

Key Message

Resyca's PFSI device maintains anti-microbial ingress valve and delivery performance post-storage at freezing conditions. This finding further demonstrates the suitability of Resyca's technology for the delivery of biological products such as proteins and RNA based formulations, where maintaining sterility without preservatives is important and which are frequently stored at sub 0 conditions.

Background

- COVID-19 accelerated mRNA technology considerably. These products are sensitive to aerosolization stress.¹
- In a previous DDL paper we showed the suitability of Resyca's Pre-filled Syringe Inhaler (Fig. 1) technology for the delivery of these sensitive products.²⁻³
- Current mRNA products require storage at freezing conditions. For example, Spikevax mRNA COVID vaccine requires storage between -50 °C and -15 °C to maintain its activity.⁴
- This study investigates the impact of storage at sub 0 conditions on the performance of the PFSI soft mist inhaler, considering anti-microbial ingress valve functionality, particle size distribution, and emitted mass uniformity.



Figure 1: The Pre-filled Syringe Inhaler (PFSI™)

Methods

- Syringes are filled with ultrapure MilliQ for the valve functionality test. For device performance testing, syringes are filled with 0.9% saline (B.Braun) and placed in devices. Samples are frozen at -20° C for 48 hours and thawed for 4 hours. These are compared to unfrozen baseline samples.
- During the valve functionality test, the plunger in the syringe is moved forward with a defined step by a Universal Testing Machine Z050 equipped with a 500N load cell (Zwick Roell), this increases pressure in the container closure, opens the valve, and aerosolizes the defined dose, lowering system pressure. At a certain moment, the valve closes and pressure equalizes. This is defined as the closing pressure. Each sample is subjected to 20 open and close cycles, with the closing pressure determined after each cycle. Twenty baseline samples are tested and ten stored samples. Pressure in the system is calculated by the equation $P = F/A$, where F is the force measured by the load cell, A is the area of the syringe bore, and P is the pressure in bars.
- Testing of the PFSI device performance consisted of emitted dose (shot weight) and geometric particle size distribution measurements. Emitted doses were measured by priming the device according to the IFU (actuate with mouthpiece point up until 3 sprays are visible), after which mass loss after each actuation was determined at a steady flow of 30 L/min. Ten devices at each condition were tested, with 10 actuations for the baseline devices, and 3 actuations for the post-freezing samples.
- Geometric particle size distributions were determined by a Malvern Spraytec laser diffraction system equipped with the inhalation cell in horizontal mode. The Malvern inhalation cell contained a flow straightener between the device and the measurement zone. During measurements, an airflow of 30 L/min was drawn through the device. The instrument calculated the Dv10, Dv50 and Dv90. Twenty baseline devices were tested and ten post freezing. Three actuations per device.

Results

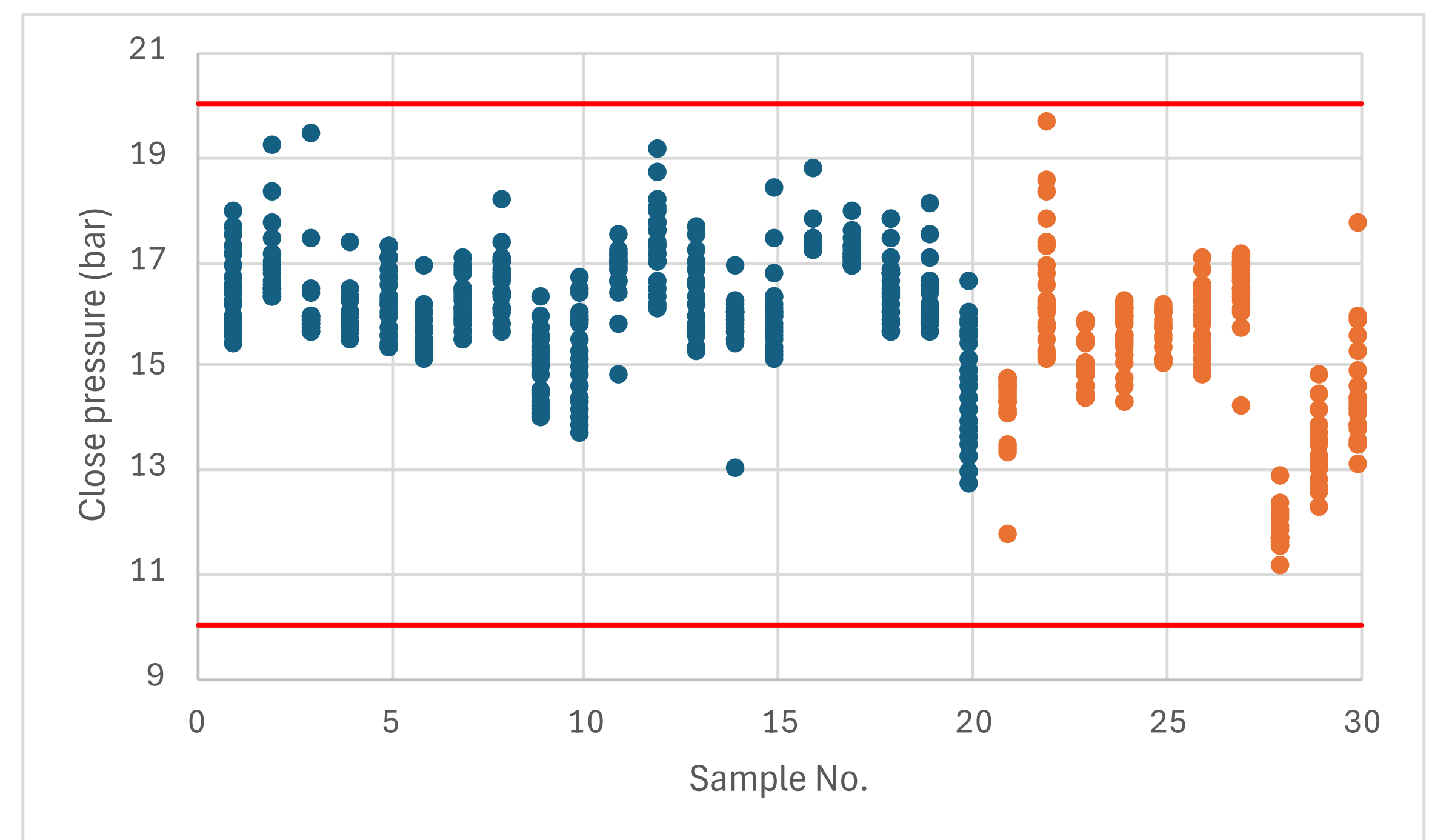


Figure 2: Individual closing pressures of valve samples, each valve tested for 20 cycles. Blue before freezing, orange after freezing at -20 °C for 48 hours. Red lines show the upper and lower acceptance limits.

Table 1: Geometric particle sizes and emitted doses obtained with the PFSI device before and after freezing (95% confidence interval)

	Pre-freezing	Post-freezing
Dv10 (µm)	2.5 – 2.6	2.3 – 2.5
Dv50 (µm)	4.2 – 4.3	4.1 – 4.3
Dv90 (µm)	6.8 – 7.0	7.0 – 7.3
Emitted Dose (mg)	30.2 – 30.6	30.0 – 30.8

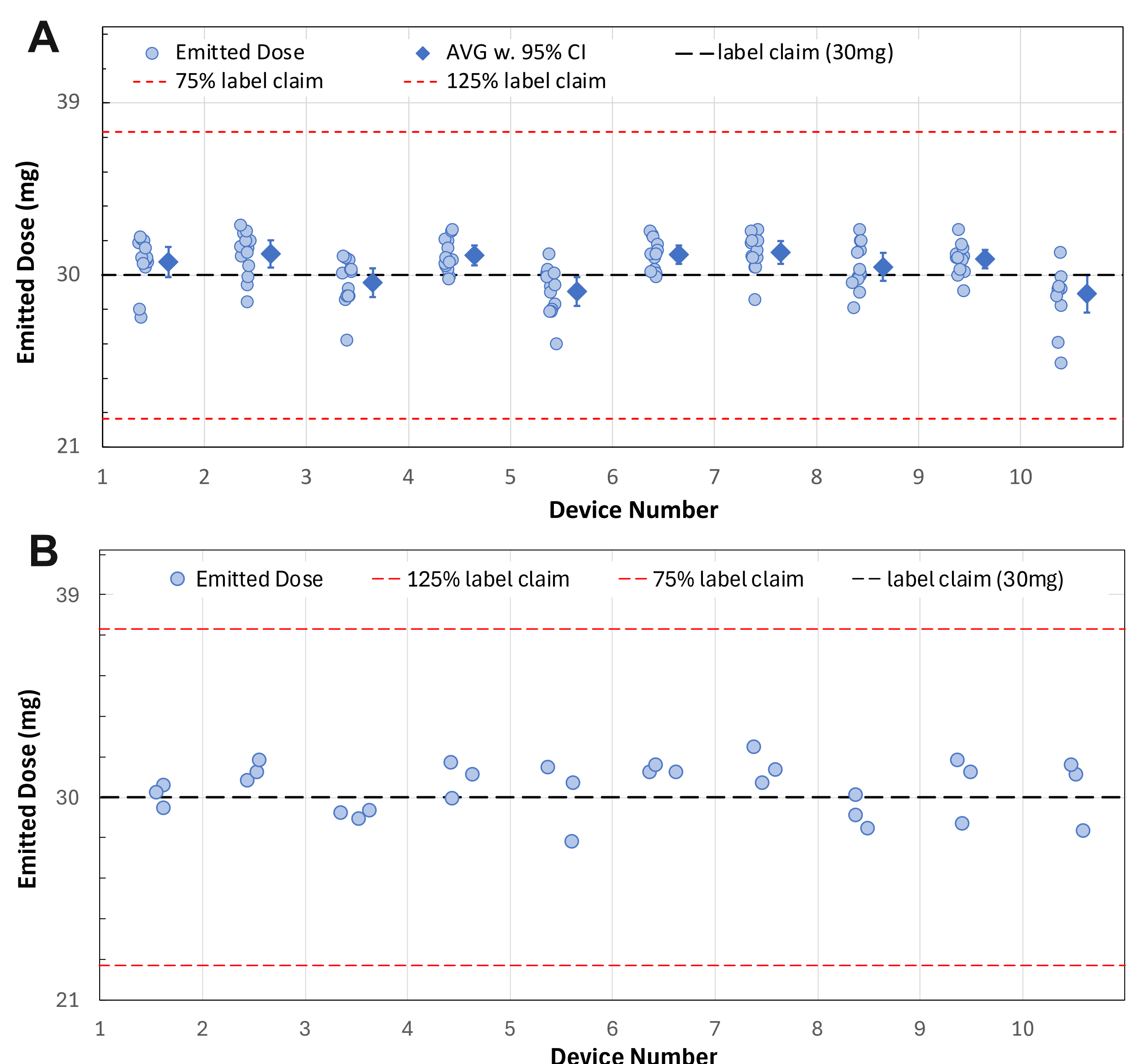


Figure 3: (A) Individual emitted doses for the 10 baseline devices, 10 actuations per device. (B) Individual emitted doses for the 10 devices stored at freezing conditions, 3 actuations per device.

Conclusion

The assessment of the PFSI soft mist inhaler before and after freezing shows that device performance is maintained. No negative impact is seen on the back pressure valve, geometric particle size distributions, and emitted doses. PFSI soft mist inhaler maintains its anti-microbial ingress valve and delivery performance after storage at freezing conditions. Underlining the suitability of this device for the delivery of sensitive RNA and biological based medicinal products.

1. Cees J. M. van Rijn, Killian E. Vlaming, Reinout A. Bem, Rob J. Dekker, Albert Poortinga, Timo Breit, Selina van Leeuwen, Wim A. Ensink, Kelly van Wijnbergen, John L. van Hamme, Daniel Bonn, Teunis B. H. Geijtenbeek. Low energy nebulization preserves integrity of SARS-CoV-2 mRNA vaccines for respiratory delivery. *Sci Rep* 2023 13:8851
2. Sibum, I.; Müllinger, B.; Buchmann, N.A.; A device screening method for predicting delivery of inhaled mRNA via a nebulizer (Abstract). Presented at: Drug Delivery to the Lungs, Edinburgh, United Kingdom, December 6-8, 2023.
3. Gurumurthy, P.; Sommerer, K.; Sibum, I.; Buchmann, N.A.; Müllinger, B.; Assessment of the delivery performance of a novel Soft Mist Inhaler using a pre-filled syringe based container closure system (Abstract). Presented at: Drug Delivery to the Lungs, Edinburgh, United Kingdom, December 6-8, 2023.
4. European Medicines Agency "https://www.ema.europa.eu/en/documents/product-information/spikevax-epar-product-information_en.pdf" Accessed 7 July