An Innovative Strategy for Nasal Spray Bioequivalence

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PURPOSE

In 2004, the U.S. Food and Drug Administration introduced the Critical Path Initiative with the intent of modernizing generic drug development by incorporating recent scientific advances into the process[1]. Recently, the Office of Generic Drugs (OGD) supported approval of the first generic drug to utilize this approach, a nasal spray containing mometasone furoate[2]. This poster will provide an overview of in vitro approaches using an innovative technology (i.e. automated Raman spectroscopy), as well as device testing methodologies, in lieu of the traditional clinical pharmacokinetic (PK) studies to support bioequivalence of a generic and innovator drug[3].

Innovative technologies play a major role in the Critical Path Initiative for generic drugs. This poster focuses on the utilization of the Single Particle Explorer© (rap.ID, Germany) automated Raman spectroscopy system and its ability to measures the count, size and shape of particles, in addition to chemical characterization of the particles using automated Raman spectroscopy. The information from this innovative technology allows for the identification and comparison of the active pharmaceutical ingredient (API) particle size distribution (PSD) in the generic and innovator drugs. The active pharmaceutical ingredient (API) size distribution is critical as it relates to bioavailability, rates of absorption, and stability of the drug product[4].

Recent investigations utilizing the SPE have also demonstrated the ability to characterize and quantify agglomerates present in the final drug formulation, thus providing a more thorough understanding of the API PSD and the APIs potential to agglomerate[4].

Aerosolized drug products also depend on performance of the delivery device which houses the drug and the device's interaction with the formulation[2]. To further demonstrate equivalence of a generic and innovator drug, device testing to include spray pattern, plume geometry, droplet size distribution was conducted.

METHODS

API Particle Size Distribution:

One (1) innovator nasal spray (Flonase™; fluticasone propionate) and a corresponding generic nasal spray (Equate; fluticasone propionate) were both primed according to manufacturer recommendations and two (2) actuations collected onto individual aluminum-coated microscope slides. The deposition of the nasal spray was spread across the aluminum-coated slide using a clean glass microscope slide, in order to create a thin monolayer. The slides were allowed to dry prior to analysis in a laminar flow environment. A minimum of 100 API particles were counted, sized and characterized utilizing the Single Particle Explorer© (SPE), (rap.ID, Germany). The rap.ID Single Particle Explorer (SPE) System utilizes optical microscopy of a bright field image of the chosen region of interest (ROI) in conjunction with binarization of the optical image and an automated sizing algorithm to perform the sizing of all particles present, followed by automated Raman spectroscopy to characterize the API, excipients, and foreign particulate present in the sample. Agglomerates were identified using the 50x images collected during analysis and agglomerates removed from the data. Statistical calculations were then performed on the sizing data for comparison of the two samples.

Device Testing:

Three (3) innovator nasal sprays (Flonase™; fluticasone propionate) and three (3) corresponding generic nasal sprays (Equate; fluticasone propionate) were primed according to manufacturer recommendations. Automated actuation systems (NSx and Vereo, Proveris Scientific) were used to perform droplet size distribution, spray pattern and plume geometry testing. Droplet size was measured by laser diffraction (Spraytec, Malvern Instruments) and reported as a volume-based distribution. Both spray pattern and plume geometry were quantified by a non-impaction laser based system (SprayVIEW, Proveris Scientific). All tests were performed at a working distance of 3 cm and 6 cm from the spray nozzle in accordance with the FDA Bioequivalence Guidance (3).

RESULTS

API Particle Size Distribution:

Both the innovator and generic drug samples were analyzed using the rap.ID SPE. Following the counting and sizing of all particles present in the ROI, automated Raman spectroscopy was performed. For each particle analyzed, an image is collected, the sizing information and analysis parameters are reported, and a resulting spectrum and database hit are displayed, as shown in Figure 1. Enough ROIs were analyzed in order to obtain data for a minimum of one hundred (100) API particles. All data for excipients was disregarded.

As the automated system collects a Raman spectrum for the particles chosen for analysis, it also collects a 50x image of the particle of interest (Figure 2), which allows for manual identification of agglomerates. In order not to skew PSD data, identification, and sizing data from agglomerates can then be removed from PSD reporting. Since the SPE uses optical microscopy instead of the Raman signal to perform sizing of the particles present, all agglomerates must be removed from the data. However, API particles can also be manually relocated and further investigated with manual Raman spectroscopy to determine whether the agglomerate is API-API or API-excipient, thus leading to a more complete understanding of the agglomerated particles and API bioavailability.

Once agglomerate particles were removed from the size distribution data, the data tables were tabulated to show single particle API particles, agglomerates and the total API particles present in both Flonase™ and the generic, as shown in Tables 1 and 2, respectively.

Particle size distribution statistical calculations were calculated for both the innovator and generic nasal sprays for comparison of the particle size data and the results are shown in Table 3 below; the corresponding histogram is shown in Figure 3.

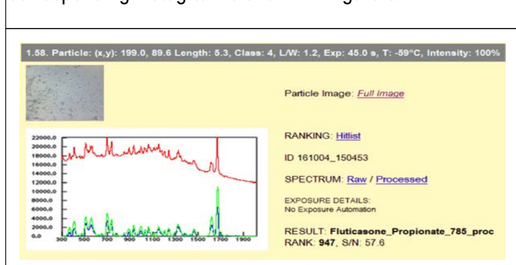

Figure 1. The abbreviated data collected by the SPE during an automated analysis.

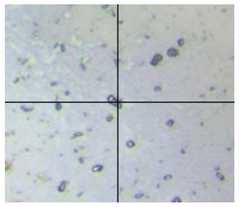

Figure 2. A 50x image of a particle chosen for automated Raman analysis and identified as API and agglomerate (center of crosshair).

FLONASE™: Size Distribution (non-cumulative) of API Particles											
	Number	Size Distribution [µm]									
-	-	>=2.00	>=3.00	>=4.00	>=5.00	>=6.00	>=7.00	>=8.00	>=9.00	>=10.00	>=25.00
Fluticasone Propionate	137	53	44	29	8	1	2	0	0	0	0
Agglomerates	46	0	2	13	13	6	4	6	1	1	0
Total API	183	53	46	42	21	7	6	6	1	1	0

Table 1. API Particle Sizing Results for Innovator Nasal Spray (Flonase ™)

GENERIC: Size Distribution (non-cumulative) of API Particles											
	Number	Size Distribution [µm]									
-	-	>=2.00	>=3.00	>=4.00	>=5.00	>=6.00	>=7.00	>=8.00	>=9.00	>=10.00	>=25.00
Fluticasone Propionate	102	31	19	23	19	2	2	0	0	0	0
Agglomerates	36	0	0	5	11	11	2	5	0	2	0
Total API	138	31	19	28	30	13	4	5	0	2	0

Table 2. API Particle Sizing Results for Generic Nasal Spray (Equate)

	Innovator (Flonase™)	Generic (Equate)
D10	2.2	2.2
D50	3.2	3.6
D90	4.8	5.5
Min	2.1	2.1
Max	7.7	7.6
Mean	3.41	3.80

Table 3. API PSD Statistics; Single Particles Only

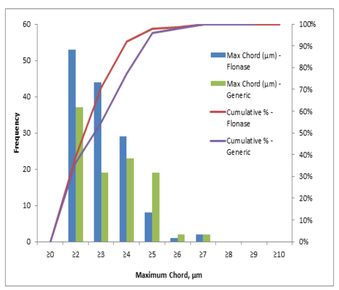

Figure 3. Fluticasone Propionate Maximum Chord Diameter histogram and cumulative percentage (Flonase™ and Generic), with agglomerates removed

RESULTS, cont.

Device Testing:

The average results representing the metrics compared during a bioequivalence study are shown in Tables 4 and 5. Both the results for 3 cm and 6 cm indicate comparability in performance. Representative plume geometry images are shown in Figure 4. Although there are potential differences in the Area as measured by spray pattern at 3cm, the ranges (130.0-217.9 Innovator vs 165.3-230.6 for Generic) indicate the potential for bioequivalence as measured by population bioequivalence.

A full in vitro bioequivalence would include testing using the above device tests as well as single actuation content uniformity, amount of drug in small droplets, priming, re-priming and particle size analysis of the API. The device performance tests measure the interaction of the formulation and pump. Droplet size distribution is based on the size of the emitted droplets whereas the results shown in Table 3 represent the particle size of the drug itself. In both cases, droplet size distribution and particle size distribution indicate that the Generic and Innovator are similar.

	Droplet Size		Spray Pattern		Plume Geometry	
Drug Product	Dv50 (µm)	Span	Ovality Ratio	Area (mm²)	Spray Angle (°)	Plume Width (mm)
Innovator (Flonase)	42.20	2.03	1.248	158.0	63.6	37.3
Generic (Equate)	45.46	2.02	1.191	200.4	62.0	36.1

Table 4. Bioequivalence metrics comparing Innovator vs Generic at 3cm (n=3)

	Droplet Size		Spray Pattern		Plume Geometry	
Drug Product	Dv50 (µm)	Span	Ovality Ratio	Area (mm²)	Spray Angle (°)	Plume Width (mm)
Innovator (Flonase)	38.17	1.53	1.281	443.8	46.5	51.7
Generic (Equate)	40.66	1.63	1.241	458.6	48.7	54.4

Table 5. Bioequivalence metrics comparing Innovator vs Generic at 6 cm (n=3)

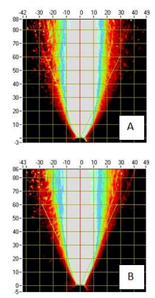

Figure 4. Plume Geometry images of the Innovator (A) and the Generic (B) at 6 cm

CONCLUSION

Comprehensive solutions to support generics and new product submissions to regulatory agencies are important in today's fast paced world of drug development. The ability to streamline the approval process is critical to both pharmaceutical companies and the patients that benefit from these products. The recent approval of the first generic drug to utilize the Critical Path Initiative demonstrates the industry's dedication to the use of new technologies in the drug development process. Innovative technologies and strategies for pursuing new processes such as the Critical Path Initiative are vital to bring life changing solutions to those who need them.

REFERENCES

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