PRESCRIPTION DIVISION

COMPARATIVE ANALYSIS OF IN-USE ACTUATION PARAMETERS WITH *IN VITRO* PERFORMANCE OF NASAL SPRAY PUMPS

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INTRODUCTION

Drugs delivered by nasal spray pumps require extensive testing during product development and quality control testing (1). Laboratory testing can be performed using hand spraying (just as a patient would use the product), but this is known to induce variability in performance, which is unrelated to the manufactured device and formulation (2 - 4). Since this variability can confound *in vitro* bioequivalence testing, the Food and Drug Administration (FDA) Draft Guidance for Industry recommended the use of automated actuation systems to robotically actuate nasal spray pumps, with the intention of minimizing the variability otherwise seen during hand spraying (1). FDA also recommended that the instrument settings should be relevant to appropriate usage of the product by the trained patient. However, they offered no advice on critical settings or whether force-controlled or velocity controlled methods should be used to derive these parameters. This study describes the collection of in-use actuation parameters from Equadel® nasal spray pumps and their subsequent use in automated actuation equipment to generate *in vitro* analytical performance data, at the extremes of use.

MATERIALS AND METHODS

Flonase Nasal Spray Formulation, 50µg, (fluticasone propionate, GlaxoSmithKline) was repackaged into bottles fitted with an **Equadel® nasal spray pump**. Actuation profiles from **20 adult participants (18 to 64 yrs)** were collected using a customized **Hand Actuation Monitor (Figure 1, HAM, InnovaSystems Inc.)** as described by Dalby et al. (5). Briefly, six actuations were recorded from each participant (total 120 sprays for the study). Actuation force, velocity, displacement, and hold time were analyzed and subsequently programmed into automated actuation equipment to generate *in vitro* analytical performance data at the extremes of use, as follows:

Droplet Size Distribution measurements were made using a Spraytec **2000 (Malvern Instruments) coupled with NSP actuation equipment (InnovaSystems)** at a distance of 4.5 cm.

Spray Pattern measurements were made using a **Spray View® Station (Proveris Scientific) coupled with NSx actuation equipment** at a distance of 5 cm.

Dose weight delivery performance was acquired using **NSP actuation equipment (InnovaSystems).**

For all measurements made, three samples were tested with two replicates from each sample.

Figure 1. Hand Actuation Monitor, (HAM, InnovaSystems) which was used to Capture Actuation Parameters

RESULTS

Actuation Force (kg)	Force Rise Time (ms)	Force Hold Time (ms)	Stroke Travel (mm)	**Droplet Size Distribution D_{50} µm (SD)**
4.5	0.2	0.1	7.4	**48.0 (2.9)**
4.5	0.2	0.2	7.4	**53.2 (2.8)**
4.5	0.5	0.1	7.4	**50.3 (3.8)**
4.5	0.5	0.2	7.4	**53.1 (3.6)**
6.0	0.2	0.1	8.7	**53.9 (1.4)**
6.0	0.2	0.2	8.7	**54.2 (4.4)**
6.0	0.5	0.1	8.7	**52.0 (2.0)**
6.0	0.5	0.2	8.7	**51.5 (1.4)**

Table 1. Droplet Size Distribution D50 for Flonase Nasal Spray repackaged with an Equadel Pump measured using Spraytec (Results are mean (SD) for n=6)

Stroke Travel (mm)	Velocity (mm/sec)	Velocity Hold Time (ms)	**Spray Pattern Ovality X/Y (SD)**
7.4	44	185	**1.2 (0.1)**
7.4	44	440	**1.2 (0.1)**
7.4	120	185	**1.2 (0.1)**
7.4	120	440	**1.2 (0.1)**
8.7	44	185	**1.2 (0.1)**
8.7	44	440	**1.2 (0.1)**
8.7	120	185	**1.2 (0.1)**
8.7	120	440	**1.1 (0.1)**

Table 2. Spray Pattern Ovality for Flonase Nasal Spray repackaged with an Equadel Pump measured using SprayView (Results are mean (SD) for n=6)

Actuation Force (kg)	Force Rise Time (ms)	Force Hold Time (ms)	Stroke Travel (mm)	**Dose Weight Delivery Mean Dose (mg) (SD)**
4.5	0.2	0.1	7.4	**100.9 (3.3)**
4.5	0.2	0.2	7.4	**103.0 (0.5)**
4.5	0.5	0.1	7.4	**101.7 (0.5)**
4.5	0.5	0.2	7.4	**102.5 (1.4)**
6.0	0.2	0.1	8.7	**105.4 (0.2)**
6.0	0.2	0.2	8.7	**105.0 (0.5)**
6.0	0.5	0.1	8.7	**104.2 (0.6)**
6.0	0.5	0.2	8.7	**103.7 (0.2)**

Table 3. Dose Weight Delivery for Flonase Nasal Spray repackaged with an Equadel Pump (Results are mean (SD) for n=6)

CONCLUSION

The *in vitro* data collected using the extremes of volunteer actuation parameters provided satisfactory Equadel® nasal spray pump performance for key characteristics such as DSD, spray pattern ovality and dose weight delivery with regard to the current FDA Chemistry Manufacturing and Control requirements (1). This work describes a practical approach that could be used to correlate in-use patient actuation parameters to *in vitro* product performance at the extremes of use for nasal spray pumps. This information may benefit the developers of nasal spray products and the regulators in terms of understanding the relationship between the drug product and the patients when using such devices.

References

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