# Development of a High Repeatability Test Stand for the Measurement of Valved Holding Chambers with Facemasks

A. Winzen[1]; K. Steinführer[2]; U. Schuschnig[2]; S. Seemann[2]

[1]PARI*tec* GmbH, Gräfelfing, Germany; [2]PARI Pharma GmbH, Gräfelfing, Germany; Contact: andrea.winzen@pari.com (www.pari.com)



## Background and Objectives

- Valved holding chambers (VHC) reduce the deposition in oropharynx and increase lung deposition when used with a pressurized metered dose inhaler (pMDI). When used for babies and young children, VHCs are often combined with a face mask.
- In vitro measurements compare the aerosol performance of VHCs (Mass median aerodynamic diameter (MMAD), fine particle dose (FPD), emitted mass (EM)) with basic protocols and test stand requirements harmonized in USP [1].
- The objective was the development of a test stand for in vitro measurements of the aerosol performance of VHC with masks not only according to standard regulations but additionally aiming at a high repeatability.

## Material and Methods

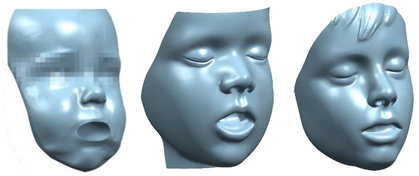
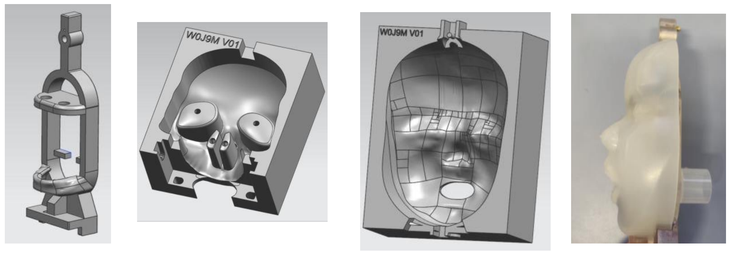


**Figure 1:** LIAM (Louis Infant Anatomical face Model) family: (left) LIAM Baby (nine months); (center) LIAM Infant (2-3 years); (right) LIAM Child (3-4 years). Scan data of LIAM Baby are anonymized for protection of data privacy.

- Three anatomic face models were implemented into the setup to account for the wide variety of children's faces in the applicable age group of kids younger than five years (Fig. 1).
- Realistic models require anatomic geometry and hardness characteristics of tissue and bones which were implemented via a two-component silicon casting process including a 3D printed frame structure, a first silicon (ShA 45) mimicking the rigid scull and a second silicon (ShA 00) for the soft facial tissue. Qualification of hardness distribution of models against in-house in vivo data measured on real children's faces was performed.




(a) (b) (c) (d)

**Figure 2:** Casting process of LIAM face models: (a) Frame and jaw; (b) Hard scull structure; (c) Soft tissue structure; (d) Sideview on final LIAM Baby model.

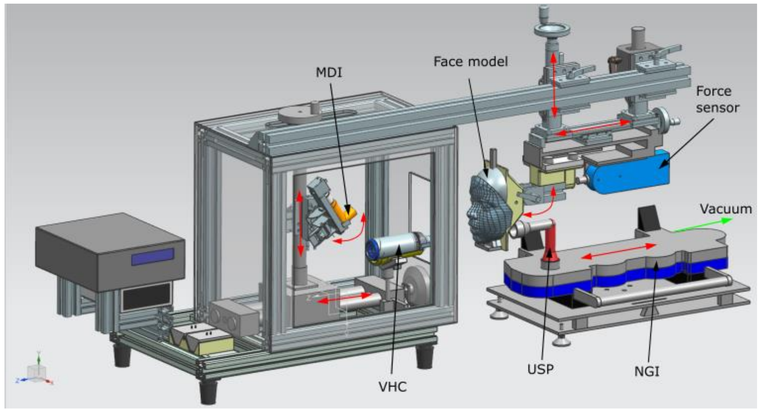



**Figure 3:** CAD model of VHC Shake and Fire test stand including degrees of freedom.

- A previously developed customized shake and fire unit [3] was combined with anatomic face models and a defined application force measurement unit via a horizontal traverse combined with a high precision force sensor (Fig. 3).
- Time between end of shaking and inhaler actuation as well as time delay between pMDI actuation and sampling onset can be chosen independently.
- The design allows standardized measurements of EM and aerodynamic particle size distribution (APSD) and additionally tests in combination with a superimposed breathing pattern by implementing a mixing inlet with NGI and breathing simulator.

**Table 1:** Overview on qualification testing design.

| Test | Method | No. Devices | No. pMDI | No. Re-plications | No. Operators | No. Tests | Time Delay] |
|---|---|---|---|---|---|---|---|
| A | EM | 2 | 6 | 3 | 2 | 6+6 | 0s |
| B | APSD | 2 | 6 | 3 | 2 | 6+6 | 0s |
| C | APSD | 2 | 6 | 3 | 1 | 6 | 2s |

- Three test configurations to investigate the repeatability with measurements performed by two trained operators to evaluate inter-analyst variation were conducted. A detailed overview on the testing design is given in Tab. 1.
- PARI's VORTEX® with frog child mask (Fig. 4) in combination with LIAM child model (Fig. 1) at 16N application force was tested.
- Breath simulations simulate standard child breathing maneuver (TV = 155 mL, 25/min, 1:2 In:Ex). NGI tests were conducted at 30L/min and inhalation delay times of 0 and 2s.
- Budiair® pMDI by Chiesi was used and the amount of deposited drug was quantified via a validated HPLC methodology.


**Figure 4:** VORTEX ® (PARI GmbH) with frog facemask age 2–4 yrs.

## Results

- Results of tests A and B (Fig. 5) show good agreement for both analysts (Op). The analysis of the statistical variation via t-test and F-test showed that the acceptance criterion of $p > 0.05$ was met for all parameters. No significant difference between the two analysts was found. Hence, the novel system gave similar results independently from the operator.
- ASPD measurements were performed by a single operator at a time delay of 2s (test C). FPD is reduced at a time of 2s compared to 0s. This is most likely attributed to gravitational sedimentation within the VHC.

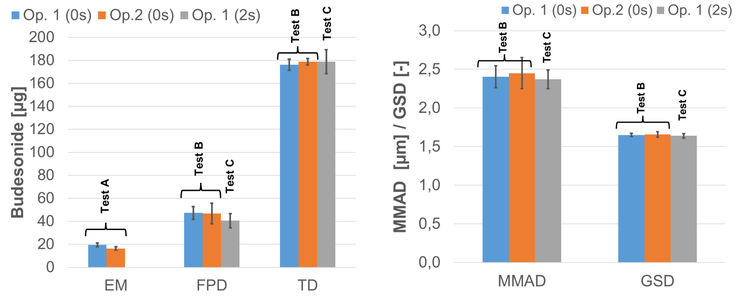



**Figure 5:** Results for tests A to C: (left) EM, FPD, total dose (TD); (right) MMAD, geometric standard deviation (GSD).

## Summary and Conclusions

- Test stand fulfills regulatory guidelines requirements as application for aerosol particle size distribution and emitted mass measurements, flexible selection of time delay, as well as selection of defined application force.
- LIAM face model family covers the entire relevant age group, representing a realistic imitation of children's faces anatomy and hardness distribution.
- Implementation of shake and fire unit to reduce common sources of operator variability (e.g., shaking technique or firing force) [2] as well as control of shaking speed, angle, and duration.
- In conclusion, the test stands allows high repeatability measurements of the in vitro aerosol performance data for VHCs with facemasks in agreement with standard regulations.

## References

[1] United States Pharmacopeial Convention (2017): USP <1602> Spacers and valved holding chambers used with inhalation aerosols- characterization tests

[2] Sule A, Singh A, Johnson J, Khan A, Majed B, Dean C, Turner R: Comparative Evaluation of Automated Shake and Fire System vs. Manual Actuation for pMDI Inhaler. Respiratory Drug Delivery, 2016. 3:515-518.

[3] Buchmann N, Kohlmann D, Steinfuehrer K, Ledermueller R: Performance Assessment of Valved Holding Chambers for Children with Budesonide pMDI, in 21st ISAM Congress 2017. International Society for Aerosols in Medicine. Santa Fe, USA: Poster 273.