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Round robin of particle sizing method of a dry powder inhalation carrier

Inhalation

The performance of a dry powder inhalation product heavily relies on the particle size distribution of its components. The size of particles is commonly determined by laser diffraction methodologies. However, since no technique is free of limitations and drawbacks, inevitable off-sets occur between different laboratories. A convenient way to quantify these inevitable off sets between laboratories is the execution of a round robin test series.

Methods and materials

- The Round Robin was conducted utilizing 2 Labs: Lab A and Lab B.
- The design involved 3 batches of Lactohale 200 (Figure 1)
- Evaluation was conducted on d_{10}, d_{50} and d_{90}.
- At every lab 2 operators performed 6 measurements per batch, i.e. n=12 per batch.
- The evaluation was conducted following guideline ISO 5725.

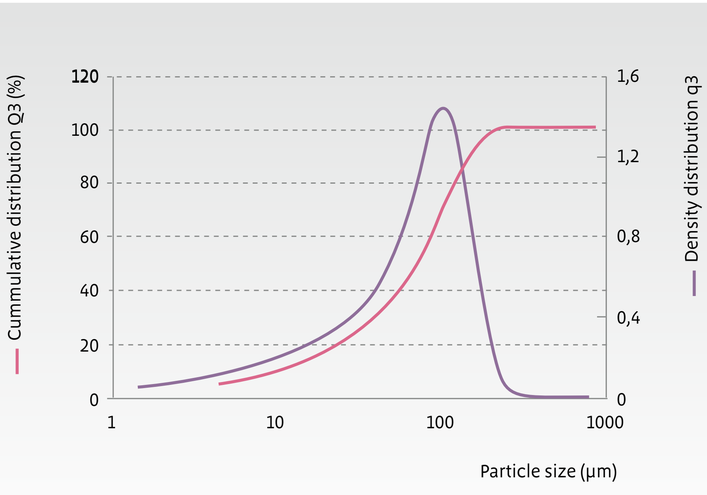

Figure 1 *PSD of Lactohale 200*

Results and discussion

- Figure 2 depicts the relative differences from the general mean.
- It was found that the inter-lab variation is up to 6 times higher than the intra-lab variation. This indicates that the overall variance is predominantly influenced by location/equipment rather than by sampling and/or repeatability variation.
- The variation at the extremes of the distribution (d_{10} and d_{90}) is significantly higher than at the center (d_{50}).
- Lab A consistently yields finer PSDs, independent of the level for the majority of the results.
- Lab B exhibits significantly higher variation of up to 10 times the variation of Lab A.

Conclusions

- Strong and consistent bias between Lab A and Lab B were found for the extremes of the distribution d_{10} and d_{90}.
- The worst case critical difference were found to be:
  - d_{10} 4.1 µm
  - d_{50} 2.4 µm
  - d_{90} 11.8 µm
- The PSD variance observed is often too big to be acceptable for registration authorities.

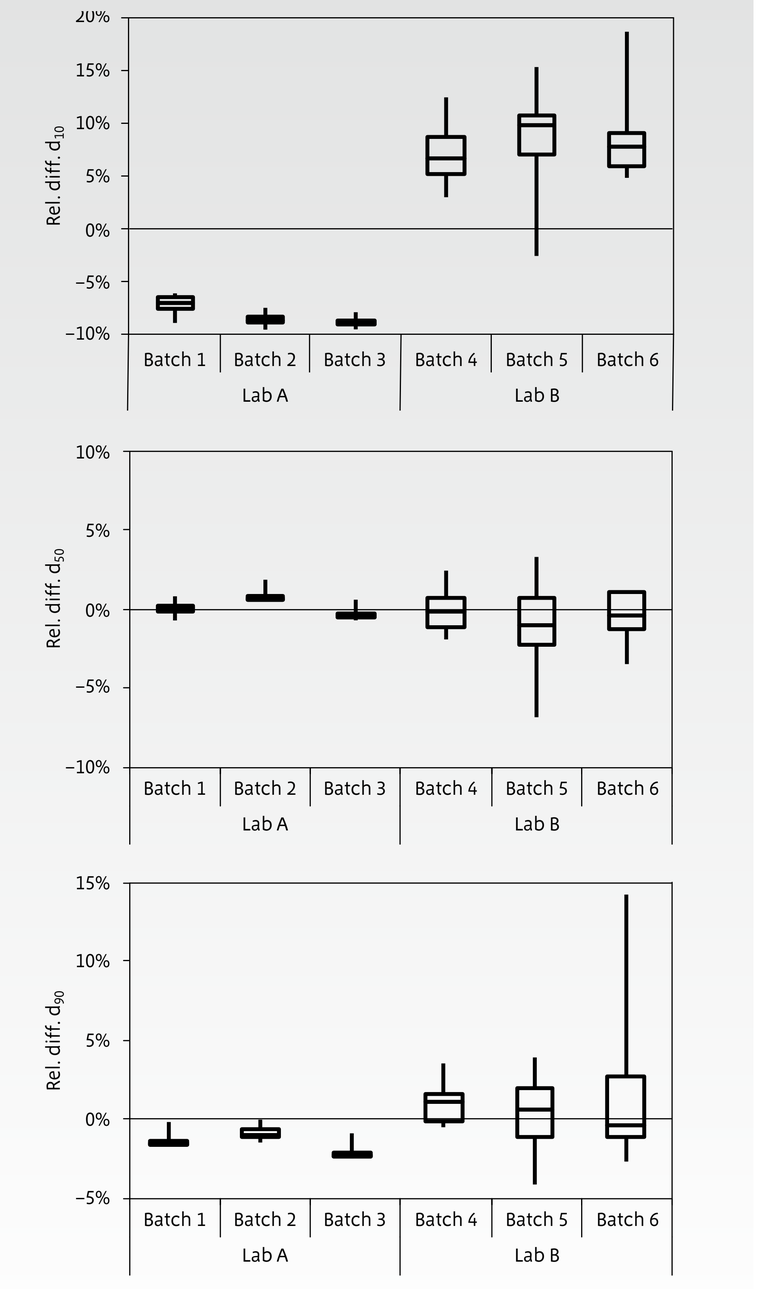

Figure 2 *Box and whisker plots of relative difference observed for d_{10} (top), d_{50} (middle), and d90 (bottom) as percentage from general mean. Shown are minimum, first quartile, median, third quartile and maximum of all measured points at each level in each lab.*

Precision results of round robin (Std.Dev: standard deviation)

PSD	Batch	General mean (µm)	Repeatability Std.Dev. sr (µm)	Reproducibility Std.Dev. sR (µm)	Repeatability limit r=2.8sr (µm)	Reproducibility limit R=2.8sR (µm)	γ =(sR/sr)
d_{10}	1	11.4	0.2	1.2	0.5	3.2	6
	2	10.2	0.2	1.2	0.7	3.5	5.2
	3	11.7	0.4	1.5	1	4.1	4.2
d_{50}	1	73.4	0.5	0.4	1.5	1.1	0.7
	2	73.6	1.2	1.2	3.5	3.4	1
	3	75.2	1.3	1	3.7	2.7	0.7
d_{90}	1	142.3	0.8	2.5	2.1	7.1	3.4
	2	153	1.9	2	5.2	5.5	1.1
	3	150.7	3.4	4.8	9.5	13.5	1.4

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