/or Product Oxidation

- Barium leaching has been connected to lead to precipitation (barium sulfate particles / precipitate), over storage time (here: 18 months), together with sulfate in the formulation
  (I. Markovic, WCBP CMC Strategy Forum, 2008, Boddapati et al., J Pharm Sci, 1980, 69)
- Aluminum leaching has been evaluated related to leaching and, with various buffers, i.e. phosphate buffers may lead to precipitation over storage time (Ogawa, T. et al., Drug Dev. Ind. Pharm. 2013, 41)
- Amber, coloured glass contain significantly higher quantities of Fe and Mn both, which can lead to product quality impairment including oxidation (e.g., Enever, R. et al., J. Pharm. Sci. 1977, 66)

3. Product Stability & Device/CCS Functionality

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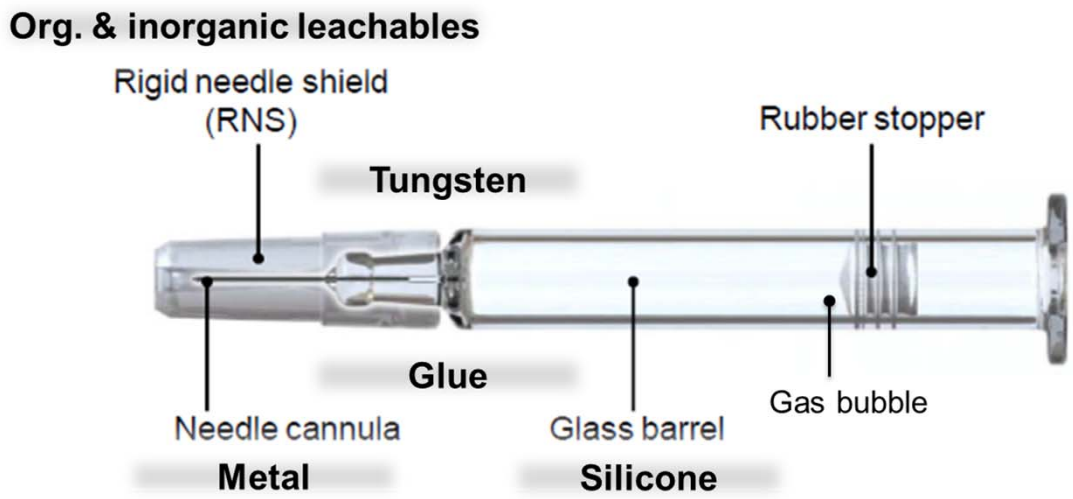
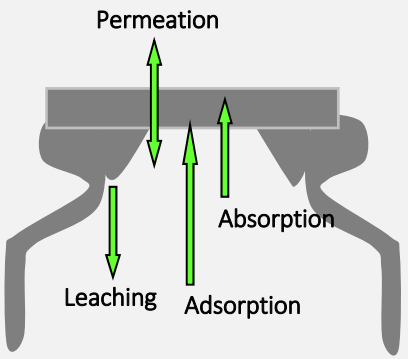
Any kind of Material Interaction could impact Protein Stability and/or Functionality





3. Product Stability & Device/CCS Functionality
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Migration through stopper or RNS components

- E.g. loss of water, or some excipients

Device Functionality Considerations

- Product "drying" and Clogging

Process Residuals or CCS Materials with potential Impact on Protein Stability

- E.g. Silicone (Auge et al., J.PharmSci. (2011), Britt et al., J.Pharm.Sci 101 (2012), Goldbach, *6th Annual Protein Formulation Development and Drug Delivery Forum, (*2015))
- E.g. Tungsten (J.Pharm.Sci, 98, 4695–4710 (2009))
- *Important to study the impact of process residuals (within process variability of the CCS manfuacturing process) on Stability (CQAs) of the protein DP. Typically, either via "spike studies" or stability studies using representative resp worst-case primary packaging*

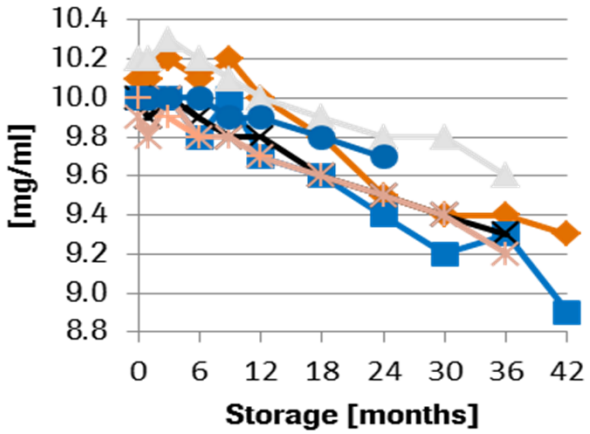
Extractables/Leachables

- Patient Safety considerations?
- Reaction with the API (protein), e.g. conjugation, oxidation, aggregation/precipiation?

Other?

- Protein or Excipient adsorption or absorption ?

Excipient loss via RNS permeation (Storage at 2-8°C)



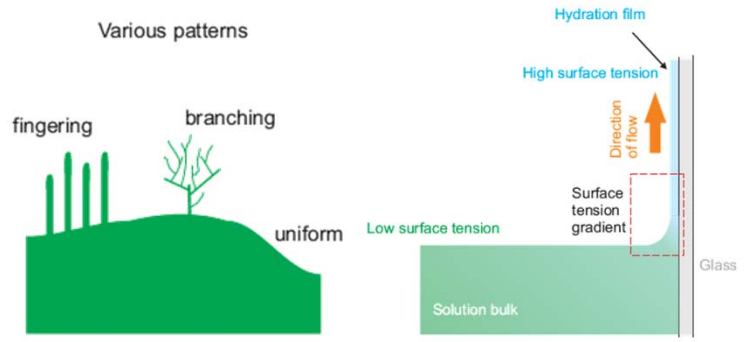
Uhlenbrock, Jegge et al., Poster, PDA Conference "Universe of prefilled syringes", 2014

Goldbach, IBC Barcelona, 2015

3. Product Stability & Device/CCS Functionality

Fogging

- (Most) Formulations are wetting the inner surface of the container
  - Depends on formulation
  - Depends on container
- When dried, these create patterns that are visible (“fog”)
- These defects can be
  - cosmetic
  - critical (CCI concern)

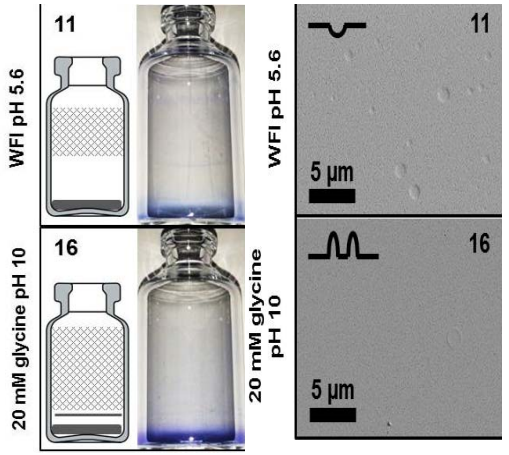


Abdul-Fatah et al., EJPB, Ditter, Poster GPEN, Helsinki, Bauer Dauphin & Mahler, PCT Application

3. Product Stability & Device/CCS Functionality

Delamination

- Glass lamellae (flakes) can detach from the glass surface and migrate as particulates into solution (unacceptable defect)
- Becomes apparent on stability/during storage
- Impacted by
  - Glass type/surface
  - Processing (e.g., sterilization after washing)
  - Storage conditions and time
  - Formulation



Ditter et al., Evaluation of Glass Delamination in Pharmaceutical 10cc Vials, accepted.

4. Other Considerations

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- Interplay with modern manufacturing (Isolators, robots, inspection..)
- Combination products dev paradigm

Summary & Conclusion

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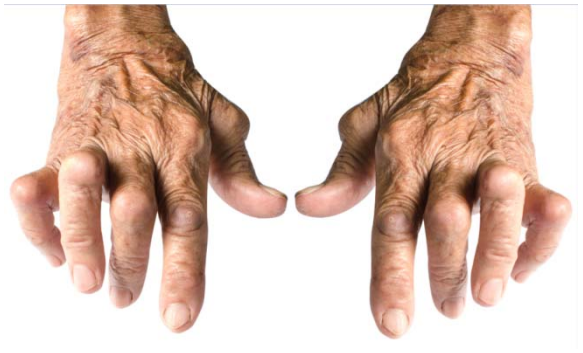
The Drug Product needs to be considered as a whole to ensure efficacy and safety for our Patients!



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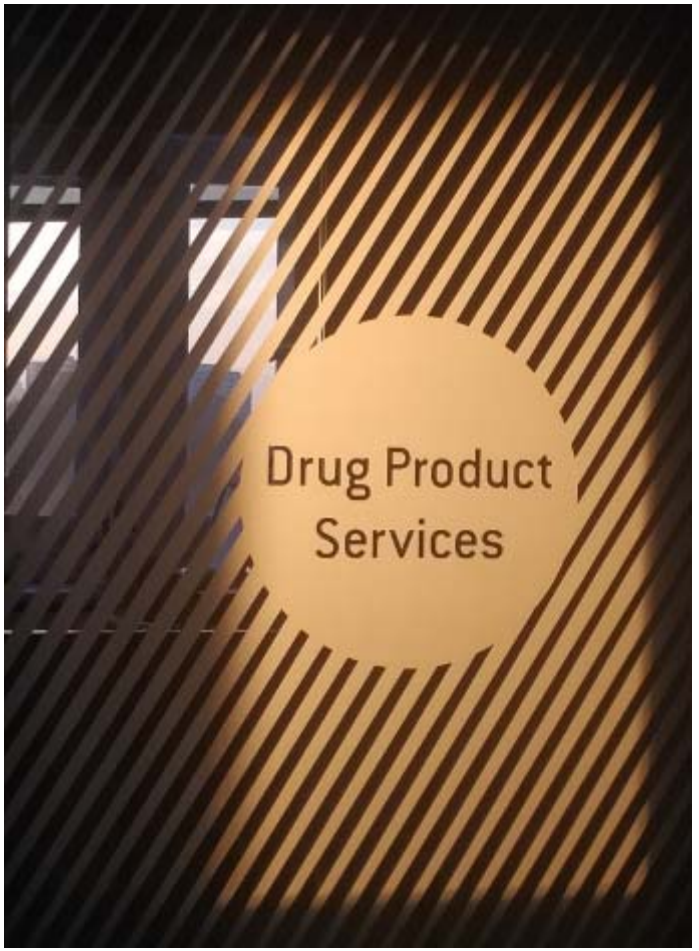

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Thank You

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Backup

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Are Plastic Containers a Solution?

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Potential advantages

- Tighter dimensions/tolerances
- Lower risk of breakage
- Avoidance of silicone oil and tungsten leachables (if found critical)
- (Improved) drainability
- Ability to mould additional features (e.g. graduations, grips etc to aid user interface)

Concerns and things to address

- Permeability (e.g. Water, Oxygen)
- Extractables/Leachables
- Discoloration
- Processing (e.g. Sterilization)
- Scratches (e.g. during processing)
- Container-Closure Integrity

Kathleen L. Miller & Michael Lanthier (2015) Regulatory watch: Innovation in biologic new molecular entities: 1986–2014 Nature Reviews Drug Discovery Volume: 14, Page:83

PhRMA's2013 New Drug Approvals Report

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Sharma B, Bader F, Templeman T, Lisi P, Ryan M, Heavner GA 2004.. EJHP 5:86-91

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Adler et al, ACS

Allmendinger et al., EJPB

Goldbach, IBC Barcelona

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Abdul-Fatah et al., EJPB,

Ditter, Poster GPEN, Helsinki,

Bauer Dauphin & Mahler, PCT Application

Mahler & Müller, 2009, Randolph et al)

Cromwell ME, Hilario E, Jacobson F. *AAPS Journal*. 2006; 8(3): E572-E579.)

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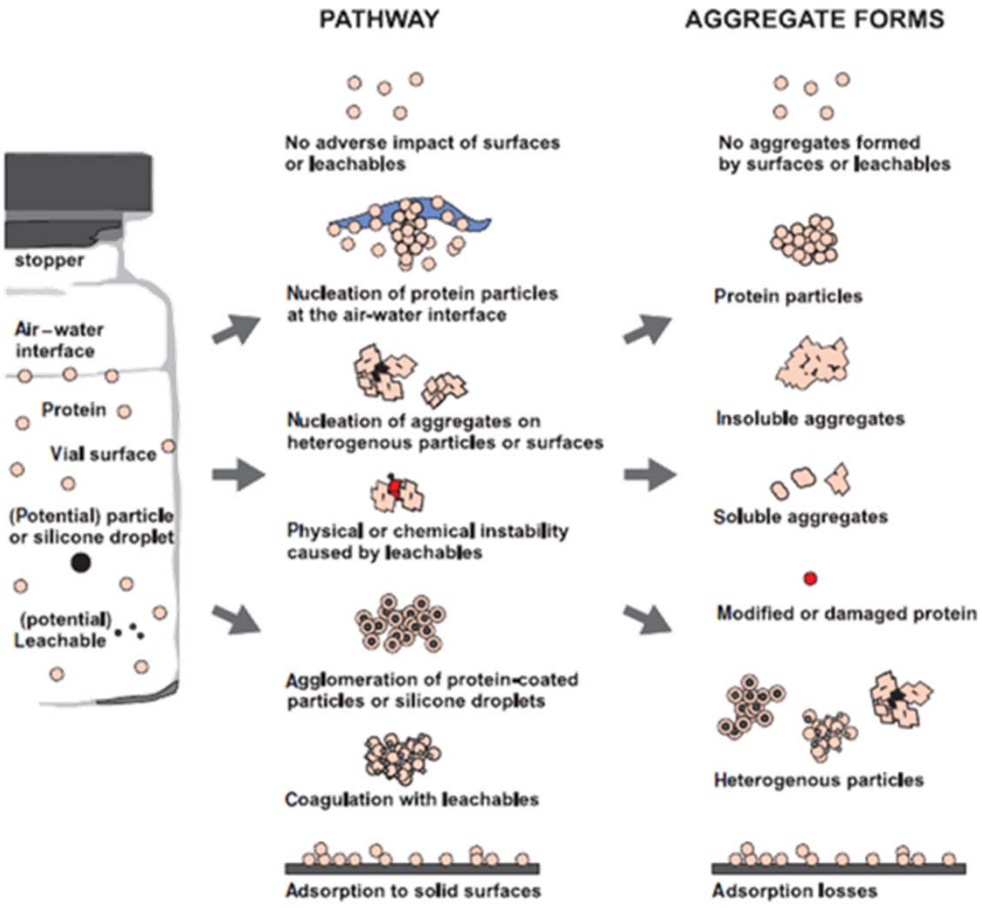
Modified from Bee et al., **J.Pharm.Sci. (2011)**



Injection Time, Injection Force & Functionality

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