Particulate Counter Installation and Qualification to manage particle loss: lessons learned

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PDA Parenteral Drug Association

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Agenda

AGENDA	Time:
1. What is the FUZZ – Unknown territory	5 min
2. Global Qualification Strategy applied	10 min
4. Learnings from the CFD's - first qualification & next steps	10 min
5. What about the ISO 14644-21 ?	5 min

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Kurt Jaecques is employee of the GSK group of companies.

TPC versus Annex1, What's the FUZZ?

EU Annex 1 2008

Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing **must be considered in the context of particle losses in the tubing.**

V12

5.9 Particle counters, including sampling tubing, **should be qualified**. The tubing length should be **no greater than 1 meter** with a minimum number of bends and bend radius should be **greater than 15 cm**.

EU Annex 1 2022 final

5.9 Particle counters, including sampling tubing, should be qualified. **The manufacturer's recommended specifications should be considered** for **tube diameter and bend radii**. Tube length should typically be **no longer than 1m unless justified and the number of bends should be minimized.**

GSK employs fixed tubing systems for routine monitoring

Is the 1m based on new science?

- The principles of particle collection have been known and documented in FS 209E in 1992
- In November 2001, Federal Standard 209E was superseded by the new ISO 14644-1 international standards.
- However much of the underlying science was omitted

B40.2.1 Particle transit considerations. The probe and transit tube should be configured so that the Reynolds number is between 5 000 and 25 000. For particles in the range of 0.1 to 1 μm and for a flow rate of 0.028 m^3/min (1.0 ft^3/min), a transit tube up to 30 m long may be used. For particles in the range of 2 to 10 μm the transit tube should be no longer than 3 m. Under these conditions, losses of small particles by diffusion and of large particles by sedimentation and impaction are predicted to be no more than 5% during transit through the tube (see Appendix C). For most applications, these tube configurations and flow conditions will be satisfactory. For special situations, more precise particle transit characteristics can be calculated (see B20.8).

The 5-micron requirement – not harmonized !

Both FDA cGMP 2004 and EU Annex 1 refer to ISO 14644-1 in terms of **classification**

ISO 14644-1 states:

Table 1 — ISO Classes of air cleanliness by particle concentration

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9[g]	c	c	c	35 200 000	8 320 000	293 000

[a] All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

[b] These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

[c] Concentration limits are not applicable in this region of the table due to very high particle concentration.

[d] Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

[e] Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

[f] In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

[g] This class is only applicable for the in-operation state.

The 5-micron requirement – not harmonized !

- EU Annex 1:

Table 1: Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

[a] Classification including 5µm particles may be considered where indicated by the CCS or historical trends.

EU Annex 1 does not specify the need for classification for 5µm but requires to monitor it !!

So, who would not classify if it is required for monitoring !

Unknown territory!

Suppliers & Manufacturers	If <1m: compliant – some basic data – Qualification ? Recommendation suppliers: ex. Tube Ø 6,35 mm based on?
External qualification labs	Core expertise is calibration of particle counters cfr. **ISO/IEC 17025: 2017** & **ISO 21501-4:2018**
Competitors & trade associations	At start: “Wait and see attitude”
ISO 14644:21 2023 NEW	Published post Effective Date Annex 1: see further

Global Project Strategy at GSK

Survey

- A review of the range of counter and configurations employed across the GSK Network

Science

- Review of the theoretical science related to particle collection

CFD

- Experimental CFD, to confirm understanding of significant variables impacting collect

Worst Case selection

- Based on CFD and Pre testing, select the appropriate "Threshold" and " Worst-Case" design for Qualification

Qualification

- Experimental laboratory physical testing to provide meaningful data in relation to GSK in-situ systems

Bracketing Approach

- Comply with Threshold by First Intent
- If not possible – modify to be within Threshold
- If not possible modify to be within Worst Case design
- If not possible apply correction factor on Action limit

Fixed parameter settings for CFD, Pre-testing & Qualification

Particle Type

- CFD and subsequent qualification to be done using solid particles
- Rationale: Main sources of particles in cleanrooms are solid (shedding; fibers, materials – Calibration is performed using solid latex spheres – EMERY: solid particles

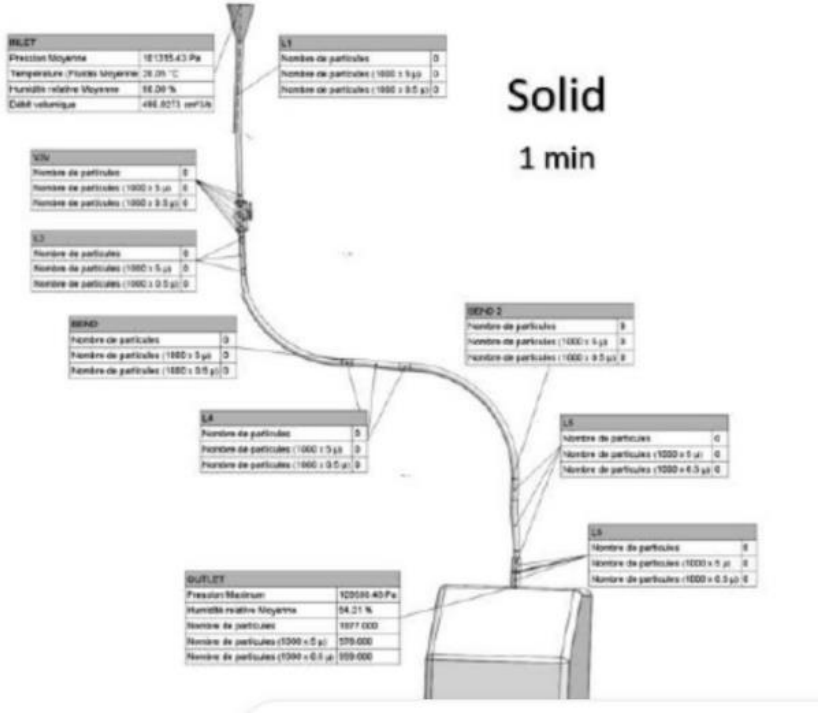
Retention Sample Time

- Particle loss to be determined in 1 min Timeframes
- Rationale: want to ensure particles to be detected within a short time period in order to obtain instant response at cubic foot level

Viable vs Total Particles

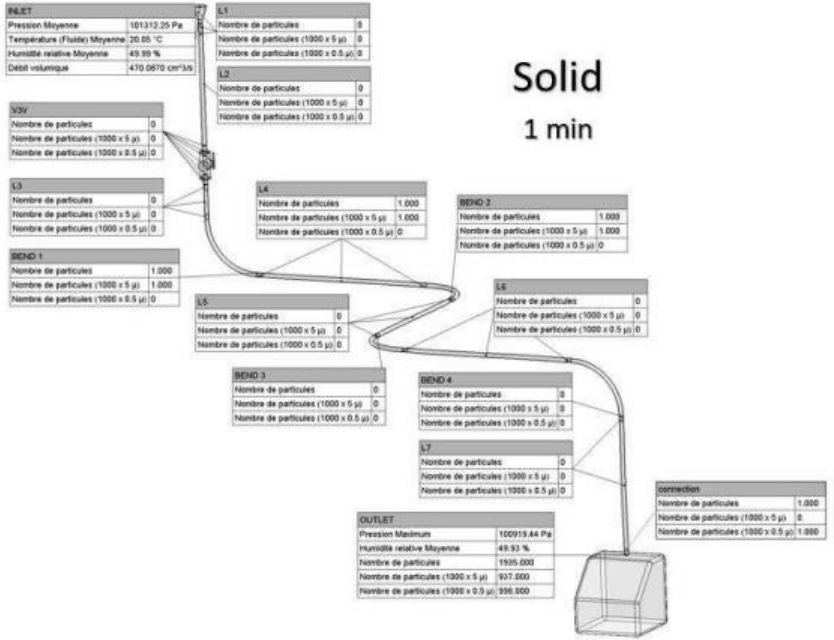
- Total particle retention relates to viable retention
- Rationale: if retention for particles is fine it should be fine as well for viables (important for BFPC measurements)

Selected Tubing configurations for First Qualification – Threshold configuration



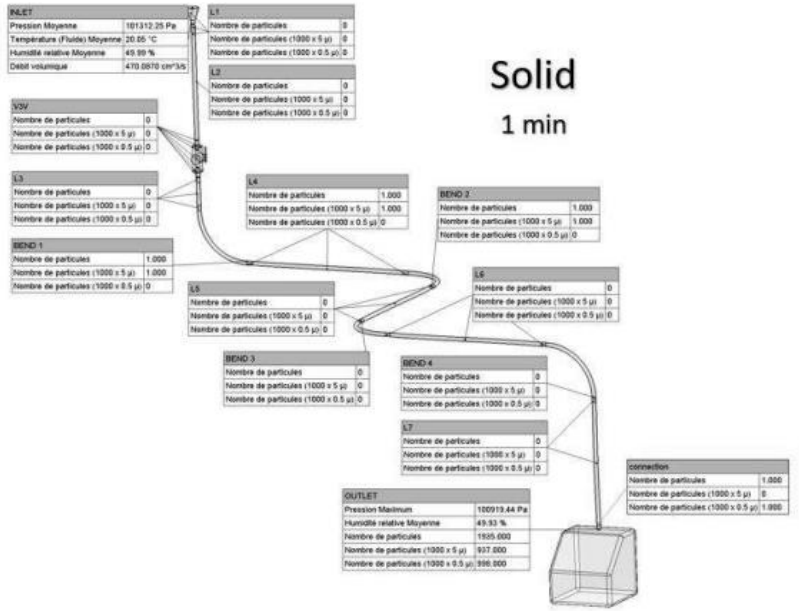
- **Threshold:**
  - Tube length: 1m
  - Bends: 2 bends 90° (radius 15 cm)
  - Tube Diameter: 6,35 mm ID (1/4 inch)
  - Material: Stainless steel (not grounded)
  - 3WV: included (vertical)
  - Connectors: 2 @ probe - @ counter + 2 to 3WV

Selected Tubing configurations for First Qualification – Worse case 1 configuration con[illegible]



- **Worst Case Nr.1:**
  - Tube length: 3m
  - Bends: 4 bends 90° (radius 15 cm)
  - Tube Diameter: 6,35 mm ID (1/4 inch)
  - Material: Stainless steel (not grounded)
  - 3WV: included (vertical)
  - Connectors: 2 @ probe - @ counter + 2 to 3WV

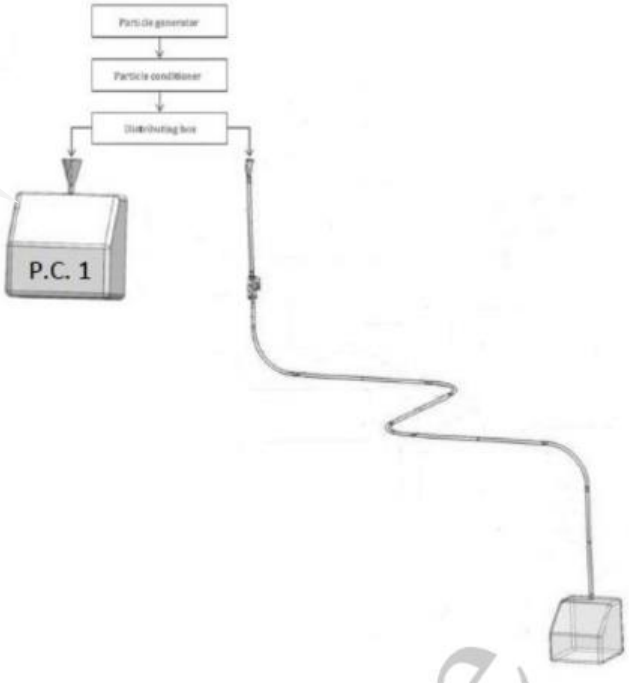
Selected Tubing configurations for First Qualification – Worse case 2 configuration

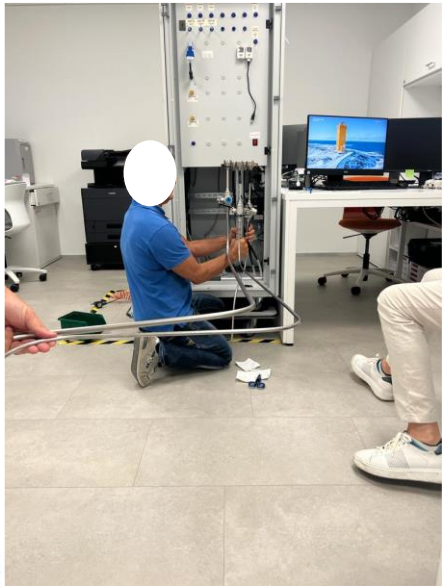


- **Worst Case Nr.2:**
  - Tube length: 3m
  - Bends: 4 bends 90° (radius 15 cm)
  - Tube Diameter: 9,53 mm ID (3/8 inch)
  - Material: Stainless steel (not grounded)
  - 3WV: included (vertical)
  - Connectors: 2 @ probe - @ counter + 2 to 3WV

Qualification Set-up

Calibrated counter without tubing (no Ref. counter)





Results First Qualification Set-up – Nothing is what is seems!

- Influence presence 3WV (or connections ?)
- Influence of tube diameter !!!

Comparison CFD versus Physical Qualification - Solid particles

			particles ≥ 0,5µm		particles ≥ 5µm		Remark
Configuration	3WV	Tube diameter	CFD	Qual.	CFD	Qual.	
Worst Case 2	Y	9,53 mm	99,8%	99%	93,7%	49%	
Worst Case 2	N	9,53 mm		108%		96%	

Comparison CFD versus Physical Qualification - Solid particles

			particles ≥ 0,5µm		particles ≥ 5µm		Remark
Configuration	3WV	Tube diameter	CFD	Qual.	CFD	Qual.	
Threshold	Y	6 mm		97%		4%	
Worst Case 1	Y	6 mm		94%		10%	
Worst Case 2	Y	9,53 mm	99,8%	99%	93,7%	49%	
Threshold	N	6 mm	99,9%	106%	97,8%	5%	CFD on 6,35mm
Worst Case 1	N	6 mm		100%		12%	
Worst Case 2	N	9,53 mm		108%		96%	

Lessons learned following Phase 1 & Phase 2:

- **Phase 1 : CFD**
  - CFD studies limited in some aspects
    - 3W valve showed marginal or limited influence - Not quite true …
    - Predictive capacity depends on the detail of the model ! More qualitative!

- **Phase 2 : Initial laboratory testing**
  - 0.5um : bends and 3 m length doesn't impact its recovery significantly
  - 5 um: many mechanical factors at play
    - loss will always occur
    - Needed to better understand the contributing factors: do some pre-testing before moving forward here! (tipping point ID; material influence; slope; design of 3WV and connections)

Phase 2 Qualification: Temporary conclusions

What is Qualified

- For **5,0µm** Tubing up to 3m length - ID 9,53mm in Bev-A-Line and/or SS with max.4 bends of max. 90° **without a 3WV**
- For **0,5µm no significant particle losses** observed for all tested configurations

Requiring mitigation

- **Tubing < 9,53mm** and/or presence of **3WV** are non-compliant: mitigation = application of a **temporary correction factor**

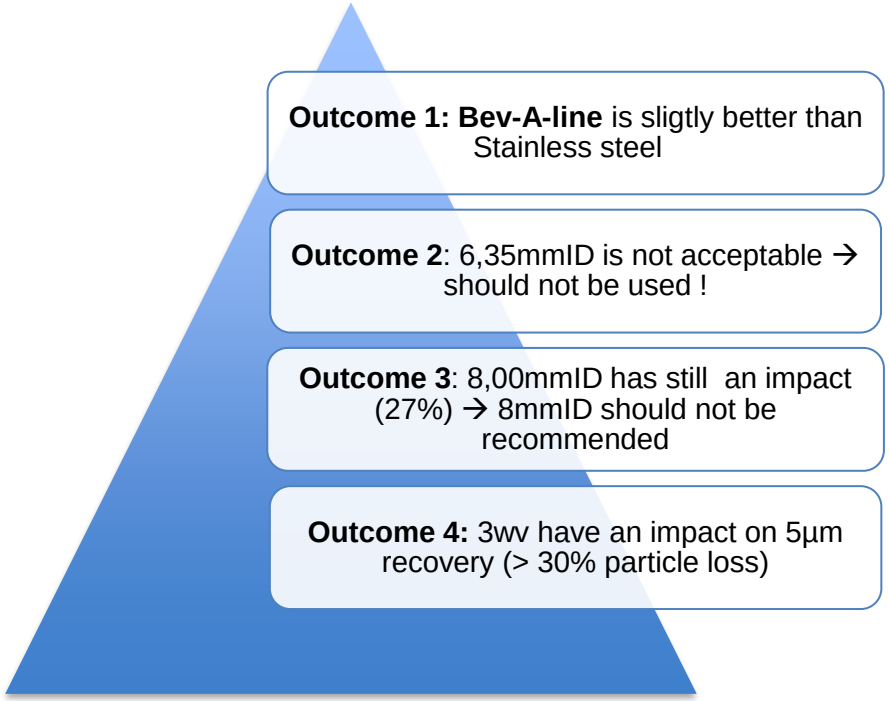
Investigation before Phase 3 Qualification Runs

- Recheck 6,35 and 8mm ID to fix Threshold case diameter (8mm instead of 6,35)
- Recheck impact of 3WV to confirm if **temporary correction factor will have to be "permanent"**
- Assess possibility to remove 3WV (testing resistance of Particle Counters to VHP)
- Recheck some other potential contributing factors e.g. material, Slope

Pretesting with focus on 5 micron particle losses

GSK installation Test Type	Test Condition	Configuration Length, bends & tube ID	>3.0um(*) channel count Particle recovery	Comments
Influence of Material Type	Stainless Steel	1m length, 2 bends, 6mm	15.39%	Material differences not deemed significant. (all 10% of each other)
	Bevaline	1m length, 2 bends, 6mm	19.52%	
	Superthane	1m length, 2 bends, 6mm	22.31%	
Internal Diameter	6.35mm ID (6mm nominal)	1m length, 2 bends	19.52%	Tubing ID deemed significant, with 9.53 providing the best recovery.
	7.75mm ID (8mm nominal)	1m length, 2 bends	67%	
	9.53mm ID (10mm nominal)	1m length, 2 bends	83%	
Slope	2 metre middle section horizontal	3m length, Bevaline, 9.53mm, 2 Bends	68.50%	As long as overall design is falling, sections can be horizontal or have slight inclines
	2 metre middle section slightly declining 3%	3m length, Bevaline, 9.53mm, 2 Bends	75%	
	2 metre middle section slightly ascending 3%	3m length, Bevaline, 9.53mm, 2 Bends	74.20%	
3-way valve	Interapp	1m length, Bevaline, 9.53mm, no bends	67%	3 way valves, even when sized for the tubing have an significant influence
	Eriks	1m length, Bevaline, 9.53mm, no bends	61%	

Pre-Testing – Contributing Factors on 5 micron retention clarified



Phase 3 Qualification based on **7 configurations: ongoing!**

Implement **Temporary correction factor as Permanent ?**

Further longterm investigation to remove 3way valves

Learnings from particle tubing qualification

Manufacturers Role ?

- Provide guidance to users in terms of appropriate bend radii and tube diameters as per Annex 1 "*The manufacturer's recommended specifications should be considered for* ***tube diameter*** *and* ***bend radii***"
- Ensure appropriate connectors to counters allowing the use of higher tube ID

How justify the past ?

- During routine monitoring TRENDING is an important consideration !
- 5-micron particles typically do not occur in Grade A ISO 5 conditions
- Typical sources of 5µm particles: humans (less of a concern using barrier technology) – deterioration of the air supply – equipment failure ! What do we have in place of controls ?
- 0,5 micron is detected with great reliability

EU Annex 1 2022

Note 2: The occasional indication of macro particle counts, especially ≥ 5 µm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

What about the ISO 14644-21 ?

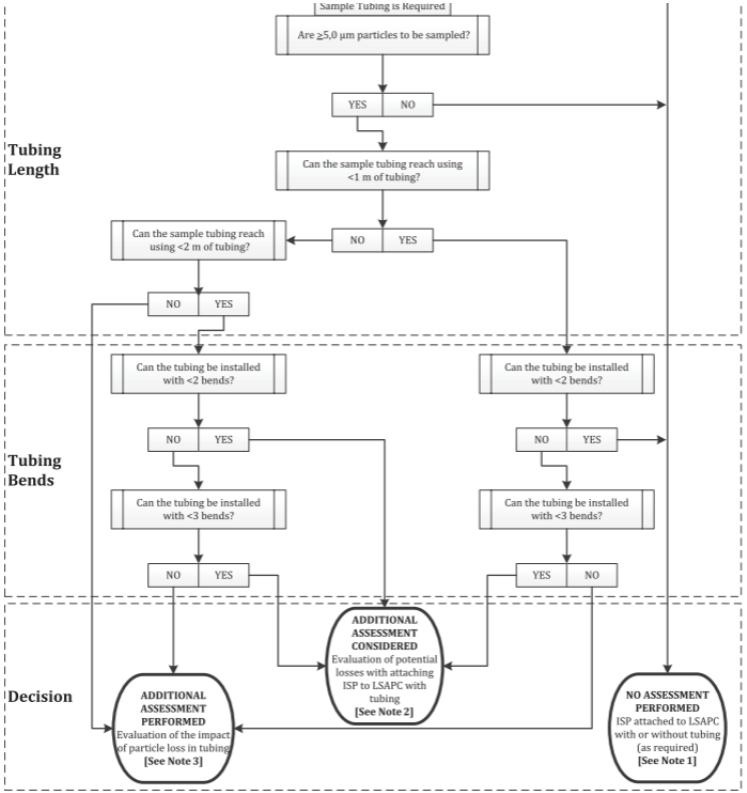
If < 1m and less then 2 bends: **no assessment** !

If < 2m & < 2 bends: **consider assessment** !

If < 2m and < 3 bends: **additional assessment** !

Missing some elements here

+ ANNEX 1: QUALIFY !!!!!



Thank you

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