Protein-Device Compatibility

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Device Development Department, Roche

Agenda

- System of Interest
- Drug/Device Interface and Aggregation Risk Factors
- Case Study 1 – Turbid Biological DP Solution
- Case Study 2 – Pushing the Limits: Ocular Applications

Regulatory Scheme for Drug/Biologic Device Combination Product

	FDA	EMA
Regulated by	21 CFR 3.2 (e)	2001/83/EEC
Definition	A product comprised of two or more regulated components, i.e. drug/device, biologic device, drug/biologic, or drug/device/biologic, that are physically, chemically or otherwise combined or mixed and produced as a single entity.	A device that combines with medicinal product to form a single, integral product designed to be used exclusively in the combination. The product is not reusable. Regulated by the medicinal product regulation.

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Attractiveness of Prefilled Systems

Worldwide market growth	Product Differentiation	Enhancing level of market share	Less Overfill
More efficient delivery system	Reduction in medication error	Lower overall cost	Less risk of sterility issue
Accurate dosing	Usability	Enabling home use	Reduction in wasted product

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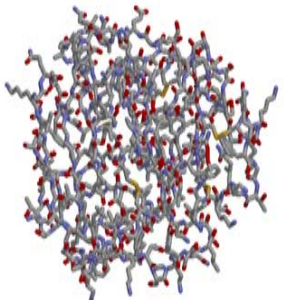
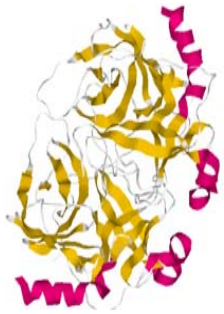
Complexity of Protein Structure

Size & Complexity – Small Molecule Drugs & Proteins

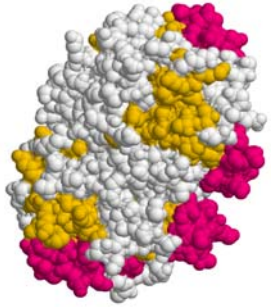
	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size			
	Aspirin 21 atoms	hGH ~3,000 atoms	IgG Antibody ~25,000 atoms



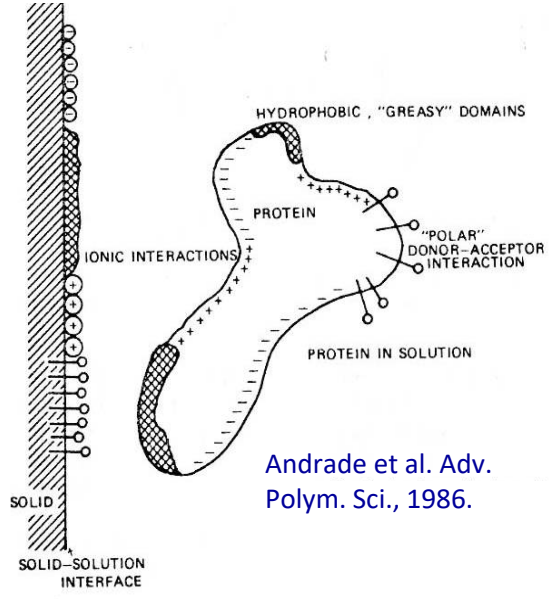
Amphoteric and amphiphilic properties



Marginal stability of folded protein structure

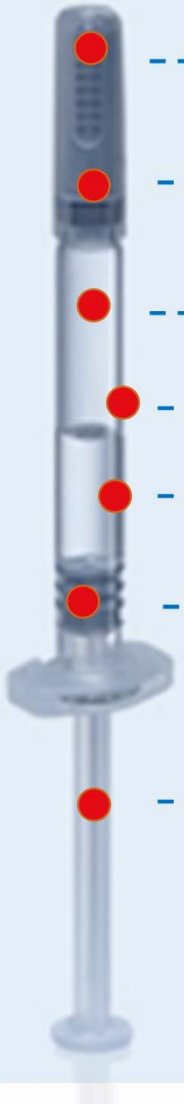


Hydrophobic core / hydrophilic shell



Andrade et al. Adv. Polym. Sci., 1986.

Why we are interested

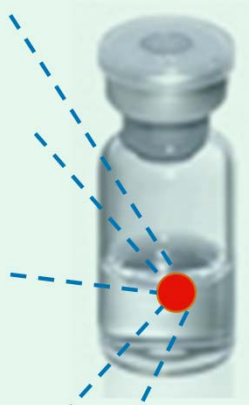


- Material Interactions Manufacturing Processes (Tungsten)
- Hydrophobic effects
- Interfacial Interactions
- Surface Effects
- Consequences of Elastomers
- Injection Forces

Container + Delivery System

Drug/Device Combinations Space

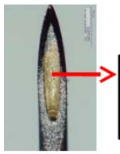
Container

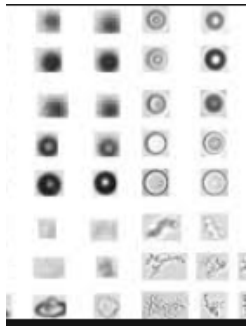


- Viscosity
- Surfactants
- Protein Stability
- Chemical Sensitivities
- Physical Sensitivities

Challenges of drug/device combination products

$$F = \frac{8QuL}{\pi R^2} * A$$

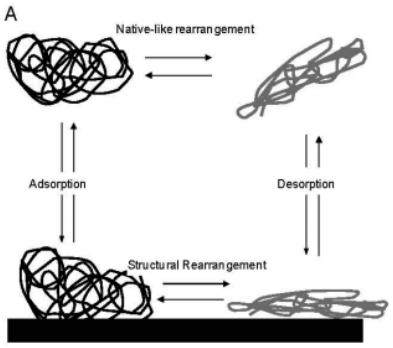




Challenges of drug/device combination products

Technique	Used to Detect
ICP/MS	Inorganic elements (W, Al, Fe, etc.)
GC/FID	Volatile organic molecules (Boiling point < 300 °C)
GC/MS	Volatile organic molecules (Boiling point < 300 °C)
HPLC	UV absorbing molecules
LC/MS	Organic small molecules (polar, containing hetero atoms O, N, etc.)
LC/ELSD	Universal detector
NMR	Organic compounds

Nashed-Samuel, Yasser, 5th Annual PFS Summit, San Diego, CA, 2015



Leaching of materials into formulation

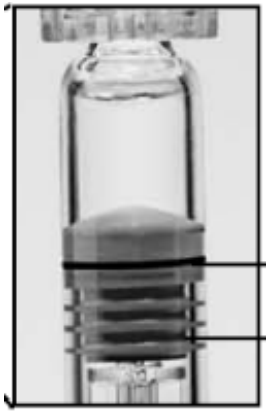
Protein adsorption: Change in delivered dose

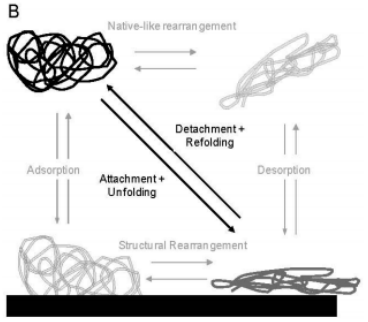
Formulator's Perspective

Interfacial effects/ Hydrophobic effects

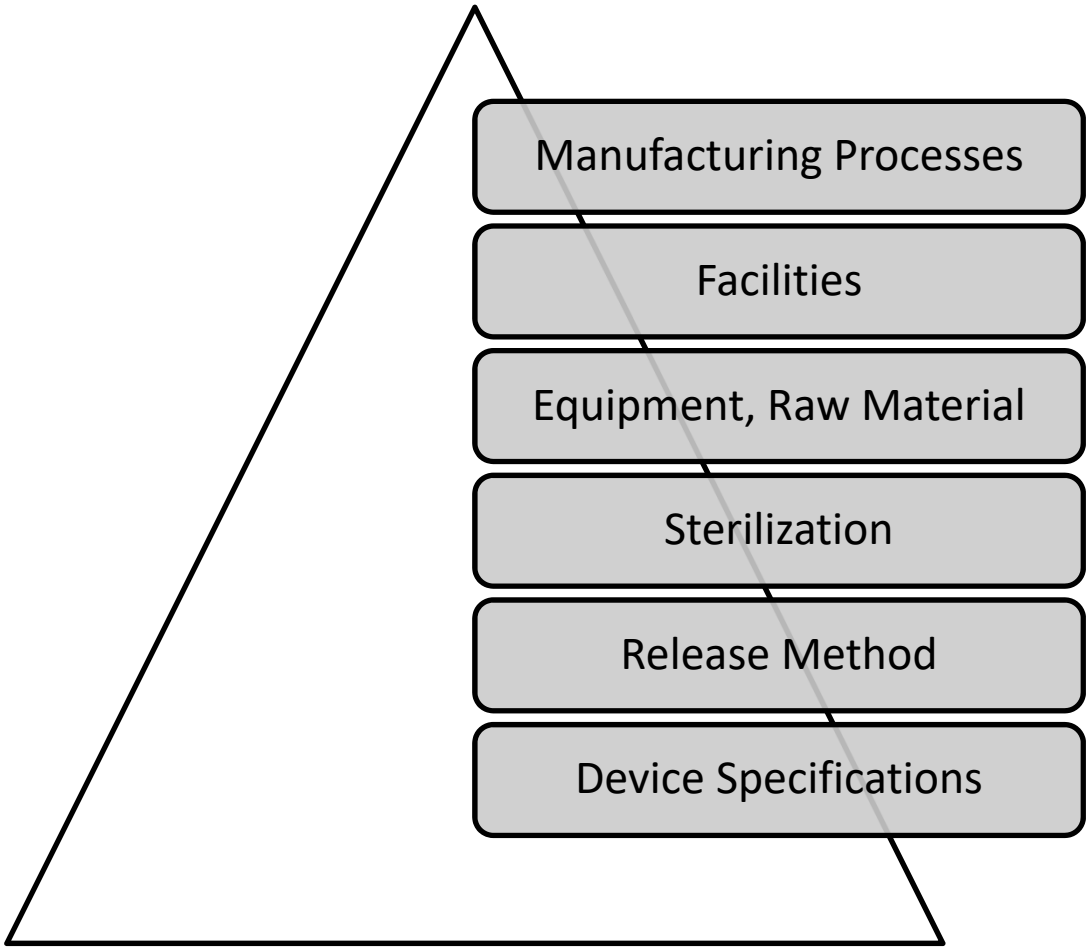
Change in drug stability during storage/ delivery

Device action impacting performance





Manufacturing Challenges can mean changes in:



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- **Case Study 1 – Turbid Biological DP Solution**
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Case Study 1: Tungsten - Background

- Used in glass forming process, high temperature shaping
- Tungsten oxide deposits
- Stoppering process can increase levels
- In acidic solutions, pH<6, W and WO can form polyionic species.
- Protein concentration and ionic strength can also induce W-induced protein degradation
- Significant batch-batch variability
- Process control

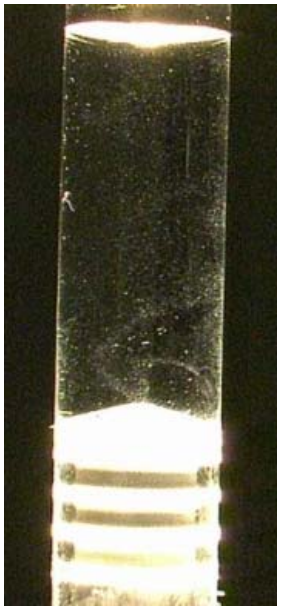
Turbid biological DP: Problem Definition

Affected product

- **Small, highly diluted protein** filled in **luer-type PFS**
- Established on the marked since 1996

What was observed?

- Already known: **individual turbid syringes** were observed during visual inspection (<0.2% / batch).
- Turbidity is described as a white tornado at different intensities
- **Recently: several failures in AQL testing**

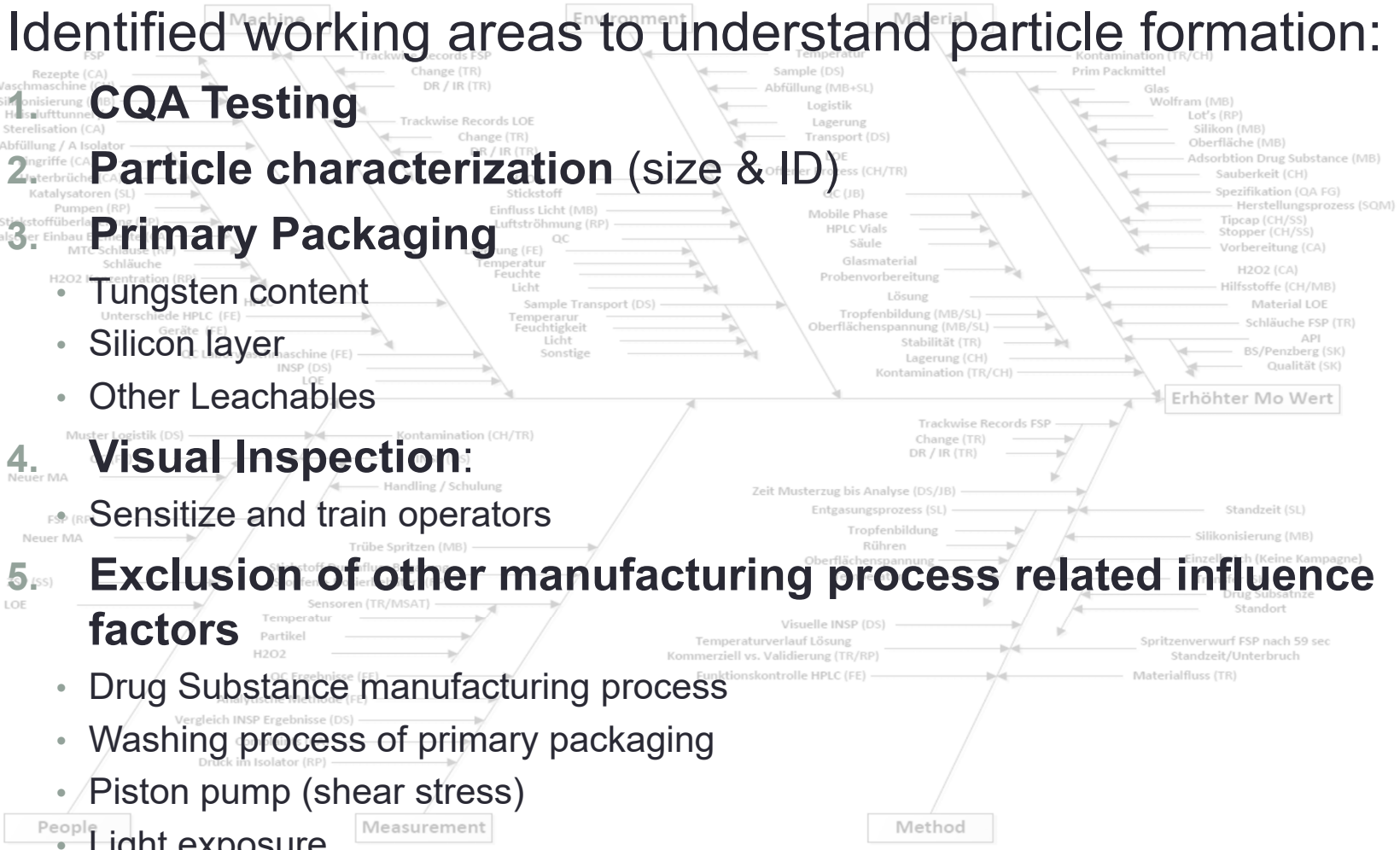


Actions

⇒ Root cause analysis was initiated to improve product quality

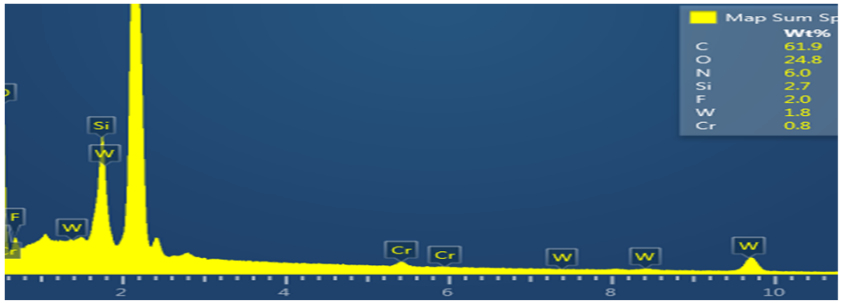
Identified working areas to understand particle formation:

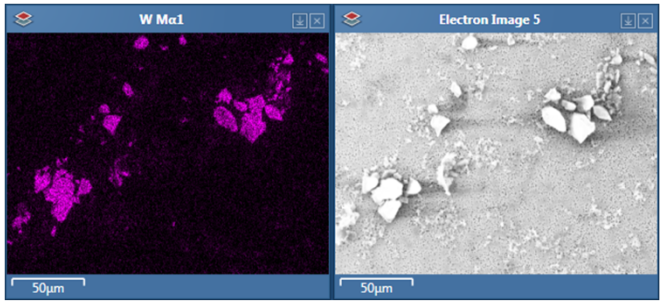
1. **CQA Testing**
2. **Particle characterization** (size & ID)
3. **Primary Packaging**
   - Tungsten content
   - Silicon layer
   - Other Leachables
4. **Visual Inspection**:
   - Sensitize and train operators
5. **Exclusion of other manufacturing process related influence factors**
   - Drug Substance manufacturing process
   - Washing process of primary packaging
   - Piston pump (shear stress)
   - Light exposure
   - VHP



Particle ID & CQA Testing of turbid syringes

EDX

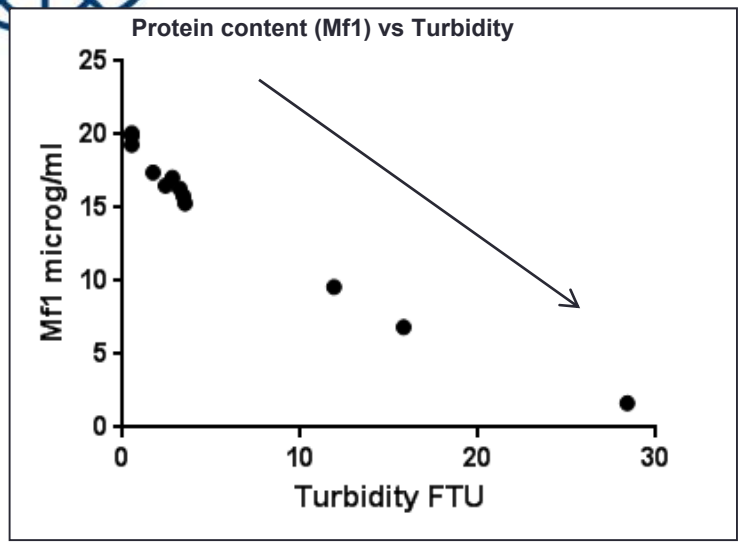


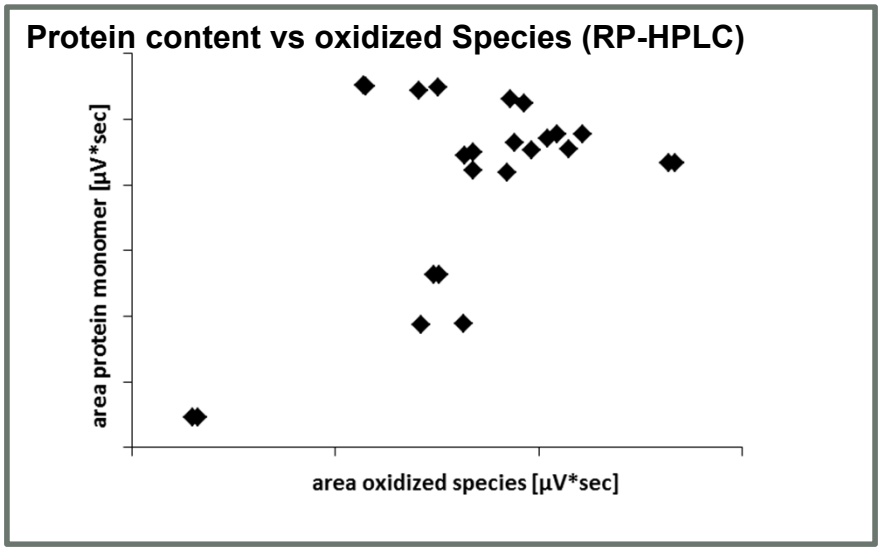


- **Particle ID** showed the **presence of protein and Tungsten** in the particles via FTIR and EDX

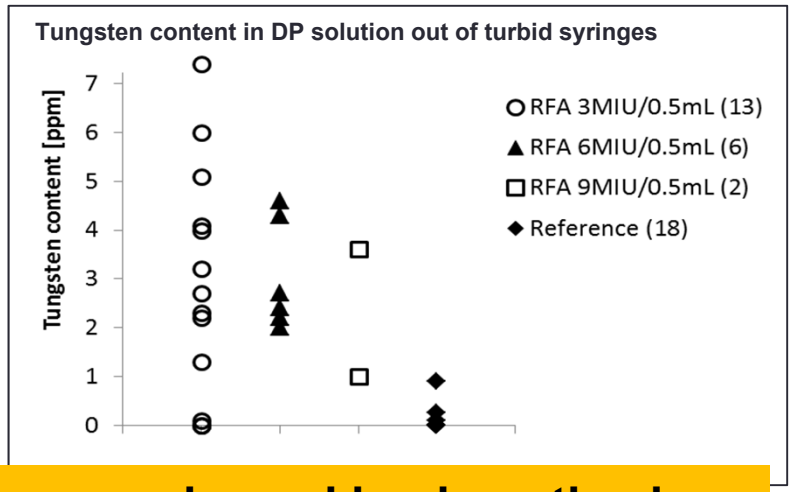
Particle ID & CQA Testing of turbid syringes

RP-HPLC & ICP-MS





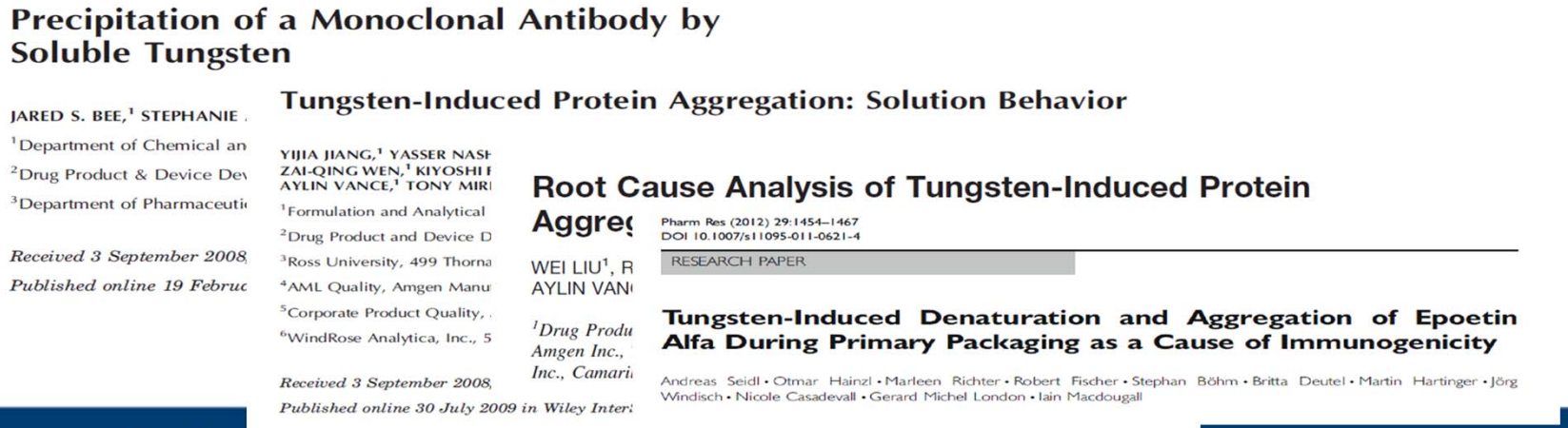
- Direct correlation between decreasing protein content and increasing turbidity
- **Tungsten content (by ICP-MS) was increased** in turbid syringes compared to non-turbid syringes
- **No clear relationship for protein content and oxidized species**, meaning no oxidation events for protein monomers



Tungsten induced aggregation as one main working hypothesis

Previous Experiences?
Tungsten induced aggregation: Experiences for highly diluted proteins

- Experiences with a **PEGylated small protein:**
  - No increased turbidity or particle formation
  - Slight increase in aggregation and other oligoforms were observed after spiking with 10 ppm tungsten
  - A tungsten limit for incoming primary packaging was set to 4000 ng/syringe (with a fill volume of 0.5mL this means 4000 ng/0.5 mL = 8ppm)
- Experiences with another **small highly diluted protein formulated in a different buffer**
  - Increase in dimer formation at tungsten concentration > 18 ppm.
- What is known in the literature



Precipitation of a Monoclonal Antibody by Soluble Tungsten

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Tungsten-Induced Protein Aggregation: Solution Behavior

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Published online 30 July 2009 in Wiley Inter

Root Cause Analysis of Tungsten-Induced Protein Aggreg

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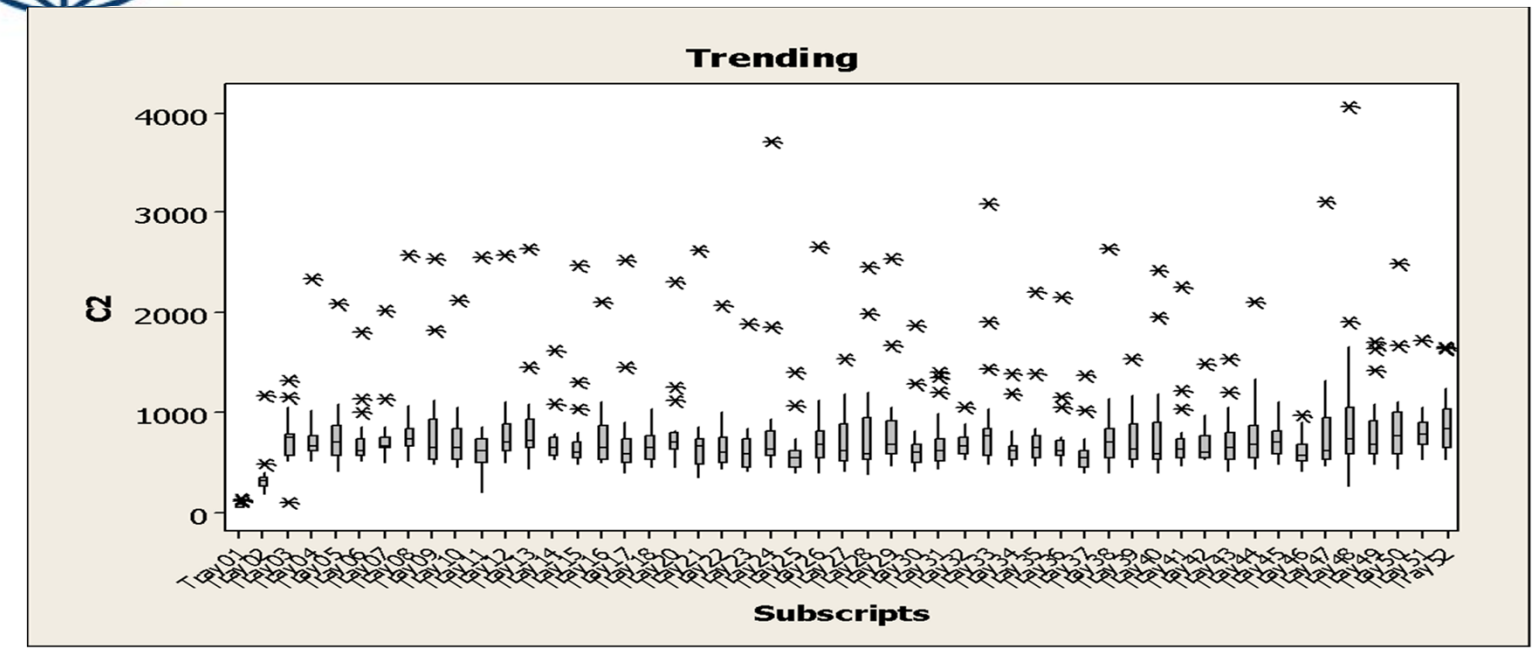
Pharm Res (2012) 29:1454–1467
DOI 10.1007/s11095-011-0621-4
RESEARCH PAPER

Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

Andreas Seidl • Otmar Hainzl • Marleen Richter • Robert Fischer • Stephan Böhm • Britta Deutel • Martin Hartinger • Jörg Windisch • Nicole Casadevall • Gerard Michel London • Iain Macdougall

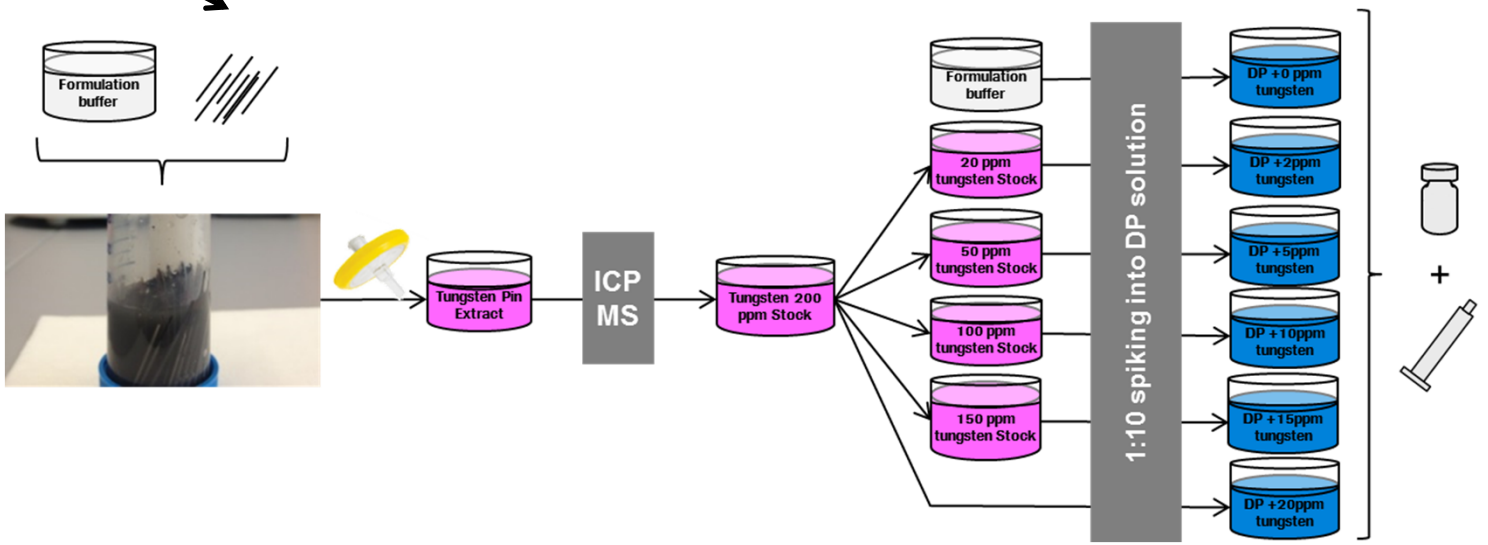
Analysis of Tungsten content within incoming PFS



- Mean tungsten content: **730 ng/PFS**
- Outliers with very high tungsten values (up to >4000ng)
- Is there a direct relationship between Tungsten content and Turbidity? What is the level of Tungsten Sensitivity for the affected protein?

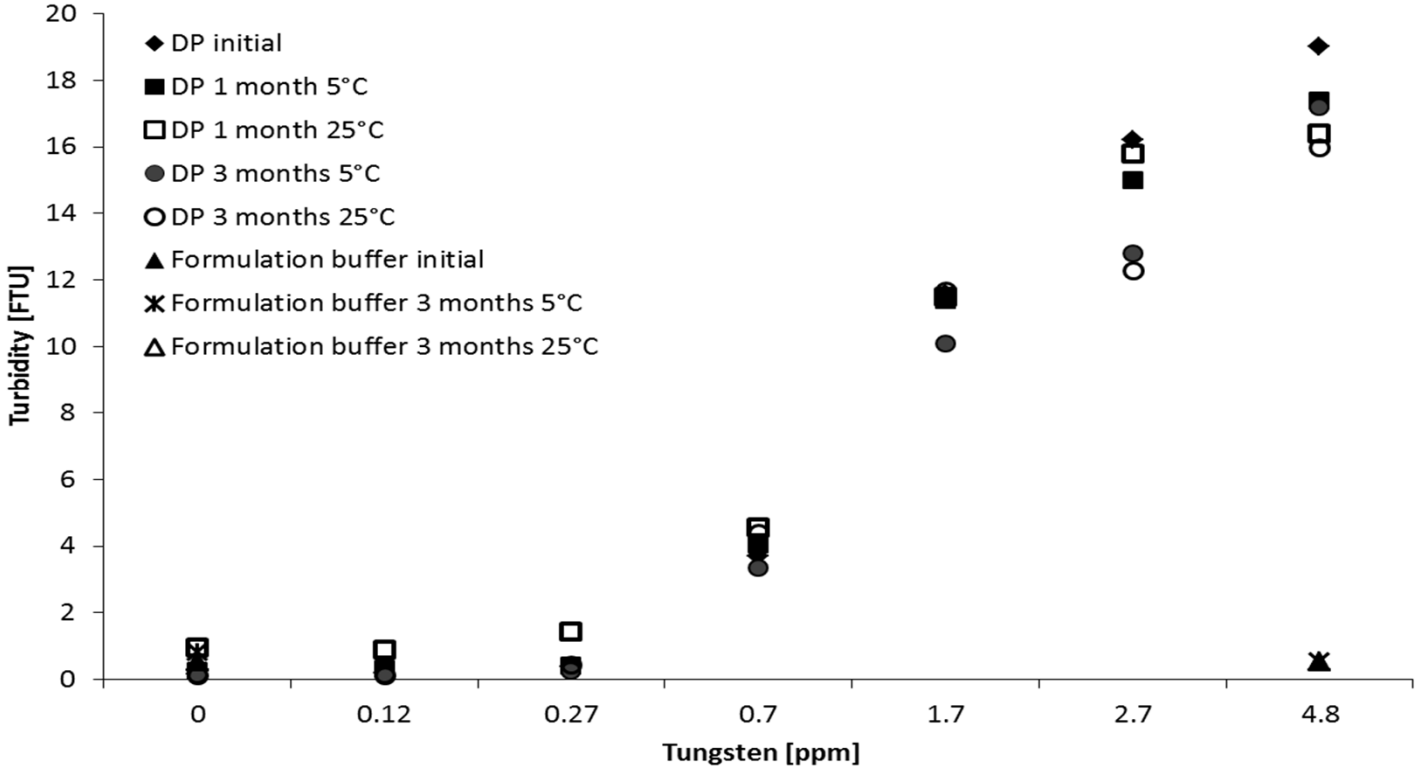
Sensitivity Evaluation
Roche's spiking study design

Source: Gerrhersheimer Buende



- Tungsten sensitivity studied by spiking different level of tungsten concentration using pin extracts
- 0-20 ppm Tungsten levels achieved
- Stability program to show effect over time
- Analytical characterization of the protein's CQA at different timepoints

Spiking Study
Turbidity Analysis

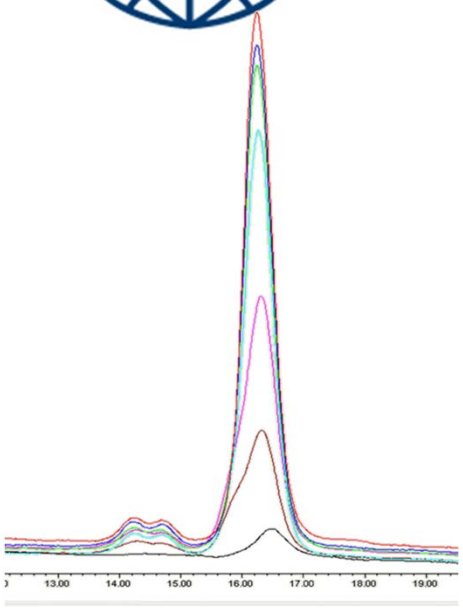


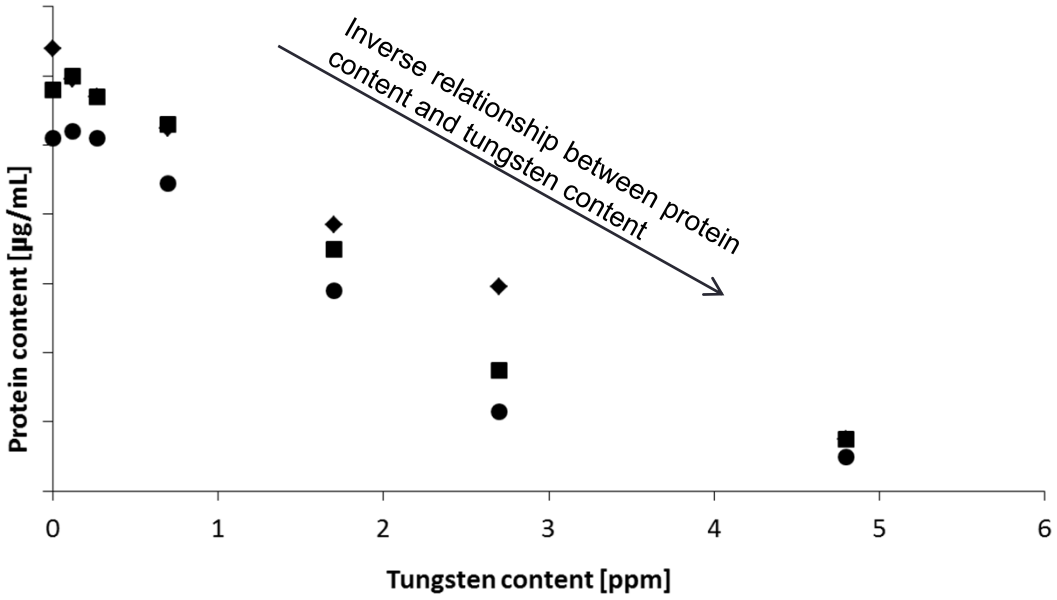
⇒ **Direct correlation**

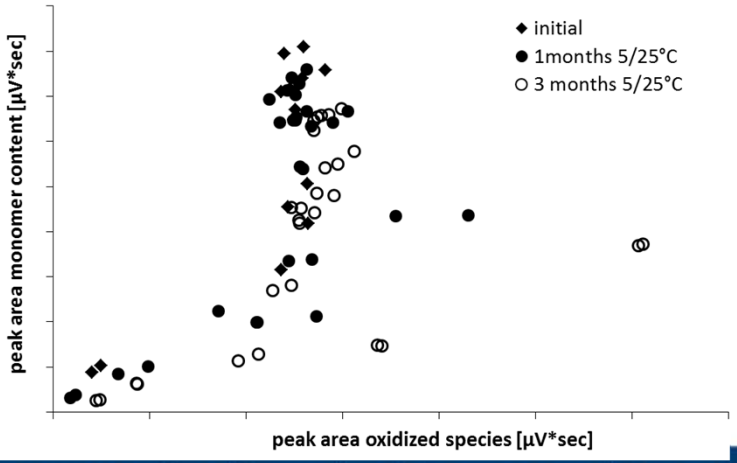
⇒ No increase in spiked formulation buffer control samples

⇒ No increase over storage

Spiking Study
Purity and protein content by RP-HPLC







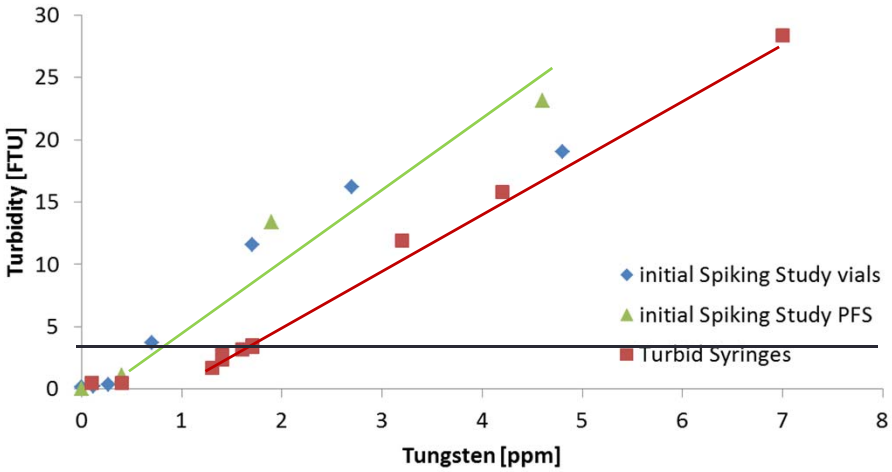
- Direct correlation
- Decrease over time can be observed in control sample as well

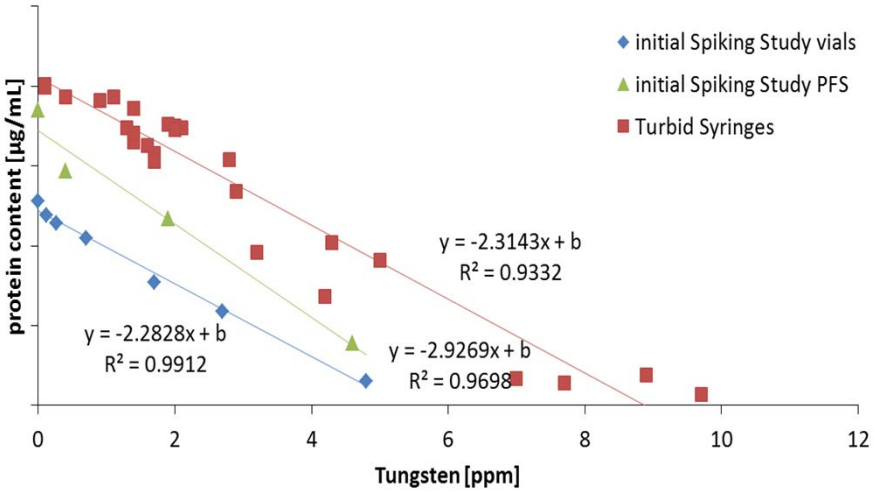
❖ Match with turbidity data

- No relationship between oxidized protein and monomer content

❖ No oxidation events of monomers

Spiking Study
Comparison to CQA Testing using turbid syringes out of commercial process





- **Turbidity**: comparable trend
  - Concentration to reach maximal turbidity specification:
    - 1.25 ppm for turbid syringes (extrapolated), 0.7 ppm after spiking
  - Higher FTU values after spiking (=> worst case conditions)
- **Protein content**: comparable trend (starting values differ due to study set-up)

❖ **Spiking Study verified working hypothesis and gives a better understanding about the impact of tungsten on the protein**

What have we learned?

1. **Tungsten as an impurity could be identified as a root cause**
2. Tungsten Spiking Studies: From 0.7 ppm onwards tungsten has an impact on protein aggregation shown by:
   - Turbidity, Subvisible particles and aggregation on SDS-PAGE
3. The correlation to CQA testing of turbid syringes showed the same effects
   - ⇒ Verification of working hypothesis
   - ⇒ Verification of Study design for Tungsten Sensitivity assessment
4. Calculation of tungsten concentrations to reach specification limits for turbidity:
   - 1.25 ppm (Turbid Syringe Study, extrapolated)
   - 0.7 ppm (Spiking Study)

- **The analyzed protein is highly sensitive towards tungsten**
- **Sensitivity values are far below the current tungsten limit (8ppm) of the syringes**

Outlook: Improvement in DP Quality

Supplier Mitigation

- Discussions to lower residual Tungsten
- Altering manufacturing process
  - Addition of washing processes
  - Specification on lifetime of pin

Alternate processes to eliminate Tungsten

- New pin materials
- Vacuum filling to minimize headspace

Evaluation of internal process optimization

- Washing process of incoming PFS
- 100% Visual Inspection

Gain more understanding of the observed effect

- Identification of protein and tungsten interaction
- Can we identify specific amino acids for Tungsten binding?
- Interaction via complexing?
- Are there electrostatic interactions?
- Is there a nucleation-dependent protein aggregation ("seeding") ?

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- **Case Study 2 – Pushing the Limits: Ocular Applications**

Ocular Delivery / System Requirements: Functional

- Low injection volumes with high accuracy
- Priming and injection steps
- IOP

Dose & Residual Volume

Container Closure & Permeability

- Seal tightness
- Impact of Moisture Vapor- and Oxygen Transmission Rates
- Impact on Usability

User Needs

- Intuitiveness
- Ease of Use
- Size and weight

Needle

- Luer vs staked
- Gauge, length, bevel, sharpness
- Siliconization

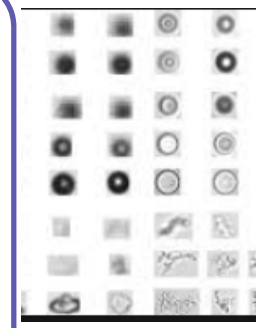
Ocular Delivery / System Requirements: Drug Formulation / Compatibility

$$F = \frac{8Q\mu L}{\pi R^4} \times 4$$

- Impact on usability
- Shear sensitivitites
- Viscosity limits for hand injection

Formulation Viscosity

- Reduction of silicone migration
- USP<789> Sub-visible particulate requirements



Low Silicone

Post Filling Sterilization

- Selection of Elastomer
- Drug compatibility consideration
- Alternative sterilization modes

Drug/ Material Interface

- Various materials interfaces during long term storage
- Low fill volume/surface area ratio

Allowed particle content of drug product according to USP <789>:

Table 1: Light Obscuration Test Particle Count

	Diameter	
	≥ 10 µm	≥ 25 µm
Number of particles	50 per mL	5 per mL

Table 2: Microscopic Method Particle Count

	Diameter		
	≥ 10 µm	≥ 25 µm	≥ 50 µm
Number of particles	50 per mL	5 per mL	2 per mL

- Very low allowed particle quantity compared to s.c. injections

Combination products for intravitreal injections: Sterility requirements

	FDA	EMA
Regulated by	21 CFR 3.2 (e)	2001/83/EEC
Definition	A product comprised of two or more regulated components, i.e. drug/device, biologic device, drug/biologic, or drug/device/biologic, that are physically, chemically or otherwise combined or mixed and produced as a single entity.	A device that combines with medicinal product to form a single, integral product designed to be used exclusively in the combination. The product is not reusable. Regulated by the medicinal product regulation.
Sterilization Requirement	Terminal sterilization should be applied	Terminal sterilization should be applied by EN-556-1, which must demonstrate a minimum SAL of 10^-6.

Combination products for intravitreal injections: Sterility requirements

- Final combination products for ophthalmic use need to be sterile, meaning:
  - Sterility has to be guaranteed for:
    - The drug product (syringe content)
    - The outer surface of the filled syringe

- A final sterilization process step has to be performed for the DP filled syringe (if the syringe cannot be packaged/blistered under aseptic conditions)
- Gas sterilatns typically used to sterilize blistered syringe
- It has to be ensured that the sterilizing agent does not compromise the drug product quality and/or syringe functionality over shelf life

Combination products for intravitreal injections: Sterility requirements

Considerations for each sterilization method evaluated

Regulatory Path

- FDA recognized?
- Long history of use in medical device industry
- FDA/ISO recognized standards?

Industry Experience

Manufacturing process

- CMO vs in-house
- Complexity of supply chain

Process Parameters

- Diffusivity
- Process temp
- Length of Sterilization process

Toxicity of residuals

Lethality

Sterilant residual levels

DP Quality Impact

- Alkylation/Oxidation (peptide map)
- SEC
- IEC

Device Functionality

- CCI, Impact of pressure differentials
- User forces following sterilization

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- Steffen Kiessig
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- Joerg Luemkemann

YOUR QUESTIONS?