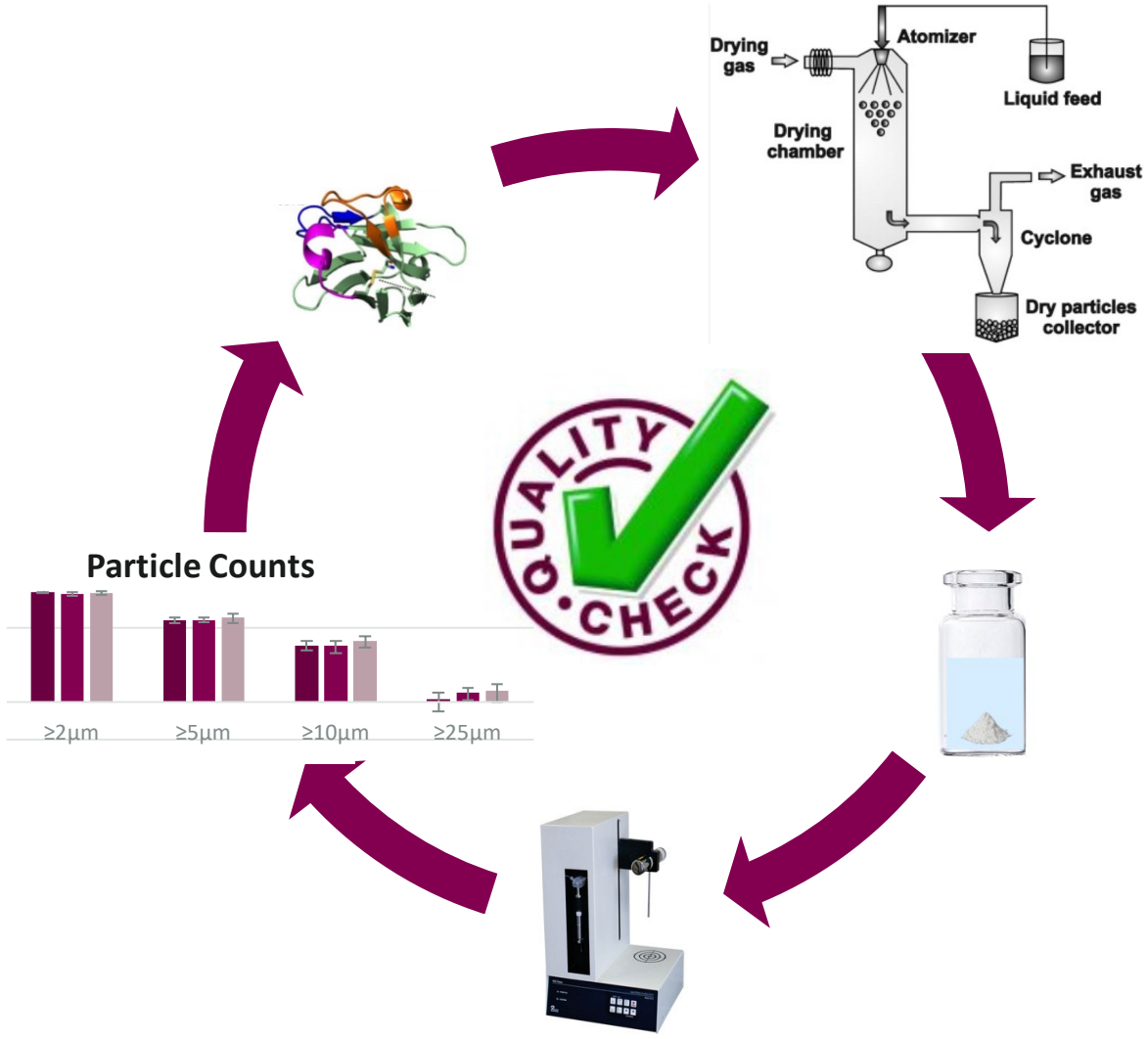
Particle Precision: The Importance of Sample Preparation in Insoluble Particle Analysis in Inhaled Biologic Powders

Scott Sides
Director
Inhalation Product Development,
AstraZeneca Pharmaceuticals LP

Introduction for Particle Precision –IPAC-RS Conference

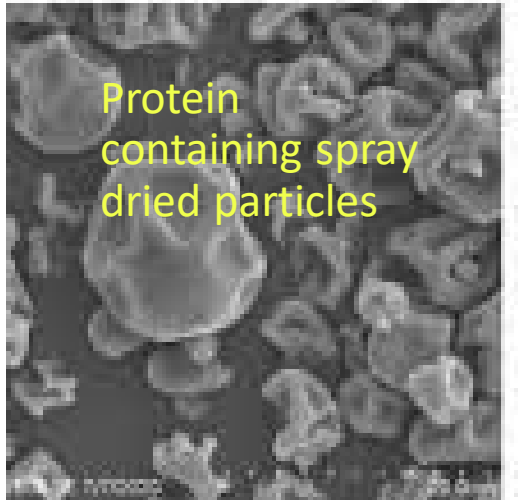
- The Challenges and Need for Aggregate Enumeration
- Manufacturing of Dry Powder for Inhalation for Biologics
- Qualitative Analyses of Insoluble Aggregated Material
- Overview Particle Analysis Techniques and Strategy
- Case Study for Particulate Enumeration by High Accuracy Liquid Particle Counter (HIAC)
  - Factors Influencing Sub-Visible Particle (SVP), Visible Particle (VP) Formation and Stability Post Reconstitution
- Foreign Particulate Matter (FPM) Strategy and Limits



The Challenge and Importance of Quantification of Particulates for Inhaled Biologics

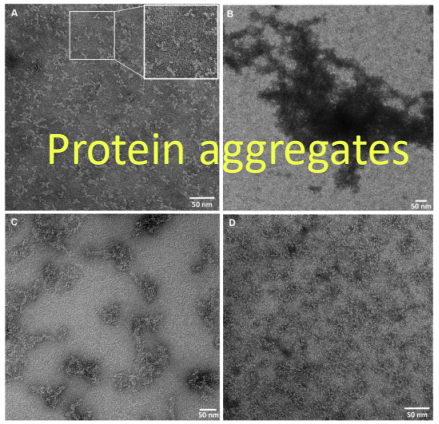
Control and measurement of particulates in protein containing formulations for inhaled “dry powder” delivery is complex:

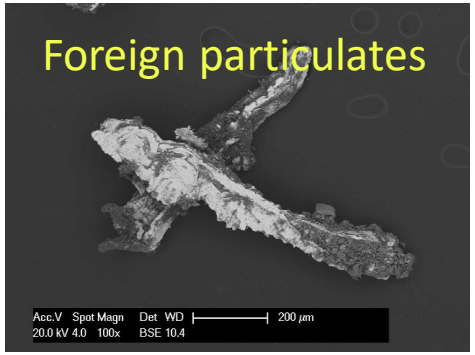
- Particulates can be inherent (e.g. proteinaceous aggregates), intrinsic (e.g. excipients), extrinsic (e.g. contaminants)
- Selectivity of common analytical techniques are limited (HIAC, MFI)
- Enumeration relies on powder reconstitution: indirect measurement of unfolded protein



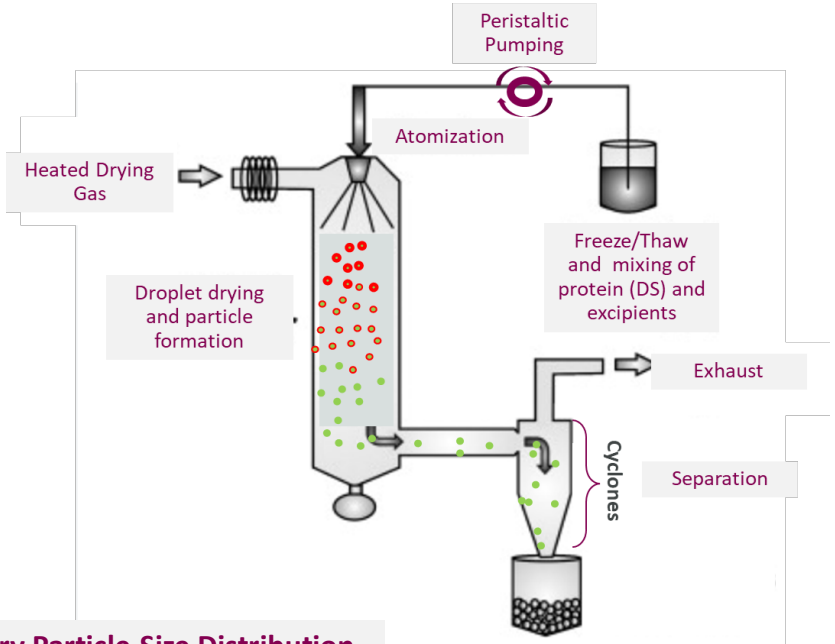
Relevance of inherent particulates in the formulation:

- Potential for aggregated protein to elicit immune response – (Safety)
- Correlation between in-vitro measurements and in-vivo impacts difficult and unknown
- General lack of guidance for what is acceptable for inherent particulates (Safety)





Manufacture of Inhalable Powder - Spray Drying Biologics



Typical Primary Particle Size Distribution (pPSD) by Laser Diffraction

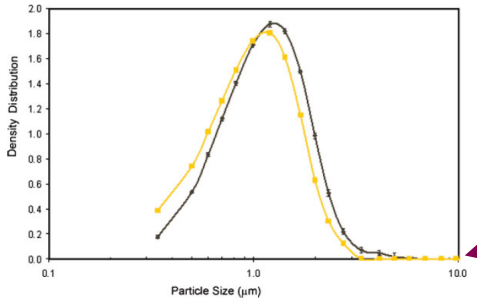
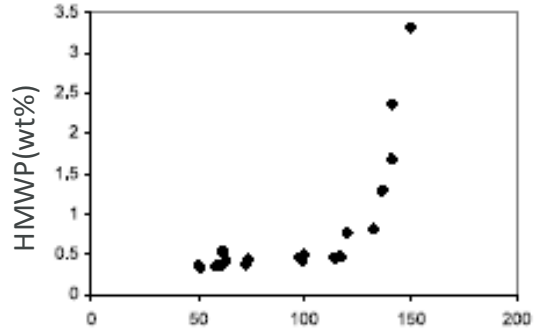


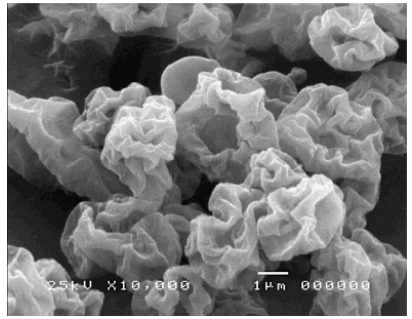
Figure 3. Addition of 2% trileucine did not significantly affect the primary particle size distribution measured by laser diffraction. A median size of 1.1 and 1.0 µm was obtained for gentamycin (diamond symbols) powders and 2% trileucine (square symbols), with a calculated volume mean diameter of 1.2 and 1.1 µm and a geometric standard deviation of 1.6 and 1.7, respectively. [Color figure can be seen in the online version of this article, available on the website, www.interscience.wiley.com.]

$d_{100} < 10$ µm

Lechuga-Ballesteros D, et al. (2008). Trileucine improves aerosol performance and stability of spray-dried powders for inhalation. J Pharm Sci. 97(1):287-302.

Protein experiences numerous conditions during spray drying that could contribute to loss of tertiary structure (unfolding): thawing, sheer forces (mixing and atomization), heat, air/liquid interface, solid/liquid interface, vibration.



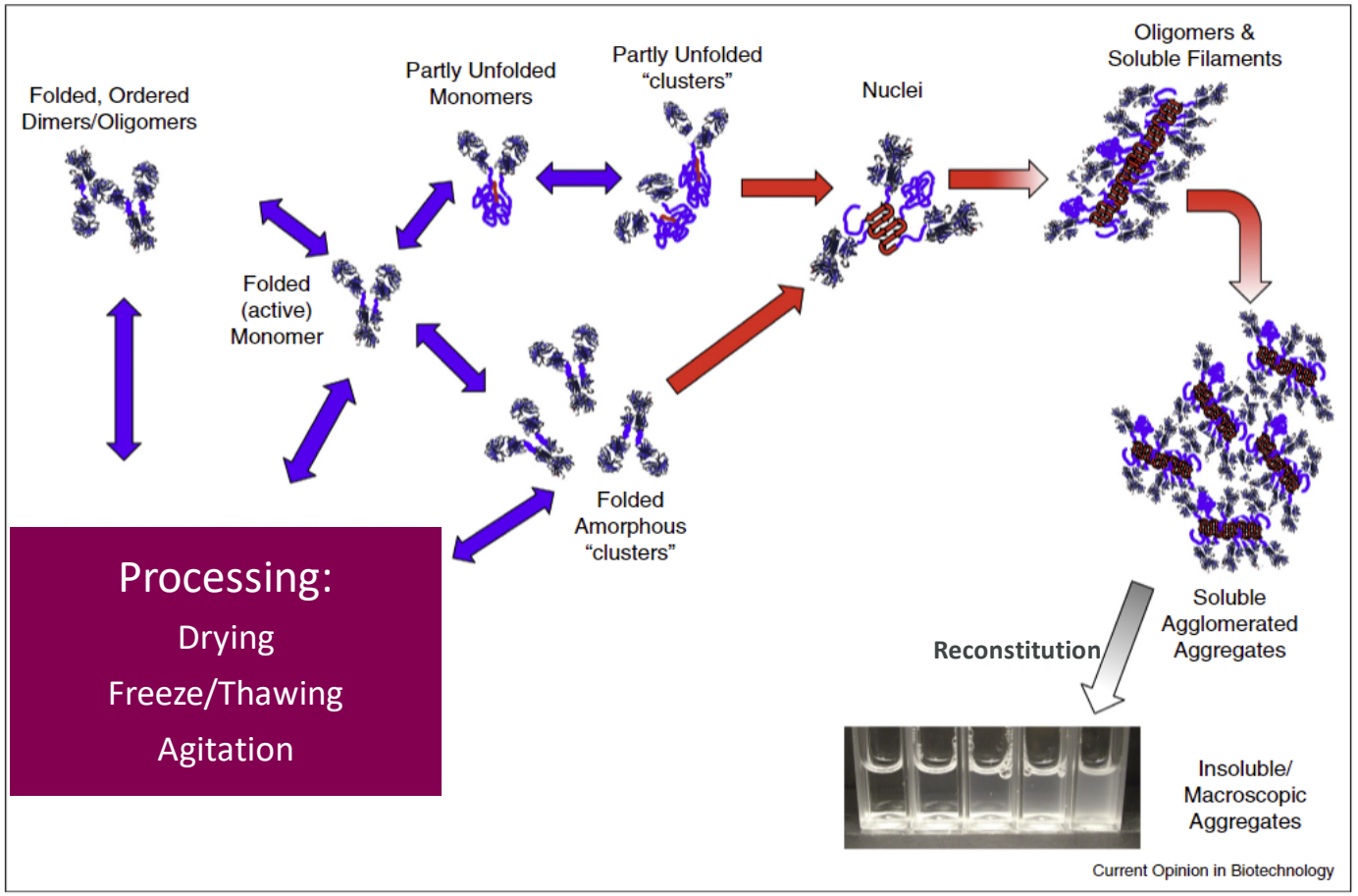


Spray dried insulin can form aggregates (HMWP) at aggressive outlet temperature conditions. Stabilization via excipients and controlling spray drying conditions enables formation of room temperature stable particles with appropriate shelf life > 24 months when kept dry

Ståhl, K., Claesson, M., Lilliehorn, P., Lindén, H., and Bäckström, K. (2002) The effect of process variables on the degradation and physical properties of spray dried insulin intended for inhalation, International Journal of Pharmaceutics 233, 227-237.

Protein Aggregation: Impact on Product Quality

Figure 1



Schematic overview of a range of different aggregated states that proteins can adopt either as folded molecule or unfolded/partially unfolded ones. The latter typically result in aggregates that are difficult to dissociate without extreme conditions (high pressure, temperature, and/or denaturant concentration). Images for liquid–liquid and liquid–crystal phase separation (bottom left) are reproduced with permission from Ref. [8], as are those for aggregate phase separation (bottom right) from Ref. [9•].

Protein Pharmaceutical Products

- Active as folded monomers
- Protein aggregation can lead to formation of soluble or insoluble aggregates
- Some soluble aggregates may be "useful", e.g.: Insulin hexamers
- Insoluble aggregates are usually not active and may pose a safety risk,
  e.g: capillary occlusion in parenteral products or unwanted immune response

Rdoi: 10.1016/j.copbio.2014.08.001. Epub 2014 Aug 28. PMID: 25173826; PMCID: PMC4266928.oberts CJ.
Protein aggregation and its impact on product quality. Curr Opin Biotechnol. 2014 Dec;30:211-7.

Identification of Proteinaceous Insoluble Particles

Isolation and characterization of particulates post powder reconstitution :

- IR spectra – position of Amide I and II bands – indicate proteinaceous particles
- Near UV Circular Dichroism spectra – suggest loss of tertiary structure for insoluble material
- Differential Scanning Fluorimetry (DSF) spectra – decreased thermal stability (T_{max}) suggest partial unfolding
- Extrinsic Fluorescence (Bis ANS) spectra – indicate increased exposure of hydrophobic surface of the protein

Tao, Y., Chen, Y., Howard, W. *et al.* Mechanism of Insoluble Aggregate Formation in a Reconstituted Solution of Spray-Dried Protein Powder. *Pharm Res* **40**, 2355–2370 (2023).

- In depth characterization of insoluble aggregates from 2 separate Fab's post spray drying
- HDX experiments suggest spray drying disrupted protein structure exposing hydrophobic residues in heavy-chain CDR-1.
- Upon reconstitution insoluble aggregate formation likely occurs due to hydrophobic interactions

Proteinaceous insoluble solids

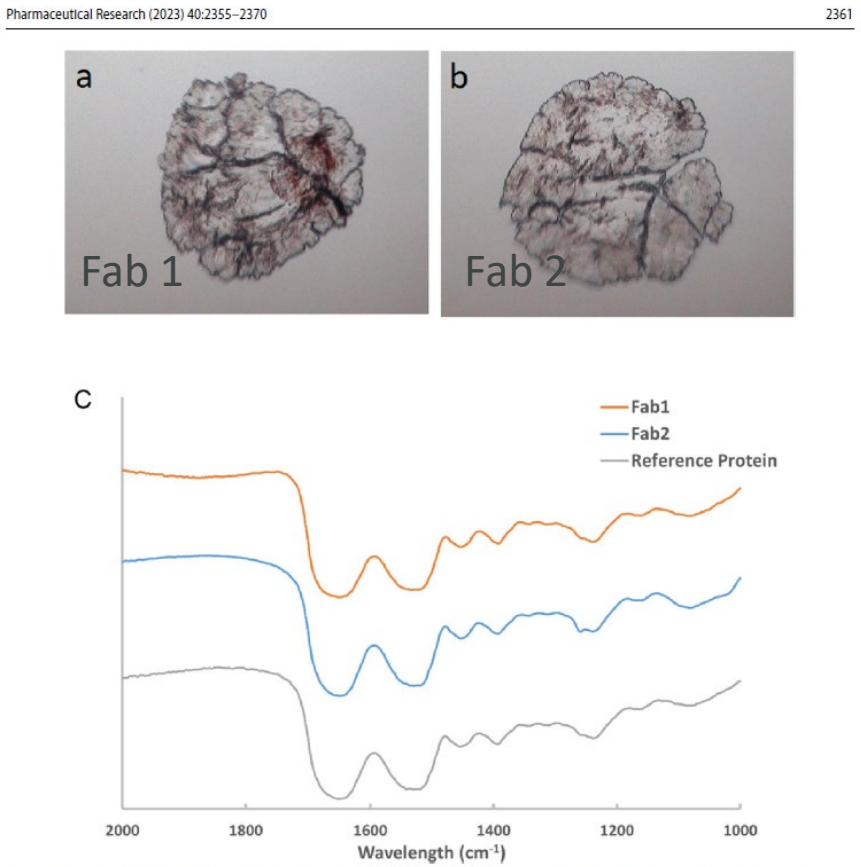
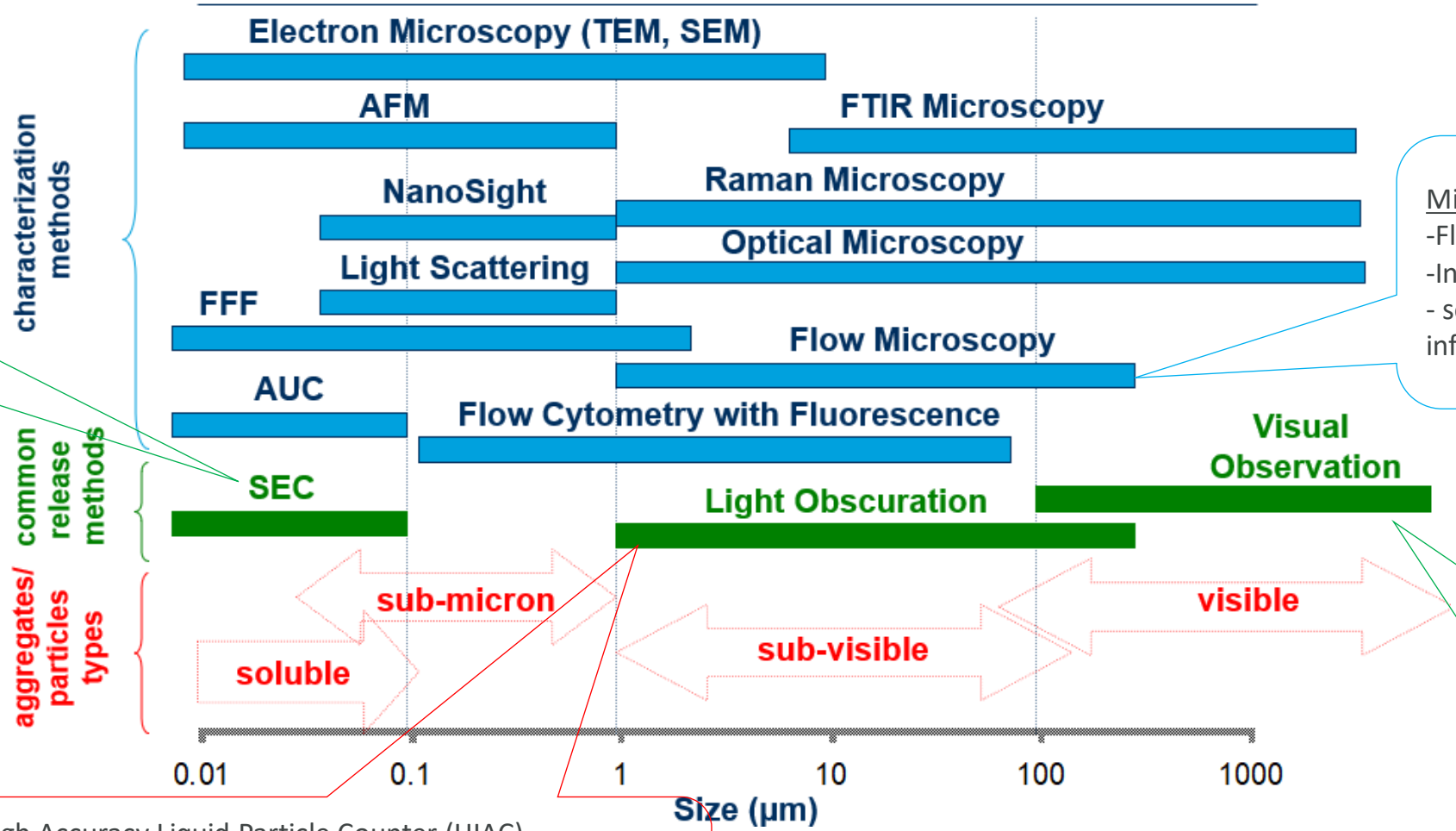


Fig. 3 FTIR analysis of the insoluble particles from the reconstituted solution. Shown are the sediments of Fab-1 (**a**) and Fab-2 (**b**) after processing from the insoluble particles under FTIR. (**c**) FTIR spectra of the sediments of Fab-1 and Fab-2 compared with an internally manufactured reference protein. The FTIR spectra of the insoluble particles were comparable to that of the reference protein, indicating protein-like structures.

Analytical Characterization Techniques Related to Aggregate Size



Size Exclusion Chromatography (SEC)
-Chromatographic
-Soluble Aggregates

MicroFlow Imaging (MFI)
-Flow Imaging
-Insoluble aggregates
- some morphology information

Appearance (Liquid)
-Visual comparison against ref. stds.
-estimate particle count and turbidity of insoluble aggregates

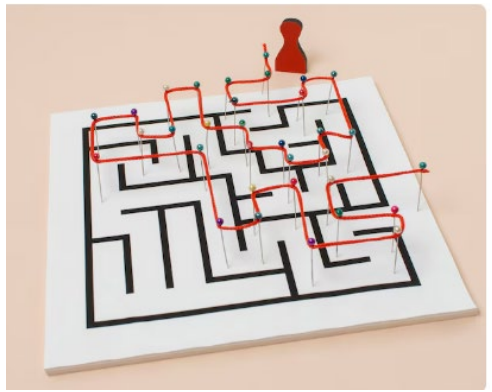
High Accuracy Liquid Particle Counter (HIAC)
-Light Obscuration
-Insoluble aggregates + excipients + Foreign Particulate Matter (FPM)
-compendial

Enumeration of Proteinaceous Insoluble Particles

Objective: To develop compendial methodology capable of enumeration of all particulates (aggregates and foreign) *post reconstitution* of protein containing spray dried powder for inhaled delivery using High Accuracy Liquid Particle Counter (HIAC).

- Control of product quality only and not intended for in-vivo relevance
- Early development studies supported by MicroFlow Imaging

The Powder Reconstitution Puzzle: What are the important factors?



Protein Concentration

Serial Dilution

Aggregate/Sample Stability (time and diluent)

Diluent: Buffer Composition and pH

Scale of Preparation

Container Type

Order of Addition

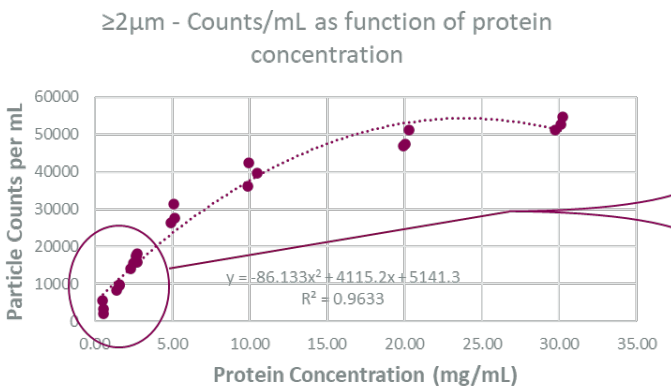
Use of Chaotrope Diluent > (FPM)

Case Study: Analytical development work for HIAC was based on spray dried powder for inhalation:

- 40% w/w active protein:60% excipients (Protein PI > 8)

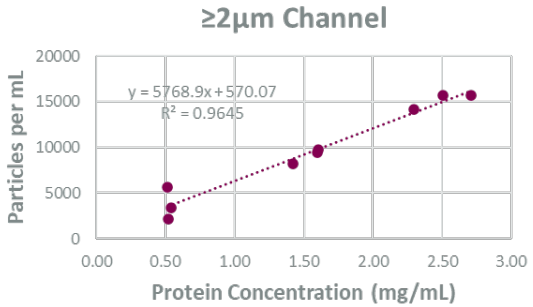
Protein Concentration versus Aggregate Formation (water diluent)

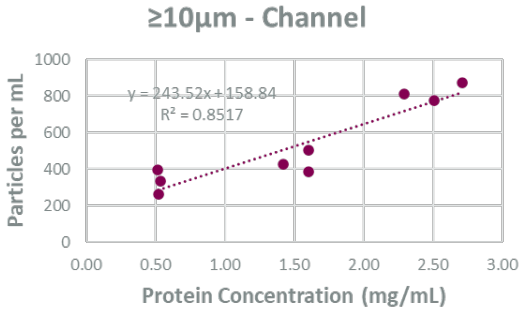
Protein concentration range: 0.5 - 30 mg/mL.

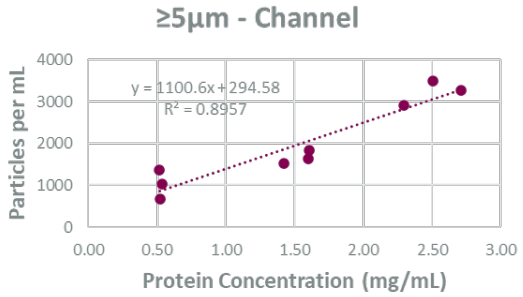


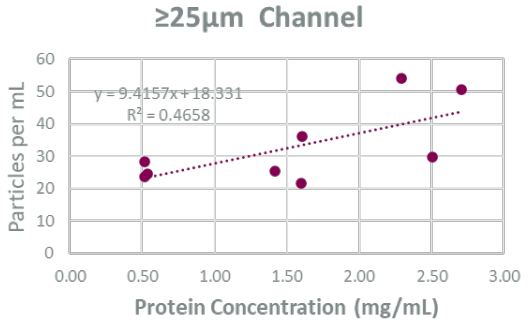
Operating range more restricted by HIAC detector saturation than protein concentration

Particle counts/mL per channel





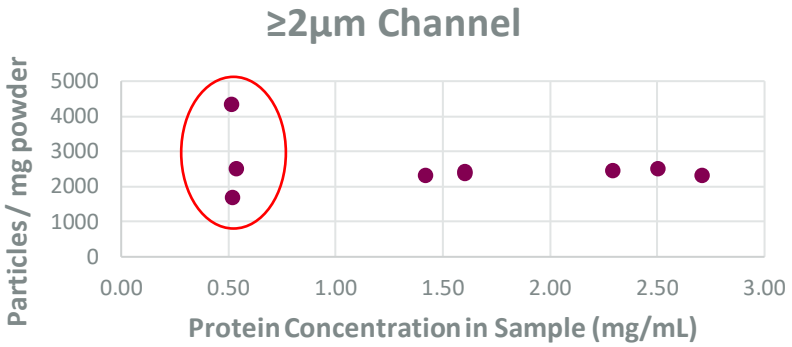


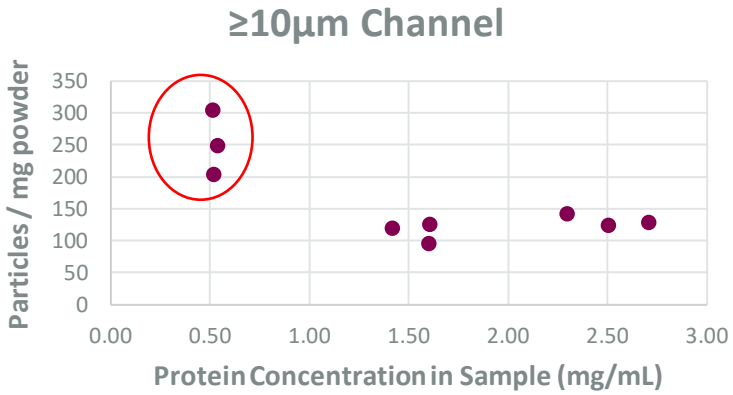


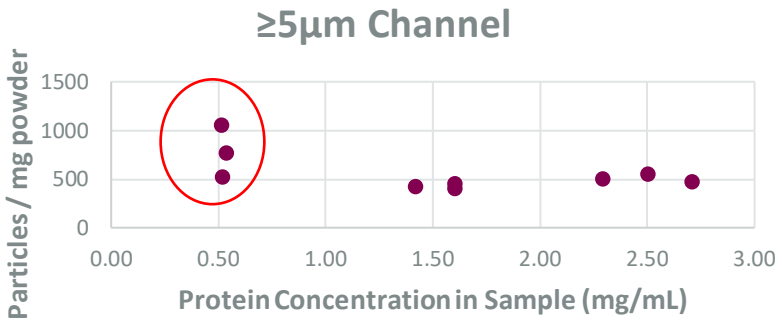
*Particle counts appear relatively linear across all channels at concentration below 2.5 mg/mL

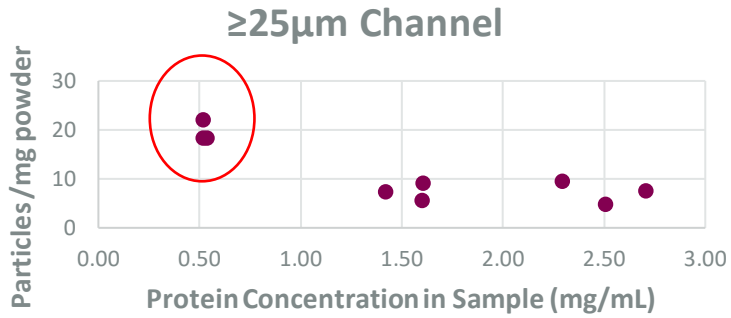
Protein Concentration – Normalized per mg Powder

Normalized Particle counts per mg powder (powder = 40% protein + 60% excipients)





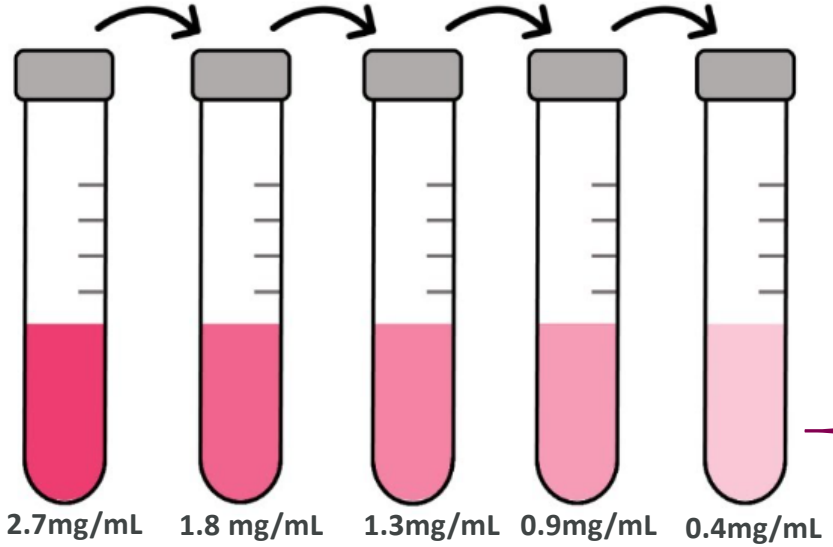




Normalized data for particle counts/mg powder indicate slight increase in counts at 0.5mg/mL compared to the 1.5 and 2.5mg/mL protein concentrations:

- Trend should be flat if response is completely independent of protein concentration
- Potentially some higher variability at the 0.5 mg/mL concentration as well.

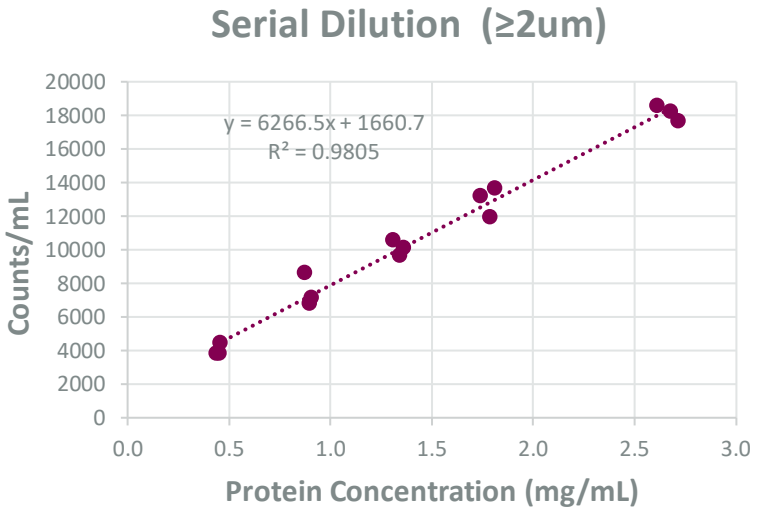
Impact of Serial Dilution (water diluent)

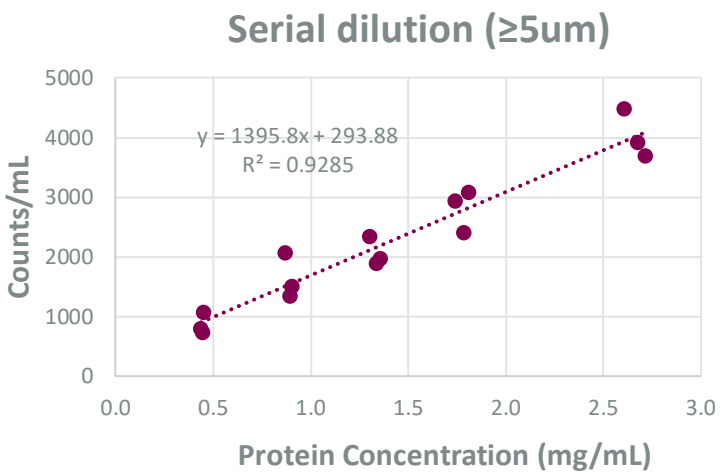


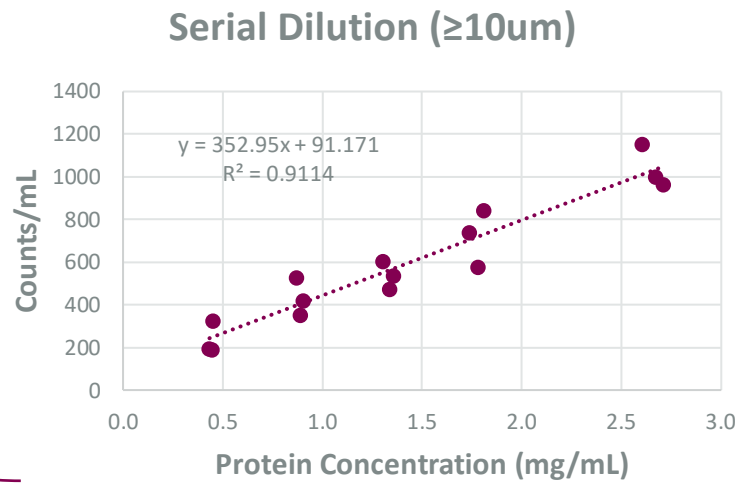
Concentration expressed as mg protein/mL

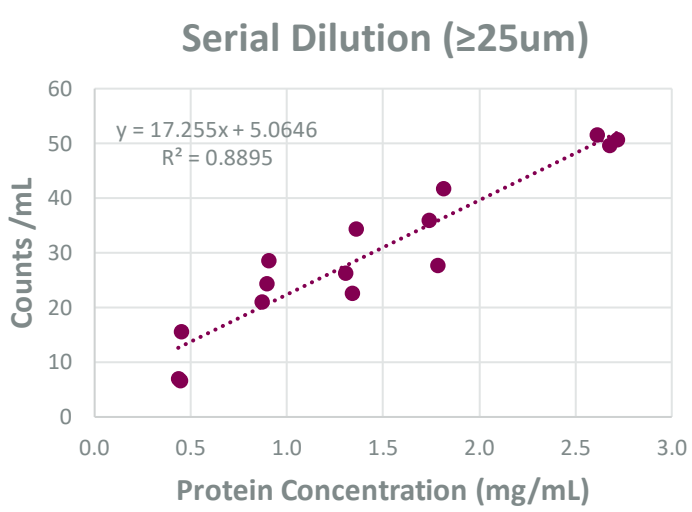
Data indicates serial dilution is relatively linear in nature

- narrow range
- no apparent disassociation or concentration dependent shift in size distribution



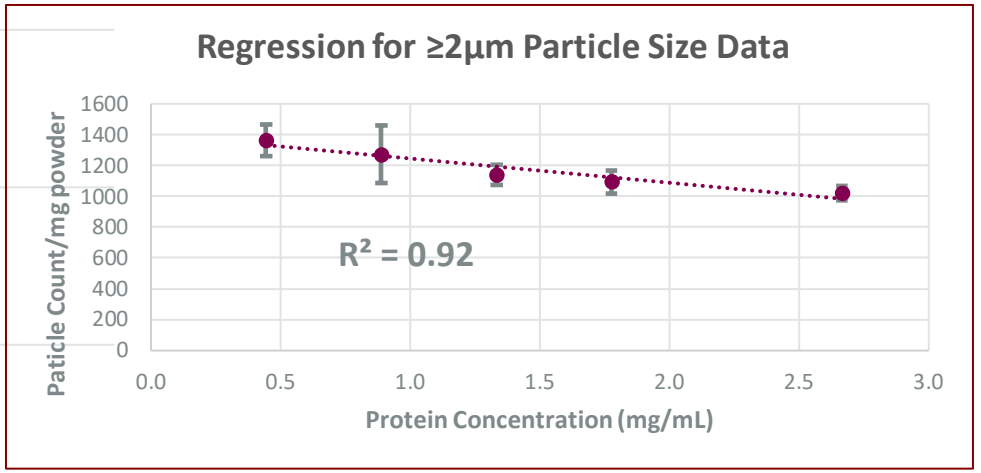






Serial Dilution - Normalized per mg Powder

HIAC Channel Particle Size	Normalized: Particle Counts/mg Powder Dilution 5 0.4 mg/mL	Dilution 4 0.9 mg/mL	Dilution 3 1.3 mg/mL	Dilution 2 1.8mg/mL	Dilution 1 2.7 mg/mL
≥2µm	1366	1273	1141	1093	1024
≥5µm	291	277	233	237	227
≥10µm	80	73	61	61	58
≥25µm	3	4	3	3	3



***Normalized particle count data shows a slight but persistent trend** of increasing particle counts as protein concentration decreases

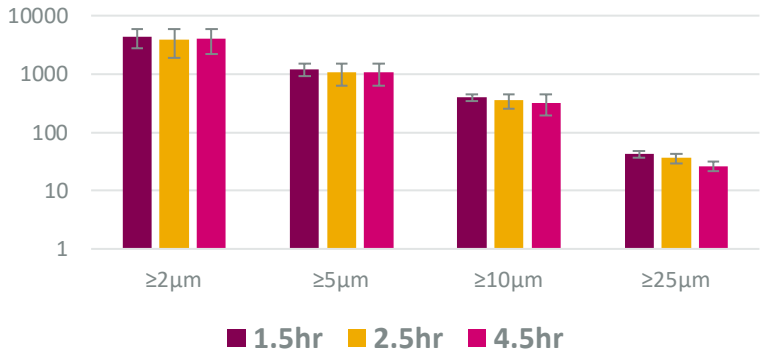
Trend is **counter intuitive to what would be expected

Aggregate Formation and Stability (water diluent)

0.5 mg/mL Protein

Average Particles / mL

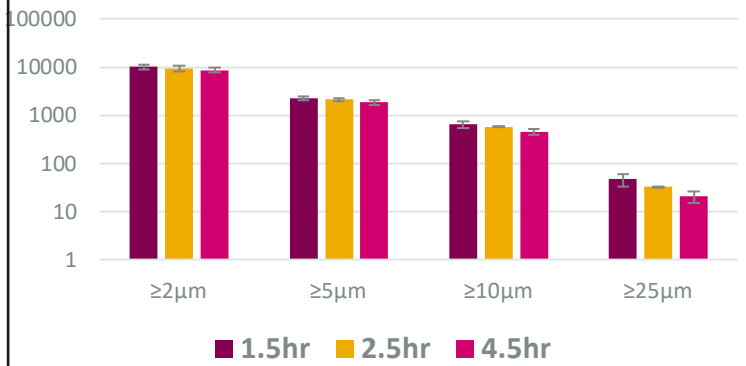
	1.5hr	2.5hr	4.5hr
≥2µm	4441	3903	4110
≥5µm	1234	1080	1074
≥10µm	407	357	321
≥25µm	42	36	27



1.5 mg/mL Protein

Average Particles / mL

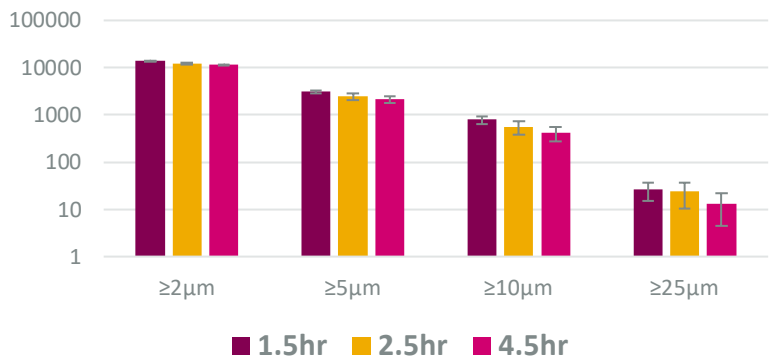
	1.5hr	2.5hr	4.5hr
≥2µm	10147	9536	8729
≥5µm	2276	2112	1843
≥10µm	640	580	458
≥25µm	47	33	21



2.5 mg/mL Protein

Average Particles / mL

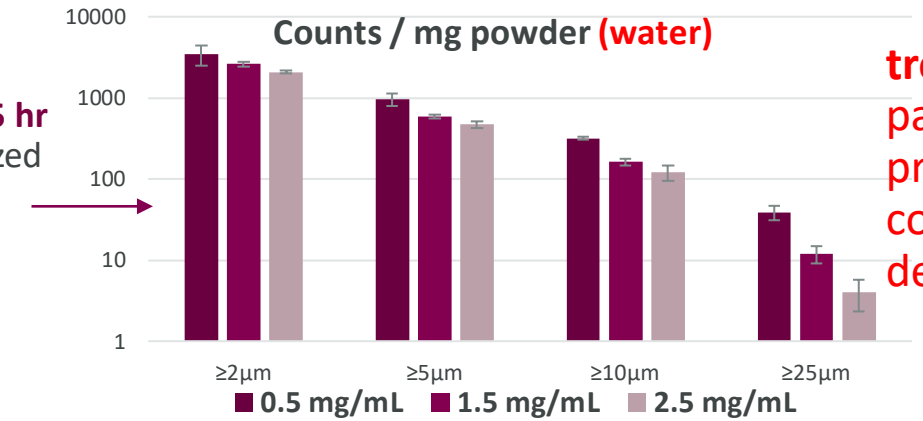
	1.5hr	2.5hr	4.5hr
≥2µm	13571	12143	11359
≥5µm	3051	2455	2137
≥10µm	789	561	420
≥25µm	26	24	13



± 1 std dev at 1.5 and 2.5 hr in all channels at all concentrations: Provides 1hr window to take particle count readings

Observed a steady but slow trend downward in particle counts with time in each channel across all concentrations (gradual aggregate disassociation, excipient solubility, degassing?)

Sub-set of **1.5 hr** data normalized to counts/mg powder

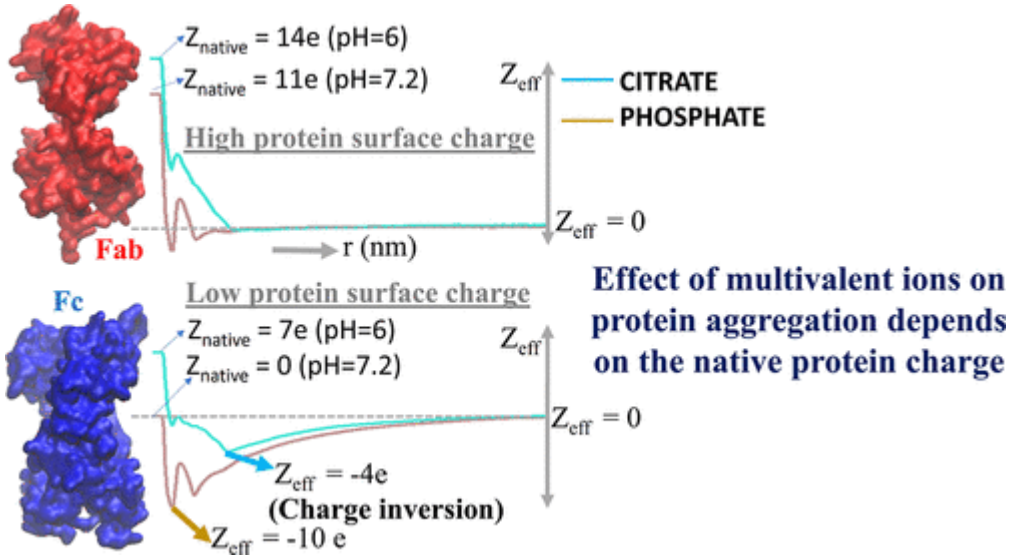


trend of increasing particle counts as protein concentration decreases

Impact of Diluent Composition on SVP/Aggregate Formation

- Previous HIAC data were generated using water as the sample diluent for reconstitution.
- 3 separate observations of slight increases in particle counts relative to decreasing protein concentration (normalized data)
- Sample preparation produces samples with varying protein concentration but also produce varying excipient concentrations and pH

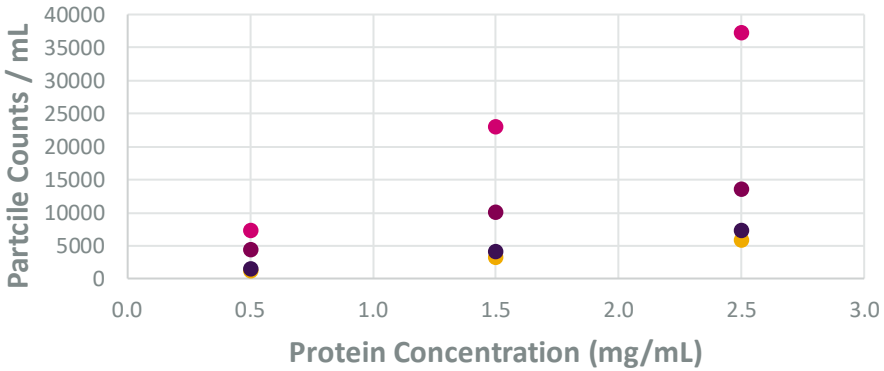
Buffer type may affect protein surface charge influencing propensity of aggregation



Saurabh S, Zhang Q, Seddon JM, Lu JR, Kalonia C, Bresme F. Unraveling the Microscopic Mechanism of Molecular Ion Interaction with Monoclonal Antibodies: Impact on Protein Aggregation. Mol Pharm. 2024 Mar 4;21(3):1285-1299. doi: 10.1021/acs.molpharmaceut.3c00963. Epub 2024 Feb 12. PMID: 38345400; PMCID: PMC10915798.

Initial Diluent Screen for Impact on Aggregate Formation

≥2µm Average Particle Counts per mL

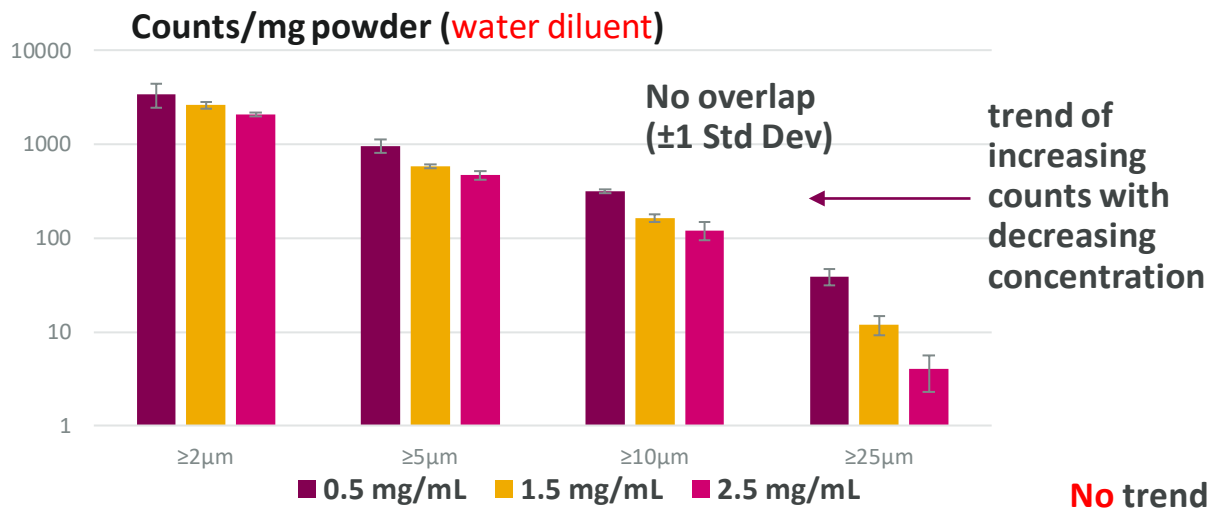


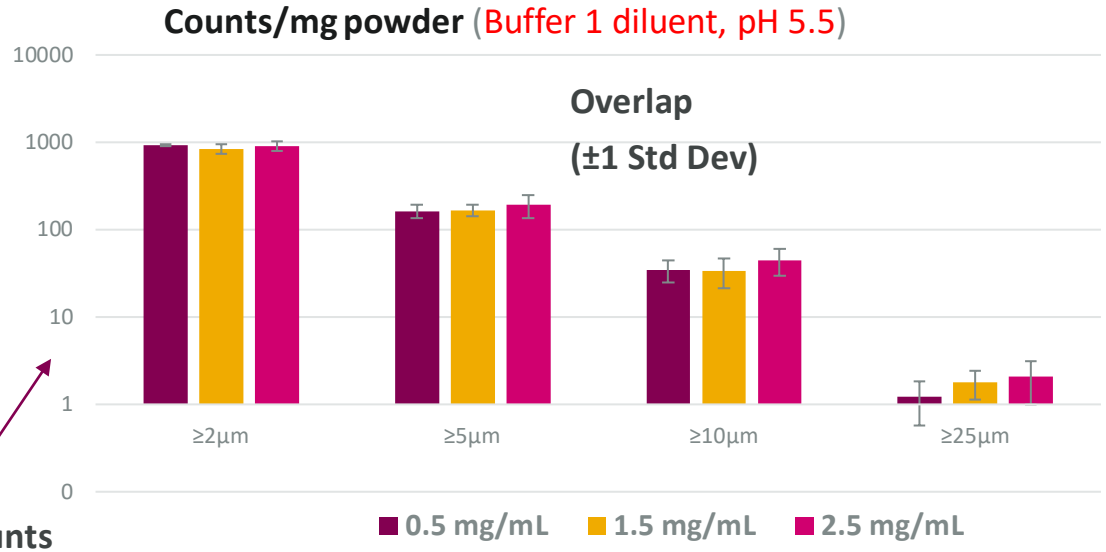
- Water
- Buffer 1 pH 5.5
- Buffer 2 pH 7.4
- Buffer 1 pH 5.5 + Primary Excipient

Observations

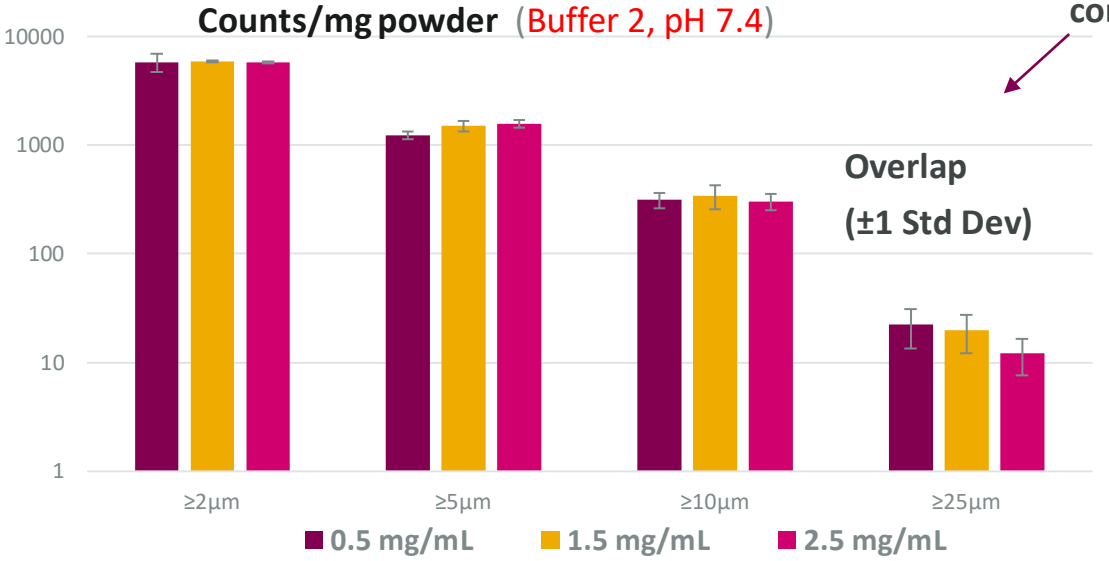
- absolute counts per mL are relatively linear in each diluent. (ie. total counts increase as protein concentration increases)
- Significantly more SVP present in Buffer 2 at pH 7.4
- Slopes of lines are different indicating rate of SVP formation is potentially dependent on diluent
- Buffer 1 and Buffer 1+primary excipient diluents practically equal (suggest Buffer 1 at pH 5.5 as the controlling factor)

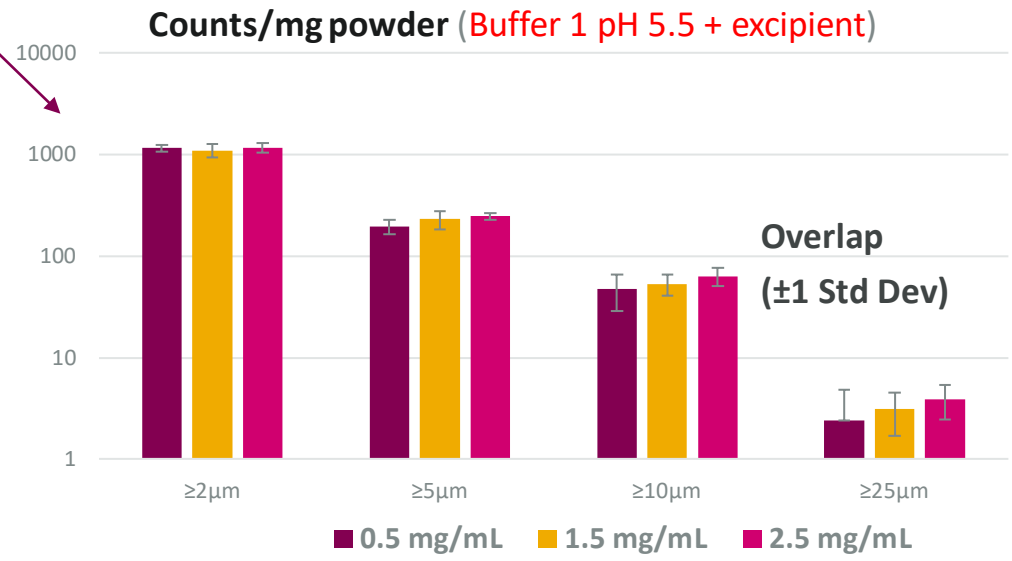
Normalized Data for Samples Prepared with Various Diluents





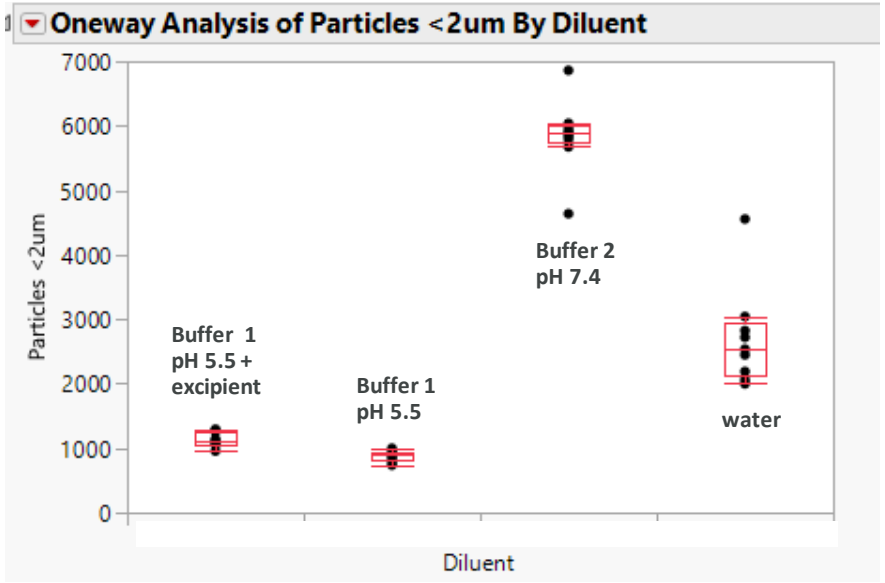
No trend of increasing counts with decreasing concentration



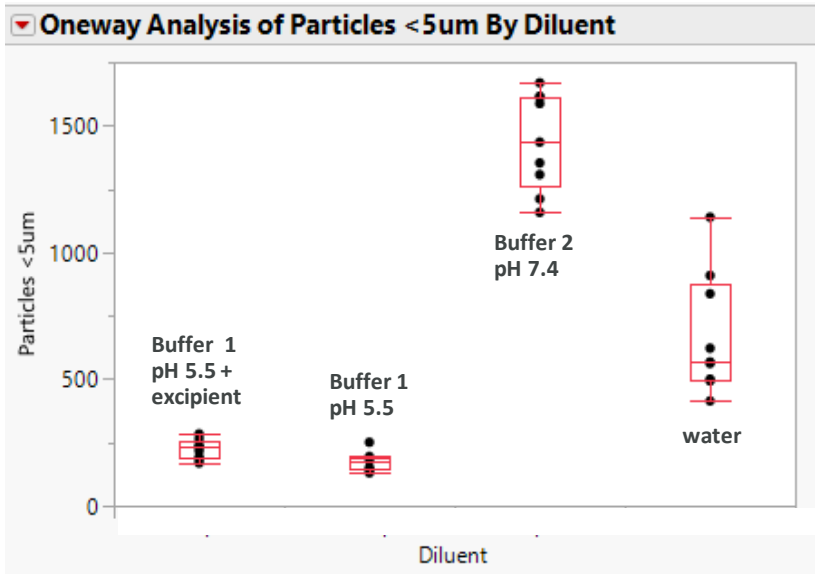


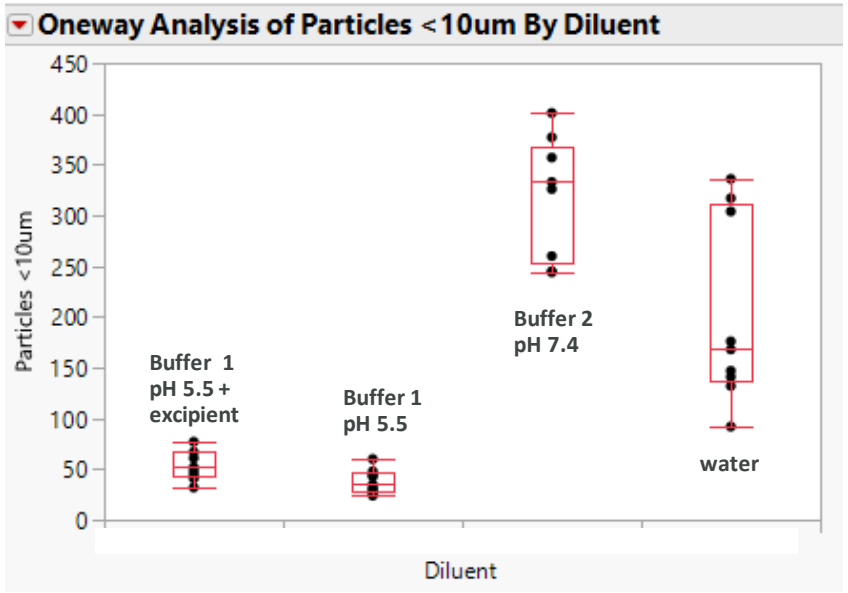
Clear impact of diluent on particle count data normalized to mg total powder, buffered diluent = better stability

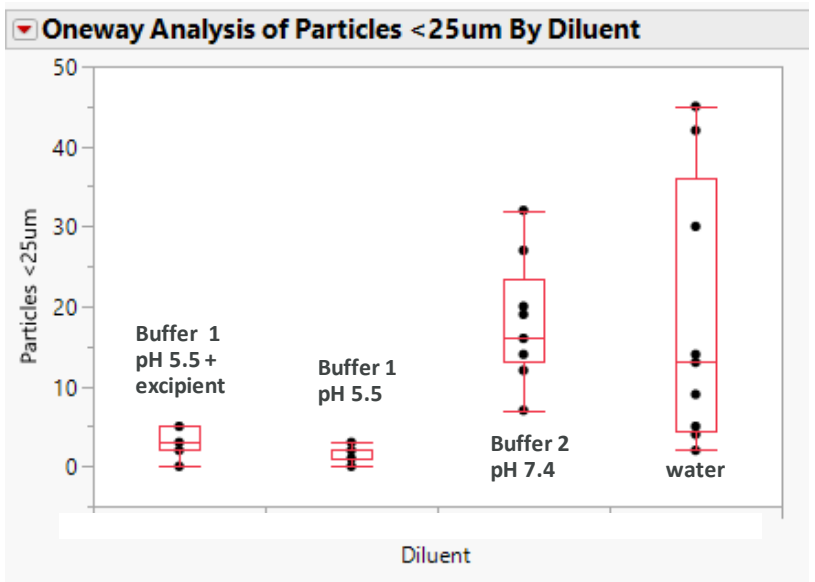
Comparison of Normalized Particle Count Data per Diluent



Buf 1 pH 5.5







Statistical box plots of particle count data normalized to mg powder in various diluents:

- Stabilized Aggregate formation on a per mg basis (normalized data) with buffered diluents
  - corrects one of the biggest obstacles encountered so far with SVP method development – concentration dependent particle counts
- Over-all, particle counts are lower when samples prepared with Buffer 1 pH 5.5 diluent.
- Wider variance in SVP counts with plots for water and Buffer 2 pH 7.4 demonstrates aggregate formation
- Presence of primary excipient less impactful than buffered diluent
- pH is impacted as excipients are diluted when diluent is **not** buffered

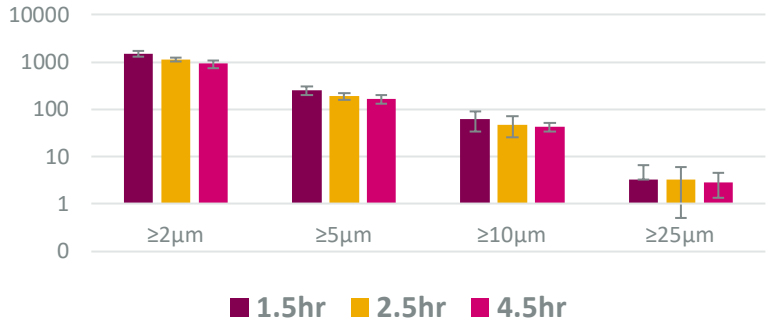
Normalized data to particle counts per mg of powder

Aggregate Formation and Stability (Buffer 1 pH 5.5 diluent)

0.5 mg/mL Protein

Average Particles / mL

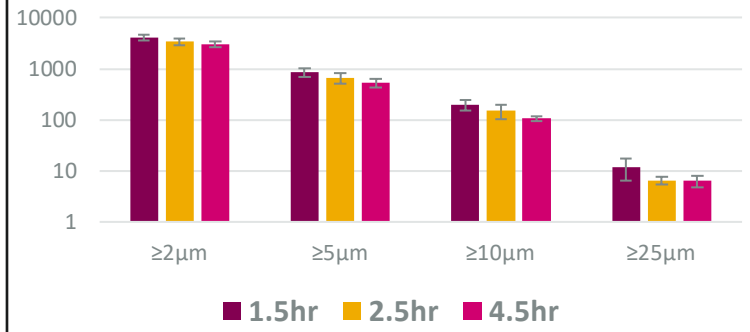
	1.5hr	2.5hr	4.5hr
≥2µm	1506	1135	917
≥5µm	254	190	168
≥10µm	62	48	42
≥25µm	3	3	3



1.5 mg/mL Protein

Average Particles / mL

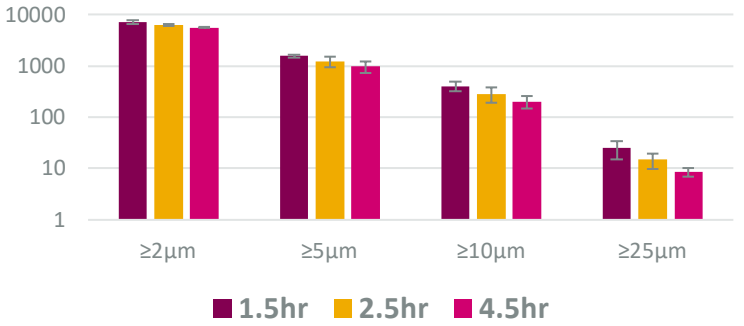
	1.5hr	2.5hr	4.5hr
≥2µm	4128	3404	3027
≥5µm	873	663	535
≥10µm	201	152	107
≥25µm	12	7	6



2.5 mg/mL Protein

Average Particles / mL

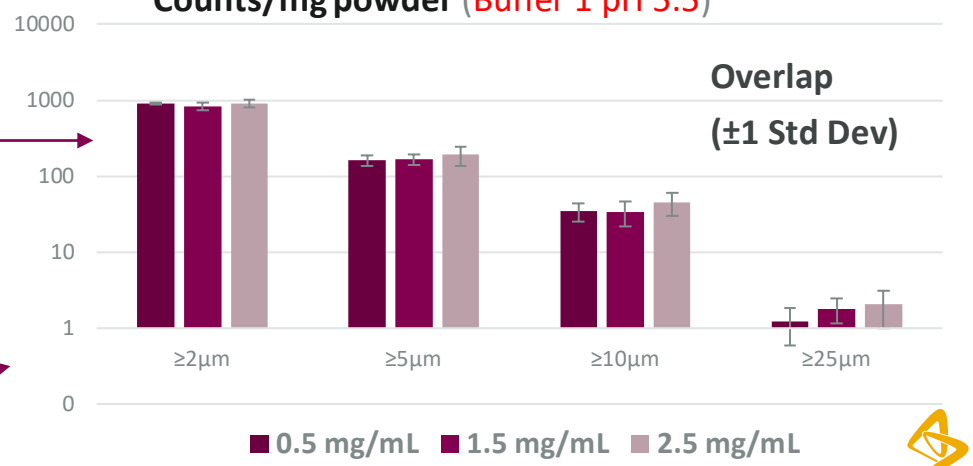
	1.5hr	2.5hr	4.5hr
≥2µm	7311	6333	5621
≥5µm	1553	1225	968
≥10µm	399	288	200
≥25µm	25	15	8



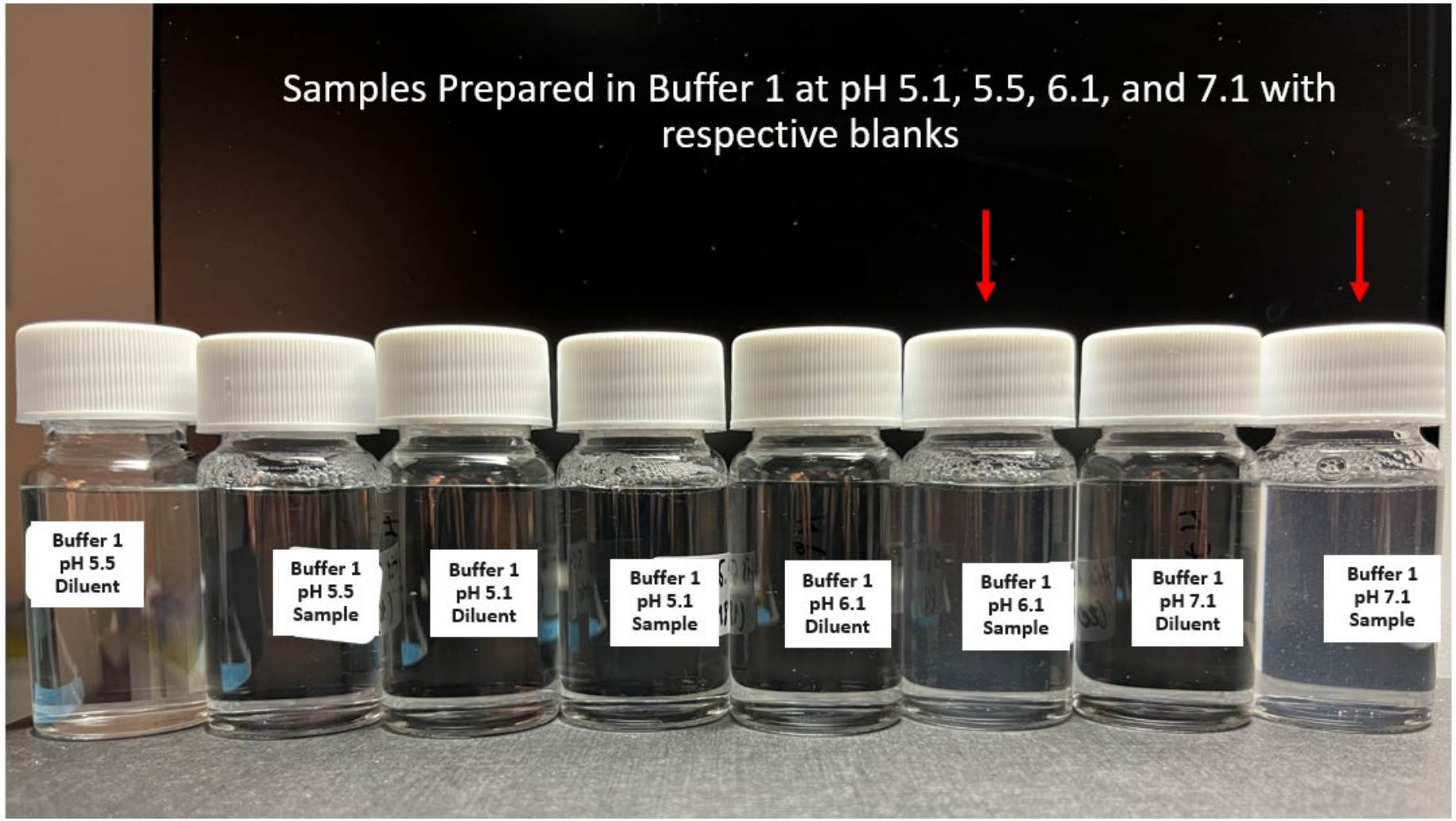
- **± 1 std dev at 1.5 and 2.5 hr in all channels at all concentrations: Provides 1hr window to take particle count readings**
- **Slow trend downward in particle counts with time in each channel across all concentrations (gradual aggregate disassociation, excipient solubility, continued degassing?)**
- **no shift in distribution (small to large aggregates)**
- **Normalized data (counts / mg powder) show no trend of increasing particle counts as concentration decreases**

Sub-set of **1.5 hr** data normalized to counts/mg powder

Counts/mg powder (Buffer 1 pH 5.5)



pH Drives SVP/VP Formation with Buffer 1

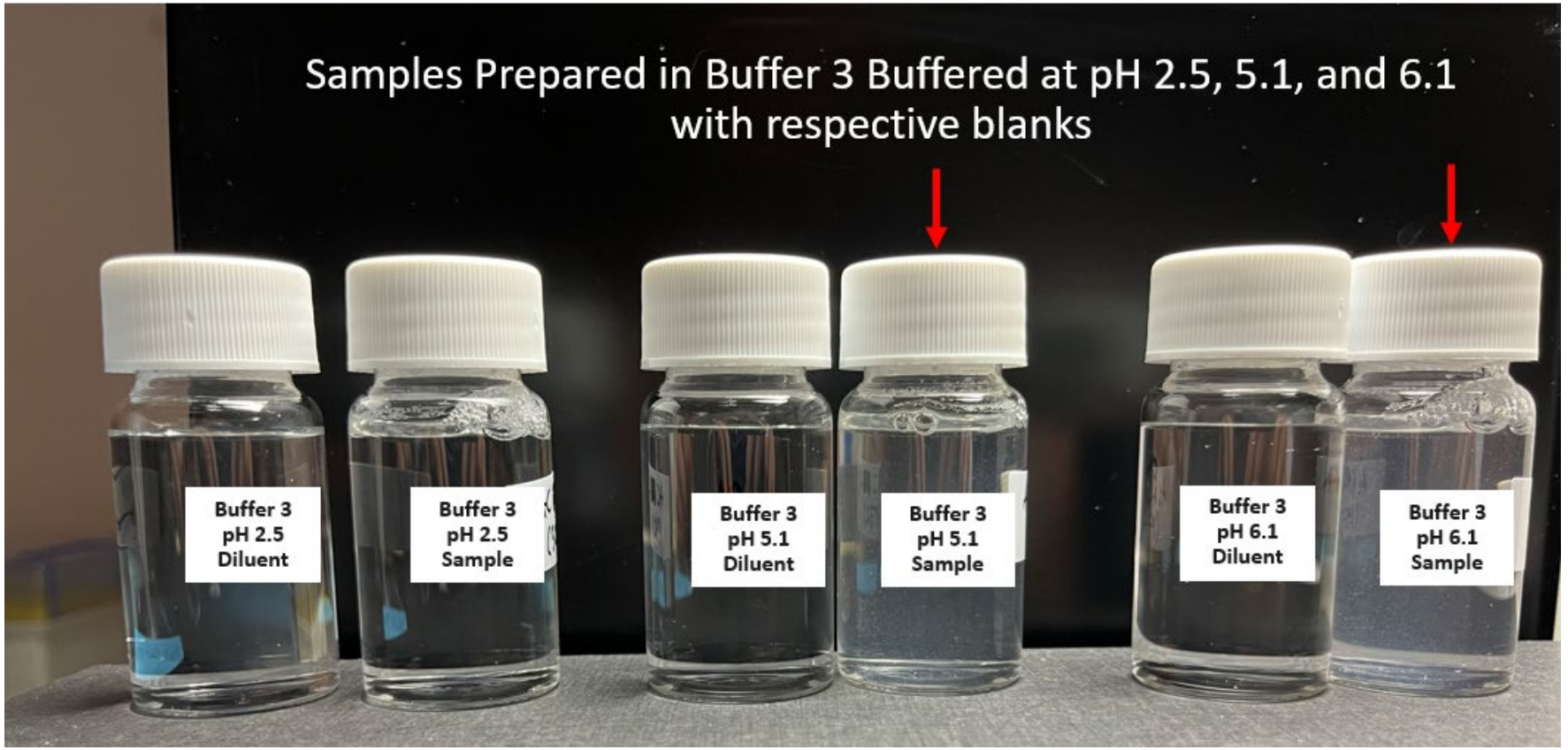


Visual Assessments made for samples prepared in Buffer 1 at pH 6.1 and 7.1 due to particle counts exceeding HIAC sensor limits

Visual assessment-clear indication of increasing SVP/VP formation as diluent pH is increased with Buffer 1

Placebo controls at all pH values were clear and free of SVP/VP by HIAC and visual assessment

pH Drives SVP/VP Formation with Buffer 3



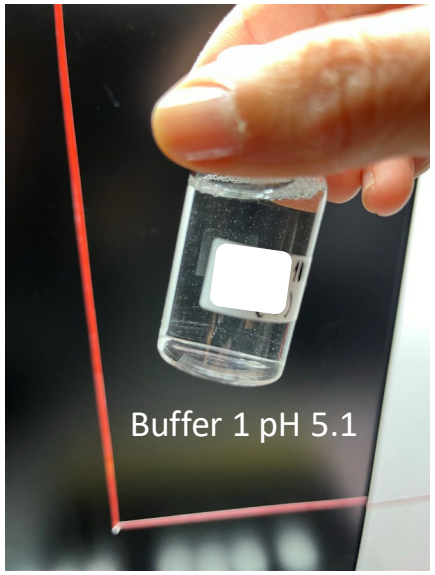
		Particles/mg powder			
Sample ID	Diluent	≥2µm	≥5µm	≥10µm	≥25µm
Diluent Blank	Buffer 3 2.5	3		0	
Placebo Powder	Buffer 3 2.5	2	1	0	0
40% Active Powder	Buffer 3 2.5	3	1	0	0
40% Active Powder	Chaotrope	9	1	0	0

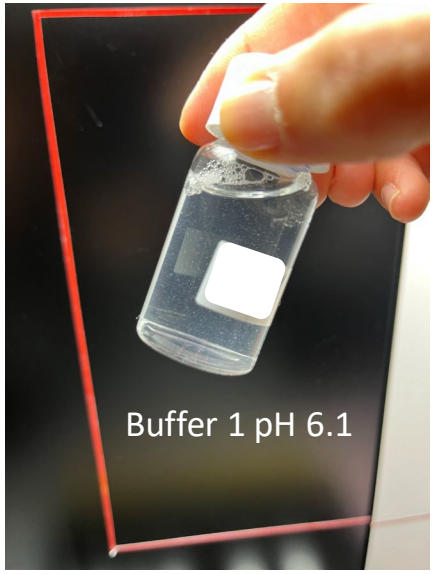
Visual Assessments made for samples prepared in Buffer 3 buffer at pH 5.1 and 6.1 due to particle counts exceeding sensor limits

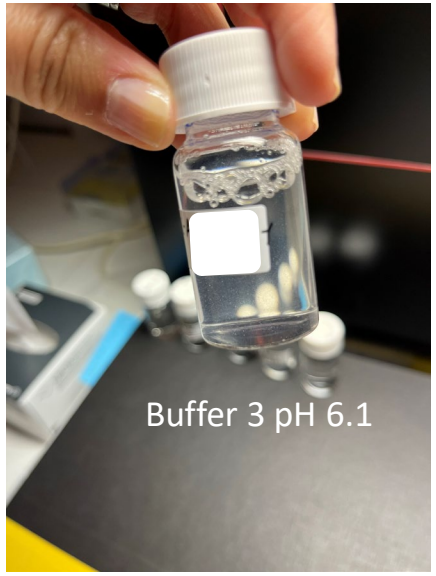
Visual assessments-clear indication of increasing SVP/VP formation as diluent pH is increased with Buffer 3

HIAC data for 40% active powder when normalized to particles/mg powder shows Buffer 3 at pH 2.5 is equivalent to diluent blank, placebo, and chaotrope preparations – **very low aggregate formation**

Buffer Selection Impacts SVP/VP Formation: Buffer 1 vs Buffer 3







Visual Assessment for samples prepared in Buffer 1 and Buffer 3 buffers buffered at pH 5.1 and 6.1.

Visual Assessment shows Buffer 3 to have more SVP formation relative to Buffer 1 at 5.1 – indicates potential for buffer selection to impact aggregate formation independent of pH

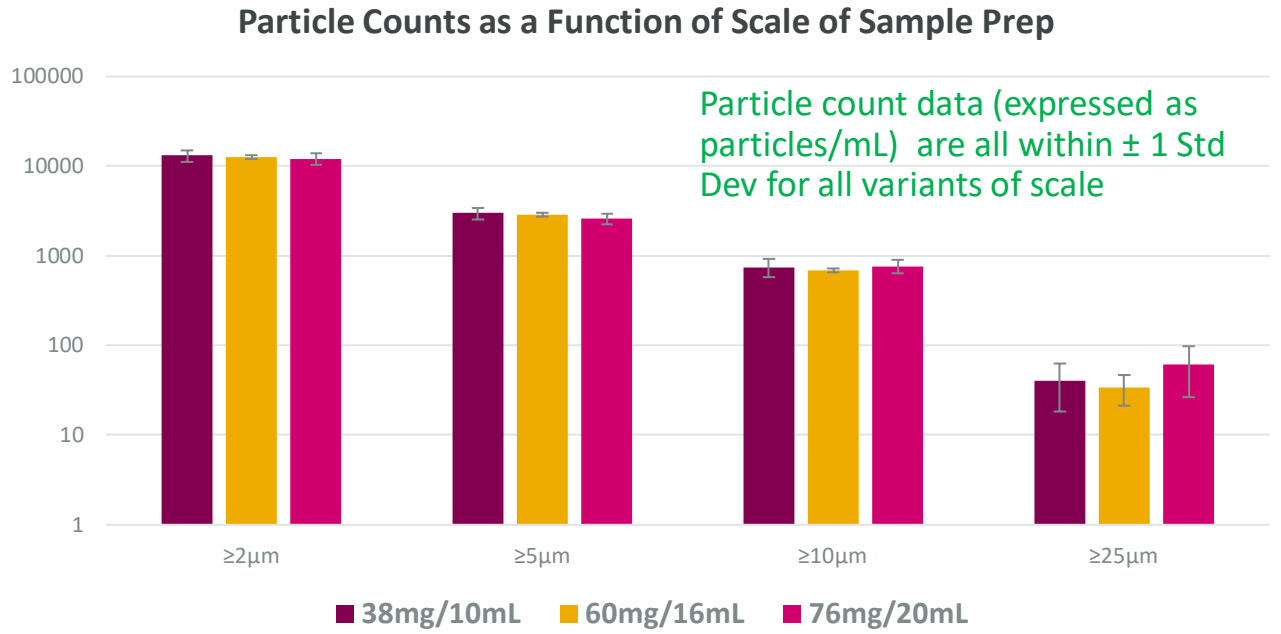
At pH 6.1 both Buffer 1 and Buffer 3 are showing significant visible aggregate formation suggesting pH is the over riding factor

Placebo controls at all pH values were visually clear of particulates and had comparable counts by HIAC as diluent blanks – indicates predominance of particulates are related to protein aggregates (inherent).

Scale of Sample Preparation (Buffer 1 pH 5.5)

Protein Concentration held constant at **1.5mg/mL** for each sample variant

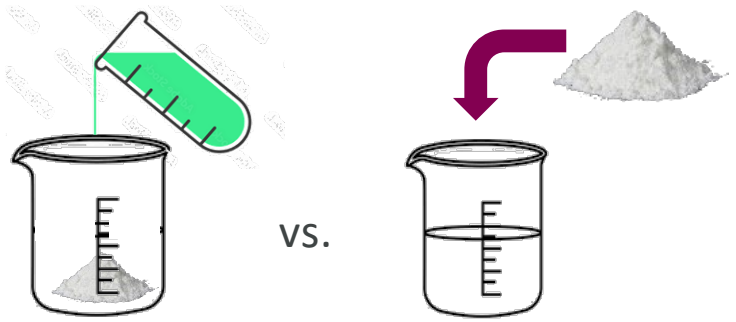
- Data suggest **minimal impact** from scale of sample preparation at a single concentration (range 38mg powder/10mL to 76mg powder/20mL)

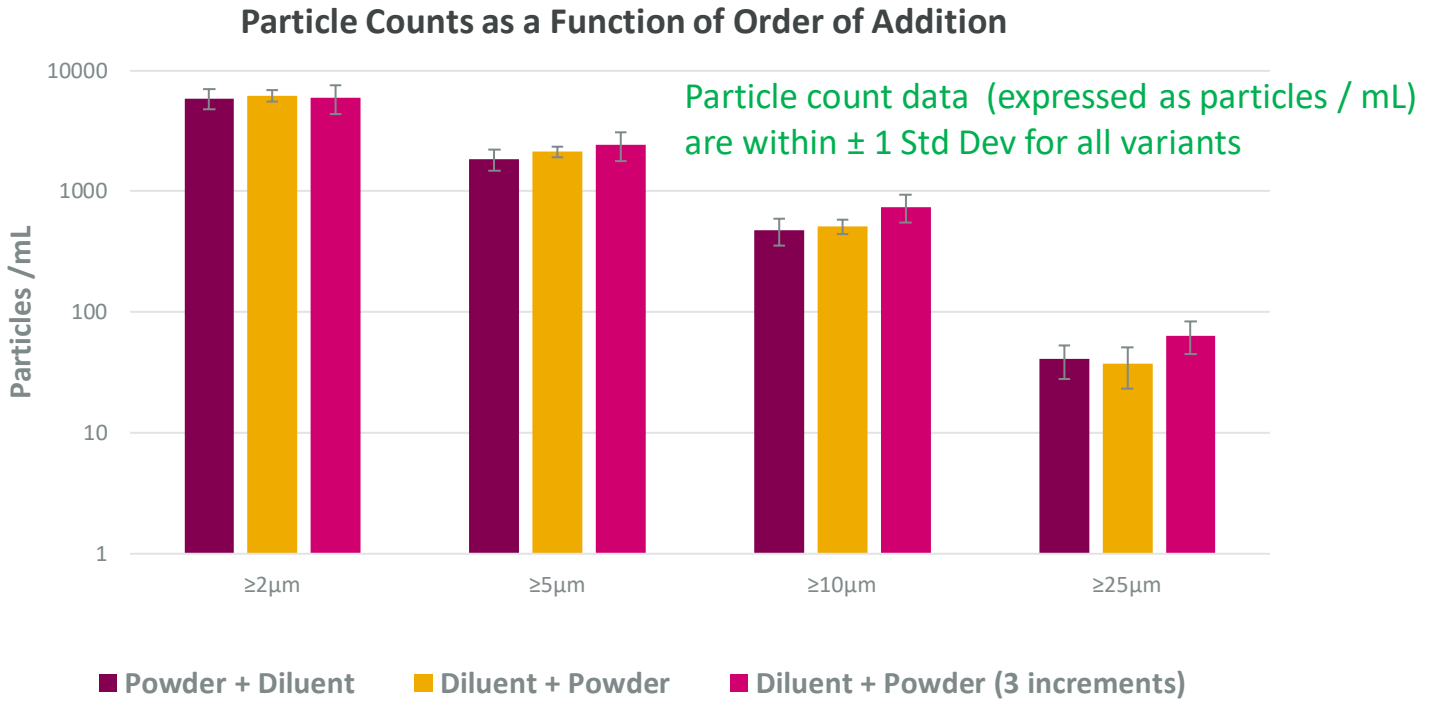


HIAC Channel	Particles/mL by Scale of Preparation 38mg/10mL	60mg/16mL	76mg/20mL
≥2µm	13040	12631	12033
≥5µm	2965	2864	2579
≥10µm	743	685	763
≥25µm	40	34	62

Order of Addition – (Buffer 1 pH 5.5 diluent)

Study targeted understanding of how the powder is wetted and if subtle changes would impact SVP formation





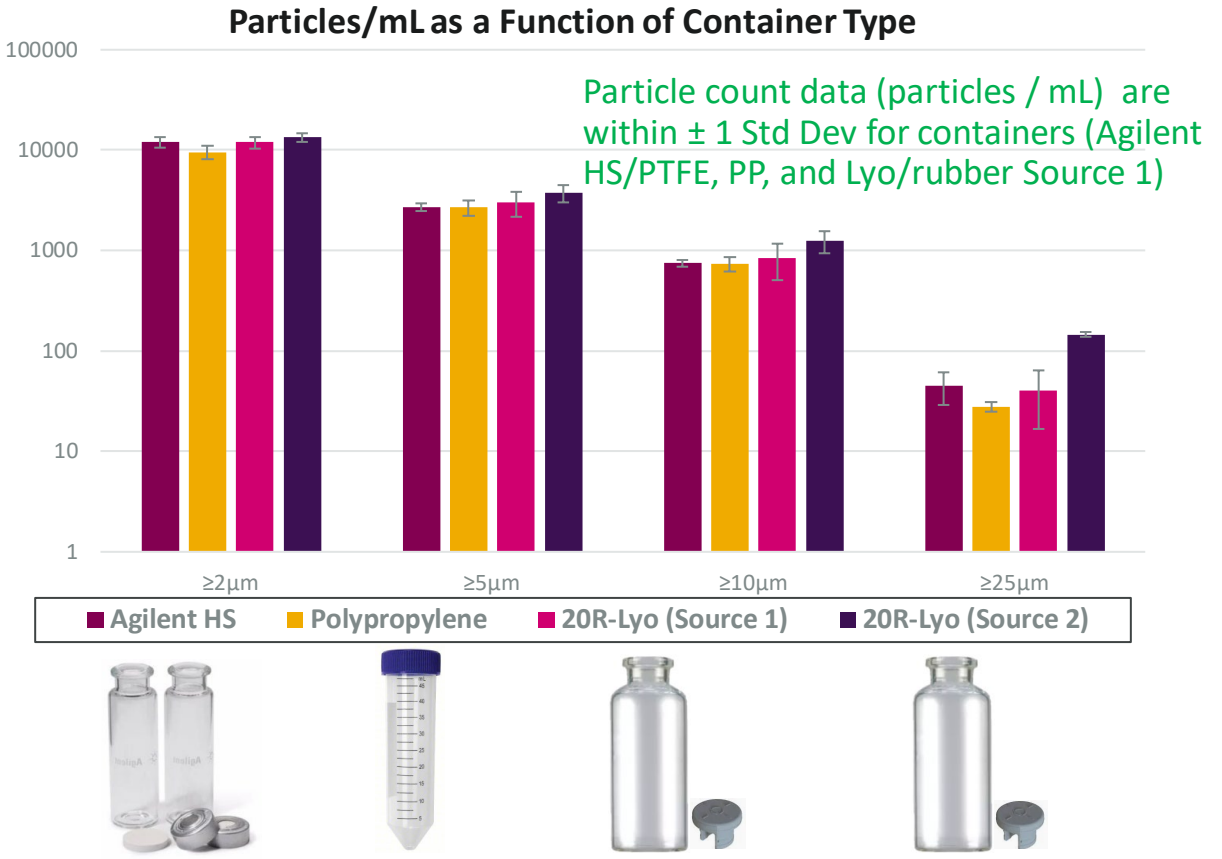
- Data suggest **minimal impact** from order addition

	Particles/mL by **Order of Addition**		
HIAC Channel	**Powder + Diluent**	**Diluent + Powder**	**Diluent + Powder (3 increments)**
≥2µm	5891	6191	5985
≥5µm	1834	2131	2437
≥10µm	473	512	744
≥25µm	41	37	64

Container Type (Buffer 1 pH 5.5 diluent)

Study targeted impact from container type and closure system on levels of SVP formed

- Polypropylene gave slightly lower compared to the glass container types
  - Easiest to work with in terms of sample prep.
  - PP would **not** allow visual assessment of visible particle measurement.
- Suggest container type and cap has **minimal impact** on SVP formation from the containers evaluated
- Lyo Vials - Source 1 vs Source 2 = different glassware cleaning processes (data indicates source 1 is a more efficient cleaning process)



Particles/mL by container at 1.5 mg/mL sample concentration

	≥2µm	≥5µm	≥10µm	≥25µm
Agilent HS/PTFA	12108	2717	748	45
Polypropylene	9533	2683	740	28
20R-Lyo (Source 1)/rubber	11974	2979	838	40
20R-Lyo (Source 2)/rubber	13478	3731	1240	145

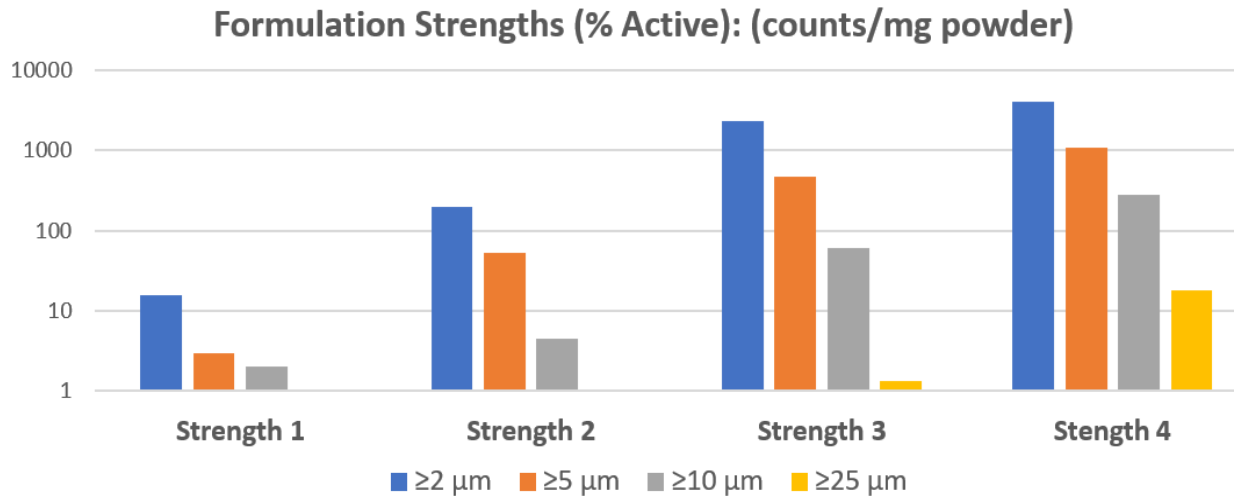
Factors Influencing Particle Precision

- Buffered diluent is critical for sample stability :
  - **reduces concentration dependent aggregate formation**
  - **affects protein surface charge influencing aggregation**
- Diluent pH : most **significant factor** in aggregate formation
  - pH changes can **increase the net charge of a protein**, which can increase electrostatic repulsion between protein molecules and **reduce aggregation in aqueous solution**
- Sample Stability : (buffered diluent)
  - Time course studies identified **1hr window**.
  - **No evidence of aggregate disassociation or shift in distribution**
- Scale of sample preparation and order of addition (powder wetting studies), and container/closure (surface interactions) studies showed little impact on SVP formation during reconstitution for this case study

HIAC Method is Discriminating

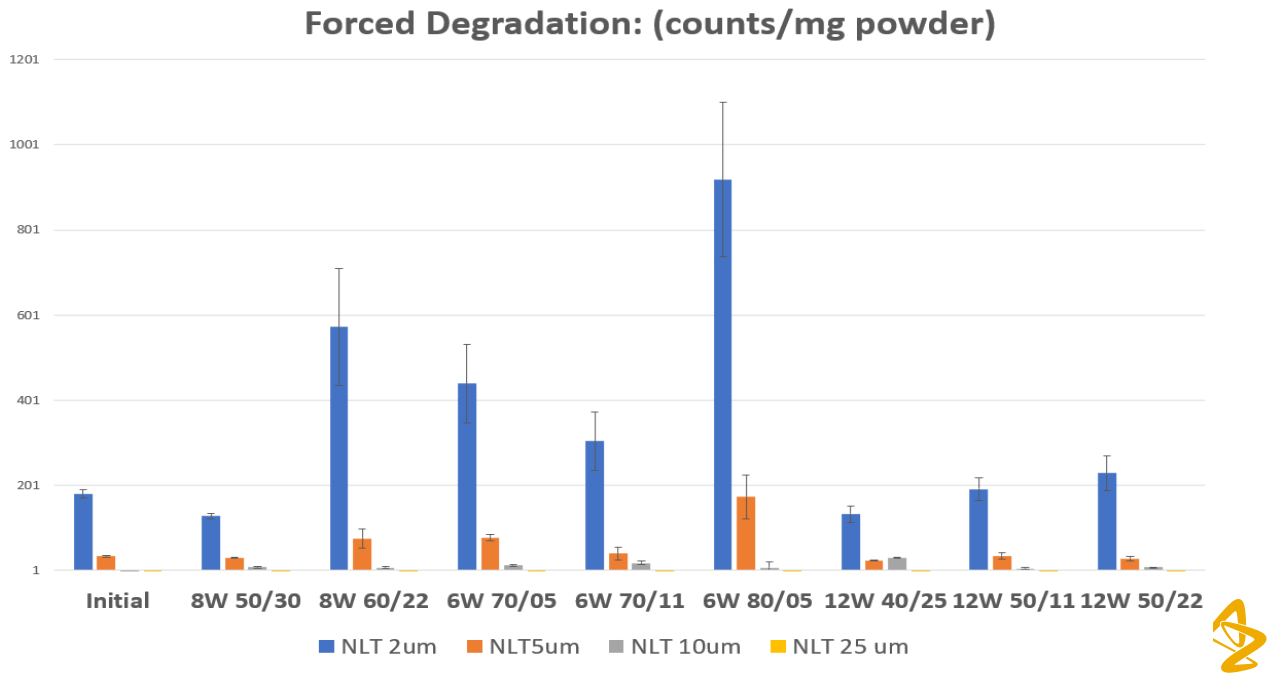
Enumeration results for spray dried powder of varying strengths (% active).

- Higher strengths = higher particulates on a per mg powder basis



Enumeration results for a protein based spray dried powder after stressing under accelerated conditions (heat and humidity).

- Indicates that enumeration method is stability indicating



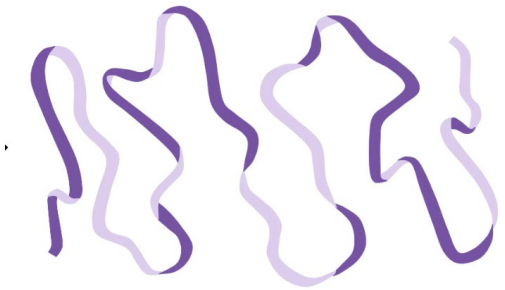
Introducing FPM Selectivity via Chaotrope Diluent

Strategy Step	Reconstitution Diluent	Replicate	Particles per mg powder ≥2µm	Particles per mg powder ≥5µm	Particles per mg powder ≥10µm	Particles per mg powder ≥25µm
1	Buffer 1 pH 5.5 (inherent, intrinsic, extrinsic)	1	1229	207	50	3
		2	1056	174	41	2
		3	1129	191	45	2
		Mean	**1138**	**191**	**45**	**2**
2	Chaotrope (extrinsic)	1	13	4	1	0
		2	17	4	0	0
		3	9	1	0	0
		Mean	**13**	**3**	**1**	**0**

Folded Protein

Use of chaotrope diluent prevents protein aggregation

Disrupts hydrogen bonding > weakens hydrophobic effect > denatures proteins



Unfolded Protein

Significant reduction in particles per mg powder (extrinsic matter remains)

Conversion of Chaotropic Diluent Data to Inhaled Mass/Day

Chaotrope Diluent for FPM

	Particles/mg ([1]FPM Buckets)		
	<10µm	**10 - 25µm**	**>25µm**
	12	1	0
	17	0	0
	9	0	0
Mean	**12**	**1**	**0**

[1]FDA DPI / MDI Guidance

Particle counts/mg powder converted to particles /capsule →

Capsule Fill Weight = 20mg

	Particles/Capsule		
	<10µm	**10 - 25µm**	**>25µm**
	240	20	0
	340	0	0
	180	0	0
Mean	**240**	**20**	**0**

Assuming all particles are 10µm with a density of stainless →

Extrinsic Mass/Capsule (mg)

	<10µm Particles
	0.0010
	0.0014
	0.0008
Mean	**0.0011**

FPM Specification Acceptance Criteria Calculated as per IPAC-RS Guidance: < 0.15 mg/day for Particulates <10µm

- **Worst-case assumptions based on a particle density of stainless steel and particle size of 10µm**
- **Refine post FPM characterization studies**

Particulate data for 10-25µm and >25µm collected for data density for potentially setting of specification

Particulate Limits USP <787> : Therapeutic Protein Injections

SVP/FPM measured by light obscuration – HIAC described in USP <787> as accepted compendial method used for particulate analysis for injectables.

- Acceptance Criteria:

Acceptance Criteria: USP <787>	
Allowable Particles/container	**Particle Size**
<6000	≥ 10µm
<600	≥ 25µm

USP <787> acceptance criteria do not seem applicable for inhaled biologic products:

- Focus particulates >10µm and >25µm - (inhaled focus is <10µm)
- Inherent/Intrinsic particulate formation is a result of reconstitution and is extremely sensitive to various factors.
  - Buffer type and pH (compound specific)
  - Correlation between in-vitro measurement and clinical outcomes

Particulate Limits (IPAC-RS) : Guidance for OINDP's

FPM Acceptance criteria of <0.15 mg /day for particles < 10µm per IPAC-RS guidance with the following considerations: (Blanchard Articles)

- US EPA national ambient air quality standard for particulate matter <10µm (PM_{10}; 150 µg/m^3)
- EPA breathing volume assumption (20 m^3 of air per day) gives 0.15mg/day maximum intake (5% of the NAAQS PM_{10} limit)
- Mass based safety limits derived using maximum density of stainless steel (8g/cm^3) and assumption that all particles were 10 µm in diameter

IPAC-RS guidance for FPM do not seem applicable for control of all particulates:

- Inherent/intrinsic particulates not present in the inhalable powder but form upon reconstitution
- Safety recommendations from current IPAC-RS guidance covers extrinsic particulates (contaminants)

Blanchard J, ., *et al.* ; International Pharmaceutical Aerosol Consortium on Regulation; Science Foreign Particles Working Group. Foreign particles testing in orally inhaled and nasal drug products. Pharm Res. 2004 Dec;21(12):2137-47.

Blanchard J, ., *et al.* Best practices for managing quality and safety of foreign particles in orally inhaled and nasal drug products, and an evaluation of clinical relevance. Pharm Res. 2007 Mar;24(3):471-9.

Key Take Aways:

- Measurement and enumeration of SVPs by HIAC in inhaled biologics (protein) powders is heavily influenced by the reconstitution process. (Protein Specific)
- Dependence on the reconstitution factors gives caution to making correlation of in-vitro results to in-vivo performance.
- In-vitro particle analysis serves as a means to evaluate and maintain product quality for this “Quality Attribute” of particulates related to protein aggregation.
- Use of chaotrope diluent provides selectivity for Foreign Particulate Matter (FPM) analysis.

<u>Recommendation for comprehensive product quality control strategy for aggregates in IB:</u>

SEC for (soluble) → HIAC for SVP (insoluble) → Visual for VP (insoluble)

↓

SVP/FPM (inherent, intrinsic, extrinsic) analysis for inhaled biologic powders covered with a 2-step (2 diluent) HIAC enumeration strategy

Acknowledgments and Key Contributors

- David Lechuga[1]
- Dana Peles[1]
- Don Kerkow[1]
- Gerard Masdeu[1]
- Aida Edvardsson[1]
- Magda Krajewska[1]
- John Hoberg[2]
- Yoen Joo Kim[3]
- Mariam Ibrahim[3]
- Prakash Manikwar[3]
- Wesley Howard[3]
- Poozesh Sadegh [3]

[1]Astrazeneca, Pharmaceutical Technology & Development (PT&D)

[2]PPD part of Thermo Fisher Scientific, Physical and Chemical Characterization (PCC)

[3]Astrazeneca, BioPharmaceutical Development (BPD)