Test Methods for Prefilled Syringes

Horst Koller, CEO, HK Packaging Consulting GmbH
Roman Mathaes PhD, Senior Group Leader, Lonza Drug Product Services
Challenges for Biologics Drug Products at the Interface of Formulation, Primary Packaging

- Choice of excipients
- Selection of dosage strength
- Considering route of administration
- Considering preclinical & clinical dose-range

- Formulation & Stability

- Primary Packaging, Device & Delivery, and Usability by Patient
- Route of administration
- Patient capability
- Patient safety
- Device functionality
- Container integrity & sterility

- Manufacturing & Processing “Fill & Finish”
- Product quality & stability
- Yield, cost of goods
- Process design

Connecting People, Science and Regulation®
High Concentration Formulations

As enabler of subcutaneous self-administration...

Drug-device combination product to enable successful SC injection

• Ready-to-use injection
• Potential self administration/home use
• Safety considerations

High concentration formulations (HCFs) to enable successful SC injection of Biologics

• SC administration as typical route for frequent and long-term treatments
• HCF’s to enable high clinical dose requirements, particularly for mAbs
  • Bioavailability typically 60-80%
  • SC injection volume typically max 1-1.5 mL
  • Dosing frequency typically 1-4 injections/month

<table>
<thead>
<tr>
<th>Therapeutic protein</th>
<th>Brand name</th>
<th>Disease</th>
<th>Injection volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Humira™</td>
<td>Anti-inflammatory</td>
<td>0.8 mL</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Ilaris™</td>
<td>Anti-inflammatory</td>
<td>1 mL</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Raptiva™</td>
<td>Anti-inflammatory</td>
<td>1.25 mL</td>
</tr>
<tr>
<td>Insulin</td>
<td>Various</td>
<td>Diabetes</td>
<td>&lt;1 mL</td>
</tr>
<tr>
<td>Interferon a2a</td>
<td>Roferon-A™</td>
<td>Antiviral</td>
<td>0.5 mL</td>
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<tr>
<td>Golimumab</td>
<td>Simponi™</td>
<td>Anti-inflammatory</td>
<td>0.5 mL</td>
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<tr>
<td>Omalizumab</td>
<td>Xolair™</td>
<td>Anti-inflammatory</td>
<td>1.2 mL</td>
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<tr>
<td>Ustekinumab</td>
<td>Stelara™</td>
<td>Anti-Inflammatory</td>
<td>1 mL</td>
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<tr>
<td>Tocilizumab</td>
<td>Actemra™</td>
<td>Anti-Inflammatory</td>
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<td>Certolizumab Pegol</td>
<td>Cimzia™</td>
<td>Anti-Inflammatory</td>
<td>2 × 2mL</td>
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<tr>
<td>Secukinumab</td>
<td>Cosentyx™</td>
<td>Anti-Inflammatory</td>
<td>2 × 1mL</td>
</tr>
</tbody>
</table>

High Concentration Formulations

As enabler of intravitreal injections...

**Intravitreal (IVT) / back of the eye (BOTE) injections**
- Direct delivery into vitreous to achieve sustained drug levels and to overcome the limitations of systemic dosing by evading the blood-retinal barrier.
- Biologics are increasingly important for BOTE treatments

**Drug-device combination products to enable successful IVT injection**
- Ready to use injections
- Sterility of ophthalmic preparation during handling

**HCFs to enable successful IVT injections**
- Low injection volume of max. 50-100 µL
- Prolonging therapeutic levels and reducing the frequency of injection

Integrated Drug Product Development

High Concentration Drug-Device Combination Product

Formulation & Stability

- Aggregation, subvisible and visible particles
- Special considerations

Container Closure System & Device

- Primary packaging compatibility
- Container closure integrity
- Functionality of devices

Application

- Viscosity and injection time
- Administration challenges
- High volume injections
Formulation & Stability Challenges

Formulation development at high concentration

High concentration formulations (HCF) come along with (known) stability challenges

- With increasing concentration, propensity to self associate and aggregate increases
- Thermodynamic non-ideality ("macromolecular crowding") leading to potentially increased level of
  - native, reversible self-association
  - aggregates, sub-visible and visible particles
- Potential impact on solution color (intrinsic or extrinsic) and opalescence (increased Tyndall effect, aggregates, liquid phase separations)

Special Considerations for IVT formulations

- Limited availability of excipients and more stringent endotoxin levels for IVT use
- Reduce off-label use for IVT formulations

Sub-visible and Visible Particles

Occurrence and clinical relevance

Particulates can be different things and can be of different relevance

• Particles can occur spontaneously on DP stability
  *Poor formulation, poor manufacturing process or poor primary packaging?*

• Particles can also be something else than protein:
  *e.g. environmental contaminants, silicone, air bubbles*

Little is known about clinical relevance of particles

• There is no clear ‘threshold’ of particles with an established link to safety

• Safety concerns are however prevalent. FDA expects product specific limits for BLAs ¹)

• Typically, benchmark what is in the market and aim to minimize as much as possible

Special concerns of particulates after IVT injection

• Uveitis, blockade of the Schlemm’s canal; Increased intra-ocular pressure

• Impaired vision depending on the particle nature and its behavior in the vitreous humor

A. Rosenberg (2012): Workshop on Protein Aggregation and Immunogenicity, Breckenridge
Sub-visible and Visible Particulates

Occurrence and clinical relevance

Visible Particles

- **Visible particle requirements:**
  - USP <1>:
    “essentially free from particles”
  - Ph.Eur. Parenterals
    “practically free from particles”

- **Visible particles tests:**
  - USP <790>, Ph.Eur. 2.9.20
  - operator based and probabilistic test method

Sub-visible particles

- **Light obscuration test**
  - USP <789>
    NMT 50 particles/ mL ≥ 10 μm
    NMT 5 particles/ mL ≥ 25 μm
  - USP <771> (ophthalmic preparations, draft/in revision)
    - Ph Eur 2.9.19
      NMT 6000 particles/ container ≥ 10 μm
      NMT 600 particles/ container ≥ 25 μm

- **Filing of product-specific limits according to clinical exposure**
Analytical Toolbox for Particles

No single analytical method can assess the whole size range

### Principle

<table>
<thead>
<tr>
<th>Nano track analysis</th>
<th>Resonant mass</th>
<th>Coulter counter</th>
<th>Flow imaging microscopy</th>
<th>Light obscuration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NTA</strong></td>
<td><strong>Archimedes</strong></td>
<td><strong>CC</strong></td>
<td><strong>MFI</strong></td>
<td><strong>HIAC</strong></td>
</tr>
</tbody>
</table>

**Tracking of Brownian motion of individual particles**
- Changes in frequency due to added mass
- Changes in resistance due to volume displacement
- Weighing of single particles passing through a flow cell
- Drop in current due to the amount of light blocked

### Raw data

<table>
<thead>
<tr>
<th>Raw data</th>
<th>Video**, #/mL/size</th>
<th>#/mL/size, particle buoyancy</th>
<th>#/mL/size</th>
<th>#/mL/size, images**, particle morphology</th>
<th>#/mL/size</th>
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<td>0.03</td>
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<td>0.05</td>
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<td>0.20</td>
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<td>0.30</td>
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<td>25.0</td>
<td></td>
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</tr>
</tbody>
</table>

### Optimal size range [um]*

| Optimal sample concentration [particles/mL]* | 3x10^8 - 1x10^9 , -20-70 centers per frame | < 8x10^5 , coincidence < 5% | ~ 2x10^6 ,  MFI: < 9x10^4 | FC: < 1.5x10^6 | < 1x10^4 |

* As for the supplier. In all the cases, the optimal sample concentration is much more higher than the typically found in nonstressed high concentrated protein samples or in stressed samples at relevant conditions

** Further analysis needed to get #/mL/size

Informative data

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Application

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- Administration challenges
- High volume injections
Primary Packaging Challenges

Container Closure System (CCS) compatibility

- “A container closure system refers to the sum of packaging components that together contain and protect the dosage form.”

- Suitability for intended use
  - Protection of dosage form and drug
  - Compatibility (CCS with drug)
  - Safety (E&L related patient impact)
  - Performance (Functionality of drug delivery system)

- Info on suitability of storage (shipping) of biologics should be included
  ...greater potential for adverse impact on quality of biologics during storage and shipping

FDA Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (1999)
Prefilled Syringes

Development concerns to address

<table>
<thead>
<tr>
<th>Factor</th>
<th>Concerns for CCS suitability</th>
<th>Mitigation</th>
</tr>
</thead>
</table>
| Tungsten residues             | • Oxidation  
• Aggregation  
• Syringe-to-syringe variability of residuals | • Spiking studies (pin extracts, salts of W)  
• Stability studies |
| Silicone oil                  | • Aggregation  
• Subvisible and visible particles                                                          | • Spiking studies (silicone oil emulsion)  
• Stability studies (including worst case siliconised syringe) |
| Multiple contact materials    | • Organic and inorganic leachables (Rubbers of stopper / RNS, needle glue)  
• Latex allergy  
• Compatibility | • E&L studies  
• Assess components for dry natural rubber (DNR) components / Latex allergens ¹  
• Stability studies |

¹ see new FDA Guidance on Labeling, March 2013
Adler M. (2012), AmPharmRevw, 15(1), 96
Prefilled Syringes

Tungsten

• **Tungsten pins are used to form the fluid path (needle channel)**
  • High temperature process with possibility for metal particles deposits (tungsten oxide, tungstate)
  • Interaction with glass leads to formation of tungsten residuals

• **Tungsten may cause protein oxidation and aggregation** 1)
  • Effect of tungsten (within process variability) on stability of protein should be assessed.
  • However, for most protein formulations, tungsten is of no issue.

• **Risk assessment**
  • Formulation – pH, concentration, ionic strength consideration (Solubilisation of Tungsten increases below pH 6)

Manufacturers’ process

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Prefilled Syringes

Extractables & Leachables

- **EXTRACTABLES**: Chemical components that are removed from a material by exertion of an artificial exaggerated force. For a rubber stopper, e.g.
  - Ingredients of the rubber formulations
  - Impurities of these ingredients
  - Reaction/degradation products during rubber manufacturing

  NB. Extraction conditions not universal.

- **LEACHABLES**: Chemical compounds that migrate from a contact material into drug products during storage at “normal” simulated use conditions
  - Typically a «subset» of extractable
  - Quantification & identity relevant

- **IMPORTANCE OF E/L-TESTING**
  - TOXICITY (incl. acute, chronic, genotox)
  - May REACT with API, DRUG COMPONENTS
  - Other (e.g. Matrix Interference with Analytical Method/QC)
Prefilled Syringes

Silicone oil

- Silicone oil is used for lubrication of the syringe glass barrel.
  - Baked-on silicone oil: ~ 0.1 mg/barrel
  - Sprayed-on (free) silicone oil ~ < 1 mg/barrel, ideally ~ 0.5 mg/barrel
- Impact on drug product stability to be evaluated 1) 2)

- (Free) Silicone shows up in Drug Product as “Particulates”
  - Sampling and measurement technique most relevant, e.g. use of flow imaging) 3)
  - Appropriate characterization required, likely considerable a non-CQA

Is Silicone a safety concern for ocular products

Intravitreal Silicone Oil Droplets After Intravitreal Drug Injections

Bakri, Sophie J. MD; Ekdawi, Noha S. MD

Retina
July/August 2008
Vol. 26 - Issue 7: pp 996-1001

Abstract

Purpose: To present the finding of tiny silicone oil droplets in 15 eyes of 15 patients after intravitreal injections of an anti–vascular endothelial growth factor agent or triamcinolone acetonide and to discuss the likely source of silicone oil.

Methods: In an observational case series, charts of patients who had undergone intravitreal injections by one surgeon were reviewed retrospectively. The finding of intravitreal silicone oil droplets was noted. The following information was also documented:

- injections of an anti–vascular endothelial growth factor agent or triamcinolone acetonide and to discuss the likely source of silicone oil.

Results: Fifteen eyes of 15 patients were found to have silicone oil droplets documented after a various number of injections (range, 1–16). Patients were asymptomatic, and there were no adverse side effects associated with the presence of silicone oil droplets at examination.

Conclusions: Silicone oil droplets may occur in the vitreous cavity after intravitreal drug injections. There were no adverse effects found associated with silicone oil in the vitreous after injections of anti–vascular endothelial growth factor agents or triamcinolone acetonide. The likely source of silicone oil is the needles and syringes used for the injections.
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Functionality Challenges

Functionality testing

**Distribution of silicone oil is critical**
- impacted by e.g. spray pattern, storage/aging, formulation interaction
- Characterize and understand lot-to-lot variability
- Set acceptance criteria
  - minimum siliconization for performance
  - maximum siliconization for particle control
- Correlate to critical functional parameters

**Functionality testing on Stability**
- Ensure syringe functionality over shelflife (PFS may «get stuck»)
  - Piston release force (Break Loose force)
  - Piston travel force (Glide or Extrusion force)
- Power injection function force (autoinjectors)
- Tip cap removal force
Prefilled Syringes

Ensuring sterility - CCIT

- All products labeled as sterile are required to be free of microbial contamination throughout their shelf life (obligatory CQA)
- Container closure integrity (CCI) addresses the maintenance of integrity to prevent microbiological ingress in sterile product packaging until the time of use
- Complex combination products feature several sealing areas and moveable parts
- Assessment of individual sealing areas with helium leak CCIT is necessary, e.g. sealing area 2 to ensure a sterile needle

Data from R. Mathaes, S. Pelaez, Lonza Drug Product Services
Integrated Drug Product Development

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Application

- Viscosity and injection time
- Administration challenges
- High volume injections
Administration Challenges

Syringability and injection time

Injection time depending on Hagen Poiseuilles’s law for laminar flow in tubes: What matters for syringability/injection time?

- Administration device configuration (needle inner diameter & length, autoinjector performance, plunger/glass friction).
- Viscosity = f(temp, conc, shear rate)
  - Protein concentration is critical (upper concentration spec!)
  - Temperature can be significant (product temperature prior use)
  - Protein can make a difference (Newtonian vs. Non-Newtonian behaviour).
- When estimating injection forces representative for in vivo situation, back-pressure of the tissue has to be considered.

\[ Q = \frac{\pi r^4 \Delta P}{8 \mu L} \]

Q = flow rate  
\( \mu \) = viscosity  
\( r \) = radius of the needle  
\( \Delta P \) = pressure drop  
L = length of the needle

Allmendinger, A. et al. (2015), Pharm Res 32: 2229-2240. DOI 10.1007/s11095-014-1611-0
Viscosity Challenges

Syringability and injection time

- Exponential increase of viscosity of mAb formulations with concentration
  - “Macromolecular crowding”: Mooney equation
  - Formulation dependent: electrostatic interactions, surface net charges
  - Temperature dependent

- A rheological characterization prior to product development is key to meet the QTTP.

\[ \eta = \eta_0 \exp \left[ \frac{2.5\phi}{1 - k\phi} \right] \]

Mooney M. J colloid Sci 6, 162, 1951
Viscosity Challenges

Shear dependent viscosity matters

- Many proteins show shear-thinning behaviour, with decreasing viscosity at higher shear rates according to the “power law” model.
  \[ \mu = K \gamma^{n-1} \]

- High shear rates up to \(10^{-6}\) s\(^{-1}\) occurring at the needle wall (Weissenberg–Rabinowitsch–Mooney equation)

References:
Fischer I. et al. (2015), Int J Pharm, 493 (1-2)
Allmendinger A. et al. (2014), EJPB, 87: 318-28
Viscosity Challenges

Specific molecules or protein/protein mixtures

Molecule specific viscosity challenges

- Viscosity in formulations of PEGylated molecules
- Impact of polymer size, variability, branching
- Few ways of reducing viscosity by excipients

Protein/Protein Mixtures

- Viscosity and rheological properties of mixtures of different proteins (e.g. mAbs) need to be experimentally evaluated
- Viscosity is expected to be different to simple additive/multiplicative rules

Administration Challenges

Specific molecules or protein/protein mixtures

During clinical studies: preparation of IVT dosing solution from a vial

- Potential lyophilisate reconstitution and withdrawal of solution from vials
- Potential dilution steps
- Downdosing: “Eject” liquid to the desired injection volume

Commercial products: often pre-filled syringe

Dosing accuracy as main challenge

- Precise delivery devices needed for low volumes. Variability in syringes used by HCP.
- High user dependent variability (e.g. air bubble etc.)
- Precision hard to achieve with HCFs:
  - Small inaccuracies in injected volume can have big impact on absolute dose delivered
  - High viscosity may impact user dependent variability.

2 http://slideplayer.com/slide/5778115/
3 http://slideplayer.com/slide/4311396/
Alternatives to High Concentrations

Pushing the Boundaries of SC Administration

Historic View on SC administration volumes

- **Limited s.c. injectable volume** (human) of approximately **1 to 1.5 ml** (Gatlin et al., 1999)
- “…**Maximum medication volume** to be injected (SC) into the site at one time should be less than or equal to **2.5 mL**…” (Caritas Health Group, Community Care Services, Regional Palliative Care Program)
- Humans and other furless animals have fibrous bands in the panniculus adiposus that reach into the deep fascia [McMinn, Rose]. These anchors reduce the compliance of the tissue space to injected fluids, such that **subcutaneous injections are generally limited to less than 2ml** (Frost, 2007)

What speaks against higher SC volumes

- Interstitial matrix limits SC injection
- Hyaluronic Acid and collagens provide a matrix and barrier in the interstitial tissue
- The tissue provides back-pressure

# Increasing the SC Dosing Volume

*Knows and unknowns about SC administration related to injection pain*

<table>
<thead>
<tr>
<th>Injection pain influencing factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection speed</td>
<td>Slow injection speed is considered to cause less injection pain</td>
</tr>
<tr>
<td>Injection site</td>
<td>The hypodermis is a highly variable tissue, which significantly differs across body sites</td>
</tr>
<tr>
<td>Temperature of the drug product</td>
<td>Drug Products at body temperature are considered to cause less injection pain</td>
</tr>
<tr>
<td>Formulation parameters</td>
<td>Limited relevant clinical data available</td>
</tr>
<tr>
<td></td>
<td>Viscosity: Influencing spreading, Osmolality, pH: Directly influence injection pain</td>
</tr>
<tr>
<td>Patient-to-patient differences in pain tolerance</td>
<td>Subjective experience of pain</td>
</tr>
<tr>
<td>Injection depth within the SC tissue</td>
<td>No relevant clinical data available</td>
</tr>
<tr>
<td>Injection needle</td>
<td>No relevant clinical data available</td>
</tr>
<tr>
<td></td>
<td>A smaller needle gauge (larger needle diameter) is considered to cause greater injection pain</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>Application of topical anesthetics before actual injection is considered to reduce injection pain</td>
</tr>
</tbody>
</table>

Alternatives to High Concentrations

Pushing the Boundaries of SC Administration

- **Increasing the SC dosing volume**
  - Recent study on injection volumes of one 1.2-mL bolus injection over 5 s and three 3.5-mL injections over 1, 4, and 10 min confirmed that all injections were well tolerated (Dias et al., AAPS PharmSciTech 2015)

Pushing max injection volume boundaries beyond the 1ml is considered a viable option

- **Other options to overcome**
  - Permeation enhancers (e.g. halozyme)
  - Increase bioavailability
  - Decrease dosing frequency
  - Increase activity: Molecular assessment


Increasing the SC Dosing Volume

Permeation enhancer Hyaluronidase (Enhancer)

<table>
<thead>
<tr>
<th>Therapeutic protein</th>
<th>Trade name</th>
<th>Disease</th>
<th>Injection volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>HerceptinSC®</td>
<td>Oncology</td>
<td>5 mL</td>
</tr>
<tr>
<td>Rituximab</td>
<td>MabtheraSC®</td>
<td>Oncology</td>
<td>11.7 mL</td>
</tr>
<tr>
<td>Immune Globulin 10%</td>
<td>Hyqvia®</td>
<td>Primary immunodeficiency</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

- **Functionality of hyaluronan (hyaluronic acid)**
  - Controls the hydrolytic conductivity
  - Impacts spreading of a SC injected fluid in the ECM
  - Enzymatic hyaluronan cleavage is reversible within 1-2 days

- **Cleavage of hyaluronan by hyaluronidase leads to**
  - Reduction of tissue back-pressure
  - Enables fast administration

What’s next for IVT Administration

Ocular long-acting drug delivery

**Drug Delivery approaches**
- Hydrogels / in-situ gelling systems
- Liposomes, nanoparticulates, microparticulates
- Biodegradable implants (injectable)
- Implanted reservoirs or pumps (surgery)

**Factors to consider:**
- High drug loading/ low burst release/ long release
- Injectability with small Gauge needle
- Particle movement / vitreous clouding
- Ocular immune system tolerance

**The alternative: molecular approaches**
- Combination therapies
- Conjugation to polymer/ fusion to carrier proteins

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1) Jamekhorshid et al. (2014), Renewable & Sustainable Energy Reviews, 31: 531-42
2) Navratil et al., On Drug Delivery: Ophthalmic Drug Delivery, 48, 2014; and DSM biopolymer
Summary

• Increased need for high concentration formulations remains for SC and IVT administration

• Viscous high concentration protein formulations pose (expected) challenges involving
  • DP stability
  • DP-CCS compatibility and functionality
  • DP administration.

• An integrated Drug-device combination product development approach is recommended.

• High concentration formulations may not be the only solution.
  • Increasing the max. SC injection volume
  • Ocular long acting drug delivery approaches
Acknowledgements