TRD BPD DPD

Application of Pharmacopeia Guidelines on Particles for the Development of Biologicals

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Biologicals – a Broad Field

- Vaccines
- Cell Therapies
- Gene Therapies
- Protein Therapeutics (mostly liquid parenteral solutions for injection or for infusion)

Protein Therapeutics

- Various types (e.g. IgG, FAB, therapeutic protein)
- Broad MW range (~ 3’000 to ~150’000 Da)
- Complex structure (primary to quaternary)
- Unstable:
  - Chemical degradation
  - Loss or change of native structure (denaturation)
  - Aggregation and particle formation

Particle Types

- Inherent (part of the formulation):
  - Aggregated protein
  - Crystallized protein
  - Degraded and aggregated excipients (e.g. surfactants)

- Intrinsic and/or extrinsic:
  - Silicone oil droplets
  - Glass
  - Rubber
  - Metal
  - Fibers

The Role of Drug Product Development

With regard to particles, drug product development should:

- Understand the appearance and the formation of particles in a product over its entire shelf life
- Minimize particles by development and selection of optimal formulation, packaging, manufacturing process, storage conditions, transport conditions, and handling conditions
- Ensure that unavoidable particle types and levels are acceptable and well tolerated

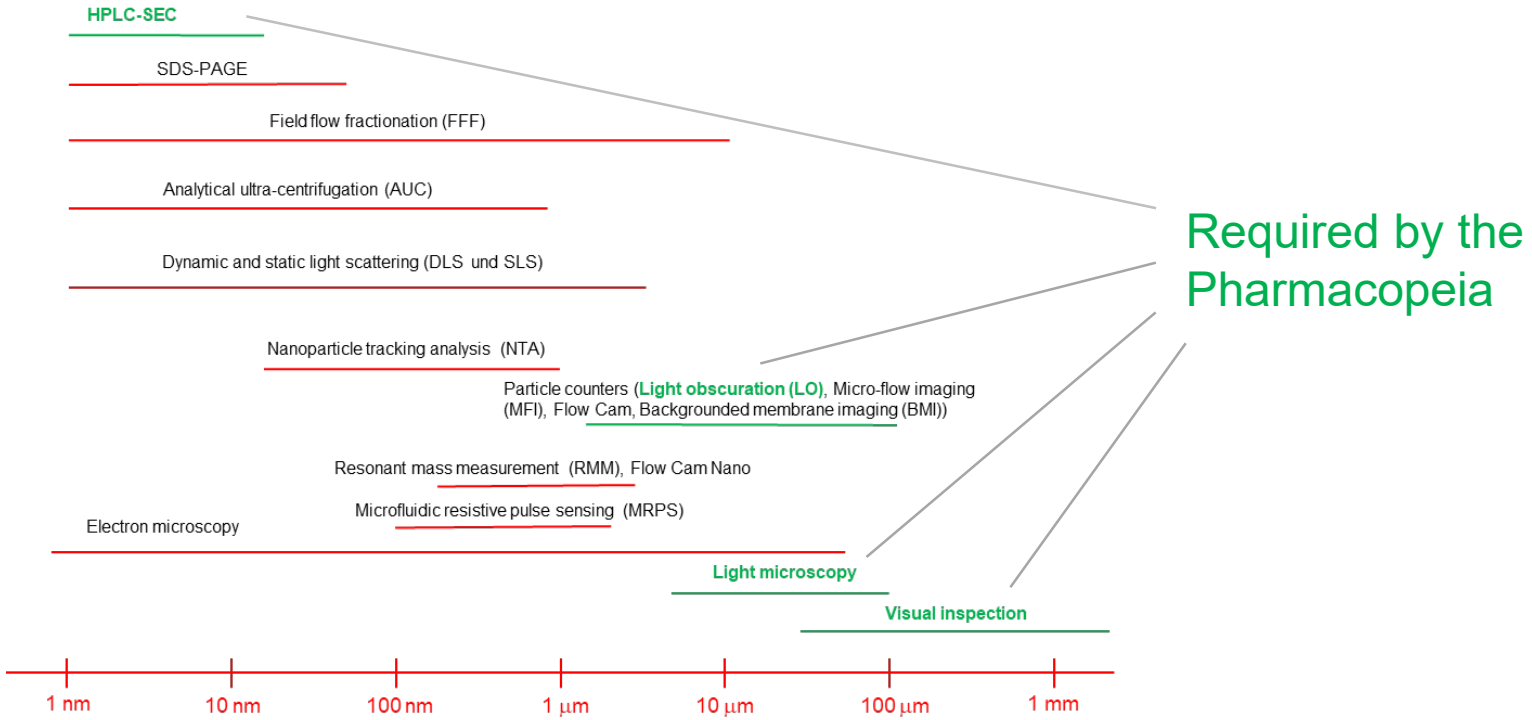
Challenges with Particles

Very different time-dependencies are possible:

- Well reproducible increase with time or after a stress
- Poorly reproducible increase with time or after a stress (stochastic behavior)
- Decrease with time (reversibility; size distribution shift)

Challenges with Particles

Very different size ranges are possible:



Visible Particles in Parenteral Products

Ph.Eur.:
Parenteral Preparations

Ph.Eur. 2.9.20

USP <1>

• USP:	"Essentially free of visible particulates"
• Ph.Eur.:	"Practically free from particles"
	"During development of the (monoclonal antibody) product it must be demonstrated that either the process will not generate visible proteinaceous particles in the final lot or such particles are reduced to a low level as justified and authorized"

USP <790>

USP <771>

Ph.Eur.:
Monoclonal Antibodies for human use

Visual Inspection

- Part of the manufacturing process of clinical and commercial batches
- Part of GMP stability studies with drug product batches
- Very useful in non-GMP development environments to understand the types of visible particles that can appear in a product

Visual Inspection in non-GMP Development Environments

Challenges:

- Reaching and maintaining a high level of training
- Investigating sufficient samples to detect rarely occurring particles (laboratory scale and pilot scale manufacturing is at lower batch size than clinical and commercial manufacturing)

Benefit:

- Visible particles are strong indicators that something is not yet optimal
- Possibility to improve formulation, packaging, or manufacturing process
- Avoid unexpected particle appearance in clinical and commercial batch manufacturing

Visual Inspection in non-GMP Development Environments

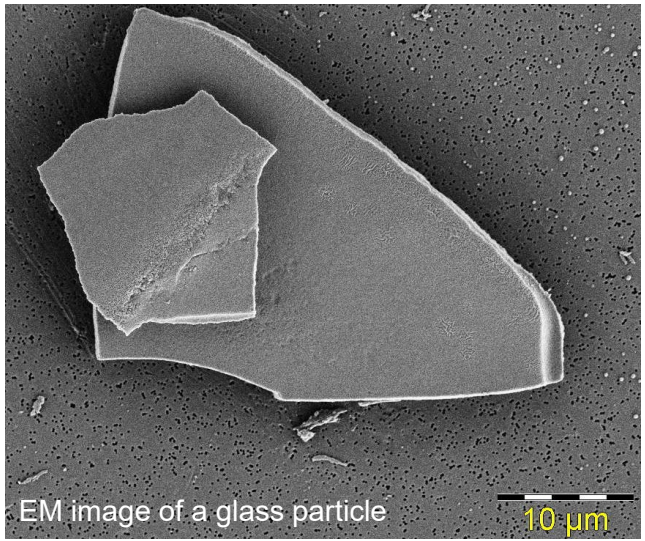
Particle(s) found

Particle identification by:
- Light microscopy
- Electron microscopy
- Energy dispersive X-ray spectroscopy
- FTIR microscopy
- Raman microscopy

Investigation of possible particle origin (re-produce the particles)

Improvement of formulation, packaging or process

Visual inspection according to Pharmacopeia



Sub-Visible Particles (in the micro-meter size range)

USP <788>

USP <787>

Ph.Eur. 2.9.19

USP <789>

• Parenteral products *: * Requirements for products with less than 100ml content shown.	≤ 6000 particles ≥ 10µm per container ≤ 600 particles ≥ 25µm per container
• Ophtalmics (USP only):	≤ 50 particles/ml ≥ 10µm ≤ 5 particles/ml ≥ 25µm ≤ 2 particles/ml ≥ 50µm

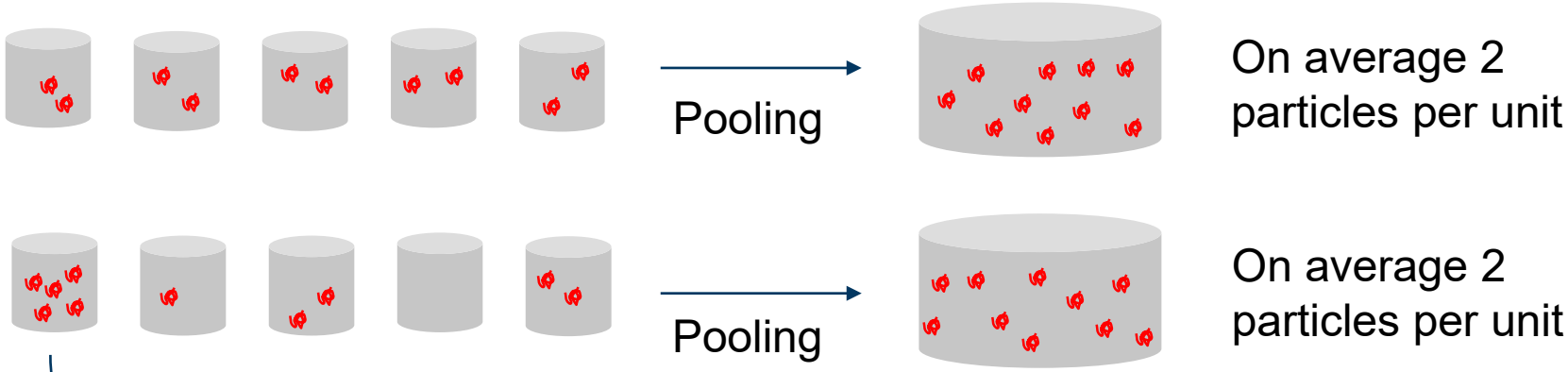
Sub-Visible Particles: Test Methods

- The pharmacopeia defines light obscuration (LO) as preferred test method, and light microscopy as alternative or additional test method
- The minimum test volume is 25 mL (except for USP <787>)
- For nominal volumes <25 mL, pooling of filled units is necessary

Sub-Visible Particle Analysis: The Limitation Caused by Pooling

Two situations with the same average:

Result:



Are there filled units with more particles per container than permitted?
Are there filled units with more particles per mL than permitted (extrapolated)?
Is this relevant according to the Pharmacopeia?

Sub-Visible Particle Analysis: Are Lower Test Volumes Permitted?

Ph.Eur.	USP
• Yes • 2.9.19. Particulate Contamination: Sub-Visible Particles • Alternative method: «...In general, for parenteral preparations that do not have a sufficient volume (e.g. less than 25 mL), performing the test using a volume of 1 mL to 5 mL may be acceptable if permitted by the instrument.»	• Yes • USP <787> Subvisible Particulate Matter in Therapeutic Protein Injections • «... specifically addresses therapeutic protein injections and related preparations, allowing use of smaller test product volumes and smaller test aliquots to determine particulate matter content...»

Sub-Visible Particle Analysis: How Reliable is Low Volume Testing?

- Several publications have shown that accuracy and precision decrease with decreasing test volume and with decreasing particle numbers

Summary of LO Results for Polystyrene Standard Beads

Nominal Concentration [#/mL]	Nominal Particle Diameter [µm]	Mean of All Sub-runs [#/mL]	Standard Deviation of All Individual Sub-runs [#/mL]	Relative Standard Deviation of All Individual Sub-runs [%]
6	25	4.8	2.3	47
	50	3.5	2.0	58
60	10	58.0	8.5	15
	25	47.9	7.8	16
	50	37.9	10.3	27
600	10	536.5	24.5	5
	25	462.4	34.6	7

For each combination of particle size and concentration, 20 measurements with 10 sub-runs (200 sub-runs in total) of 1.0 mL each were performed.

Source: M. Guehlke et. al., JPS, 109 (2020), p. 505-514

Sub-Visible Particle Analysis: A Topic at Novartis Biologics

- Currently, we use large volume and small volume methods to support biologics drug product development
- We regard small volume methods as complementary to large volume methods and not (yet) as a replacement for them
- There is an uncertainty about the true expectation behind the pharmacopeia requirements for sub-visible particles in situations when it is necessary to pool filled units for obtaining the result

Thank you

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