Using Quality by Design Approach to Correlate Patient Usage to the *In Vitro* Performance of a Nasal Spray Product

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INTRODUCTION

Current FDA guidelines for nasal spray products recommend the use of automated actuation systems that replicate actual patient actuation parameters for *in vitro* testing of plume characteristics.[1] FDA and industry research indicates a strong connection between the parameters used to control automated actuation systems and the *in vitro* performance of nasal spray products.[2-4] The user's age and physical challenges are likely to be determining factors in the usability and performance of these products.[5,6] The current study shows how high-resolution measurements of human usage ("ergonometrics") of a commercially available nasal spray pump device vary between different age groups of people, including the effect of dominant vs. non-dominant hand, and how these ergonometrics are related to *in vitro* performance.

METHODS

Study Design:

Fifteen healthy adult volunteers (described in Table 1), covering young (post-teen), middle-age and senior groups, actuated a nasal spray using their dominant and non-dominant hand (20 times each) into a spray collector; the spray collector was weighed before and after each spray using an analytical balance. Each volunteer's dynamic actuation was measured simultaneously at 5 kHz sampling frequency using the patented Ergo™ sensor (Proveris Scientific Corp., Marlborough, MA) shown in Figure 1. The Ergo-generated data (ergonomic data) includes the real-time position, velocity and acceleration levels applied by the volunteers to actuate the device. The ergonomic data were statistically analyzed to produce Design and Control Space scenarios for actuation parameter simulations using Quality by Design principles. The Control Space scenarios were programmed into Proveris Viota® software and used to systematically investigate the *in vitro* performance of the nasal spray product. A Vereo® NSx automated actuator (Proveris Scientific Corp.) was used in these experiments in conjunction with SprayVIEW® (Proveris Scientific Corp.) for spray pattern measurement and Spraytec™ (Malvern Instruments, Westborough, MA) for droplet size distribution.

User ID	Age (years)	Gender	Dominant Hand	Group
1	≥ 60	Male	Right	1
2		Female	Right	
3		Female	Right	
4		Male	Right	
5		Male	Right	
1	41-59	Male	Right	2
2		Male	Right	
3		Male	Right	
4		Female	Right	
5		Male	Left	
1	20-40	Female	Right	3
2		Male	Right	
3		Female	Left	
4		Female	Left	
5		Female	Right	

Table 1: Hand actuation study design.

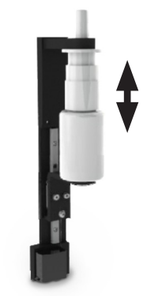

Figure 1: Ergo™ sensor. The up-down arrow indicates that the sensor measures both compression and return stroke ergonometrics.

Formulation and Device:

The study utilized normal saline solution in amber glass 10mL bottles with snap-on APF nasal pumps (Aptar Pharma, Princeton, NJ).

RESULTS AND DISCUSSION

Determination of Actuation Parameters:

All the volunteers were able to use the device as intended. The largest differences between the dominant and non-dominant hand actuations were in the case of velocity for users aged 60 years and older, and acceleration for users less than 60 years old. The dosing results show that: (1) for all age groups, the non-dominant hand required more actuations to prime the device; (2) the largest difference in droplet size distribution between the dominant and non-dominant hand actuations came from the middle-age group; and (3) the spray pattern data did not show major differences between any of the data sets.

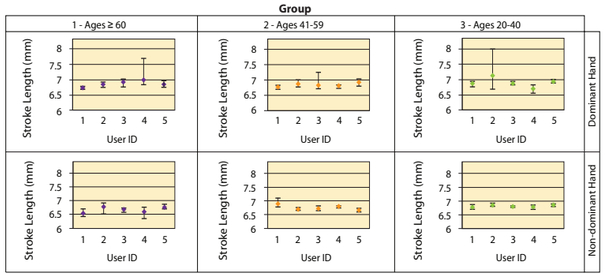

Figure 2: Stroke length evaluation.

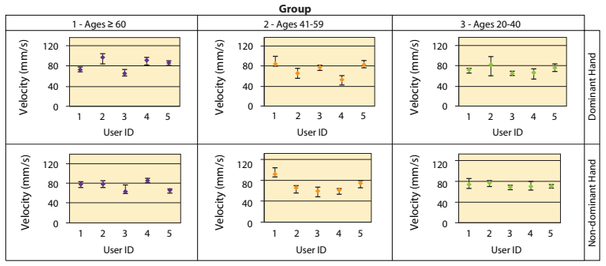

Figure 3: Actuation velocity evaluation.

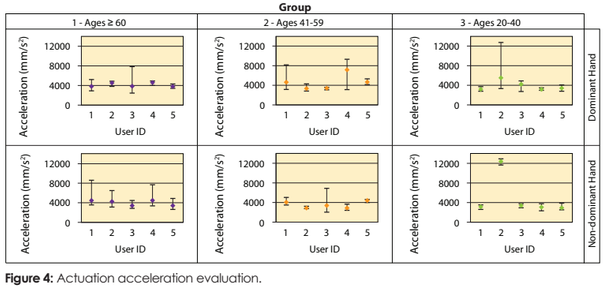

Figure 4: Actuation acceleration evaluation.
(The error bars in Figures 2-4 represent the range of results obtained.)
The actuation parameters used in the dosing studies are summarized below.

	Group: 1 - Ages ≥ 60	2 - Ages 41-59	3 - Ages 20-40	
Stroke Length (mm)	6.9	6.8	6.9	Dominant Hand
Actuation Velocity (mm/s)	82	72	72	
Actuation Acceleration (mm/s²)	4106	4631	3896	
Stroke Length (mm)	6.7	6.8	6.8	Non-dominant Hand
Actuation Velocity (mm/s)	74	70	72	
Actuation Acceleration (mm/s²)	3999	3526	5028	

Table 2: Actuation parameters from hand study.

The results from the dosing studies for dose weight, droplet size distribution and spray pattern are shown in Figures 5 and 6 and Table 3.
(The error bars in Figures 5 and 6 represent the range of results obtained.)

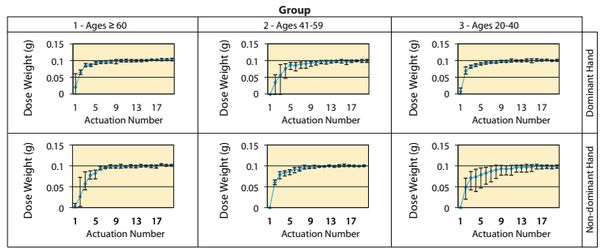

Figure 5: Dose weight vs. study group.

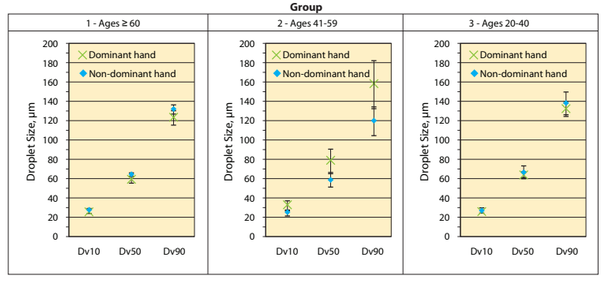

Figure 6: Droplet size vs. study group.

Group: 1 - Ages ≥ 60	2 - Ages 41-59	3 - Ages 20-40	
Dmax, mm	Ovality Ratio	Ellipticity Ratio	
25.97	1.33	1.15	Dominant Hand
22.67	1.33	1.18	
26.96	1.31	1.12	
27.31	1.29	1.16	Non-dominant Hand
29.16	1.34	1.14	
26.49	1.27	1.10	

Table 3: Spray pattern data per study group.

CONCLUSIONS

Although differences were seen in the plume data between the different test groups, these differences were minimal. For all age groups, the non-dominant hand required more actuations to prime the device.

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