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Review Article

In Vitro Characterization of Nasal Spray to Asses Bioequivalence

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A B S T R A C T

To layout the characterization of Nasal sprays and discuss the characterization method and sampling plan to assess the *in -vitro* bioequivalence of test product and reference product. The *in -vitro* bioequivalence study of nasal sprays are useful to understand the efficiency of test product in comparison to innovator so that the equivalency in the *in -vivo* studies can be assessed.

The *in -vitro* bio equivalency characterization of nasal sprays helps us to correlate the efficiency of test product with respect to the reference product, so that the efficacy and safety can be achieved in par with Reference listed drug.

The characterization studies include the product behavior throughout the unit life cycle. The nasal spray test includes the SAC, Priming, repriming, Spray pattern, plume geometry, Droplet size distribution and Drug in small particles.

Key Words: SAC, Priming and repriming, Spray pattern, plume geometry, Droplet size distribution and Drug in small particles.

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INTRODUCTION

Nasal sprays

A liquid medication that can be atomizedto deliver drug through the nose to treat allergic reaction, non-allergic condition, asthmatic condition by rapid absorption, it is effective and desired.The aim of the study is to design a pathway for the evaluation of Test product characteristics in equivalenceto the Reference product.The assessment helps us to understand product behaviour so that we can save time and cost.

Invitro characterization of Nasal sprays

The following parameters are recommended byFDA for *in-vitro* studies to assess the *invitro* bioequivalence between Test and Reference product.

1. Single actuation content [1,4, 5, 6, 7]
2. Priming and repriming [1, 3, 4,5 ,6, 7]
3. Spray pattern[1, 2, 4,5,6,7]
4. Plume geometry[1, 4, 5, 6, 7]
5. Droplet size distribution by laser diffraction[1,2, 4 ,5, 6, 7]
6. Drug in small particles and droplets [1,4,5, 6, 7]

As per FDA Recommendation three or more batches of Test and Reference products are to be characterized. At least 10 samples from each batch arerequired to test andassess the BE.

Single actuation content (SAC)[1, 4, 5, 6, 7]

Single actuation content of nasal spray is used to determine the amount of labelled drug that is delivered on a single shot.SAC of Test and Reference product is determined by Spray view and is monitored throughout container life cycle i.e., from beginning and endingof actuation to determine whether the drug product is delivered uniformly by using Assay by HPLC.

Spray view: Image captured from google

Priming and repriming[1,4, 5,6, 7]

Priming is the process in nasal sprays where initially certain number of actuations are performed to prepare the container to deliver the labelled amount of drug upon actuation accurately. Priming is to be performed before the product is used for treatment. Population of bio equivalence shall be evaluated in the priming. Priming helps us to avoid inconsistent sprays from a container. Number of primes for a container depends upon the delivery of fine sprays.

Repriming [1,4, 5, 6, 7]

Repriming of product container ensures the delivery of the labelled amount of drug after stored for a specified period PBE Shall be evaluated during repriming.

Design

Table 1: Test and Reference Product] for SAC (B andE Life stage) and Priming (B Life stage) and Repriming.

Description	**Test**	**Reference product**
Total Labelled MeteredSprays	120 sprays after priming	120 sprays after priming
Number of Primes (before the first-time use)	10 times or until a fine spray appears	10 times or until a fine spray appears
Total Sprays	130 (Includes 10 primes before first time use)	130 (Includes 10 primes before first time use)
Numberof Test/Reference Units	10 units from each batch	10 units from each lot
Spray Number	**Testing/Activity to be performed**	
1 to 10	Priming	Priming
11	SAC testing (B Life stage)	SAC testing (B Life stage)
Hold for 2 Days in in upright condition		
12	SAC testing	SAC testing
13 to 69	Fire down	Fire down
Hold for 4 Days in in upright condition		
70	SAC testing	SAC testing
71-120	Fire down	Fire down
Hold for 7 Days in in upright condition		
121-122	Repriming	Repriming
123-129	SAC determination	SAC determination
130	SAC testing (E Life stage)	SAC testing (E Life stage)

SAC: Single actuation content B: Beginning life stage E: End life stage

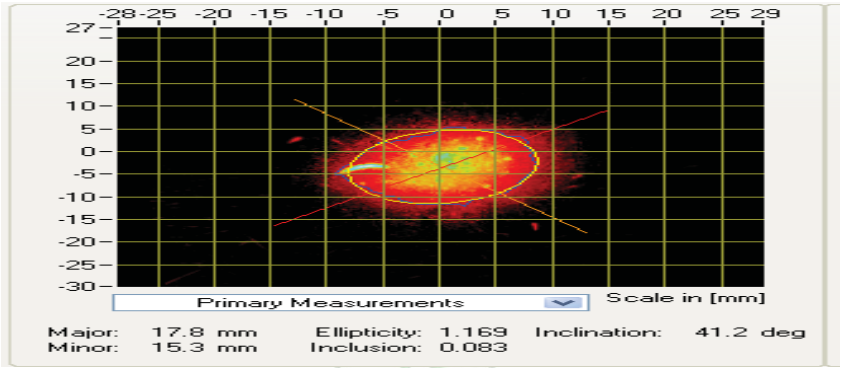
Spray pattern[1,4, 5, 6, 7]

Spray pattern test is used to characterize and quantify the shape of delivered spray plume by using impaction/non impaction methods. The test should be performed at the Beginning of container life.

The test should be conducted at two heights between nasal spray tip and laser sheet i.e. a minimum 3 cm to 7 cm distance range, D_{min},D_{max} and ovality ratio of emitted plume centre of gravity and shot weight were measured in this test. Spray view instrument is required to perform the test.

Spray pattern plume shape

Image captured from google



Design

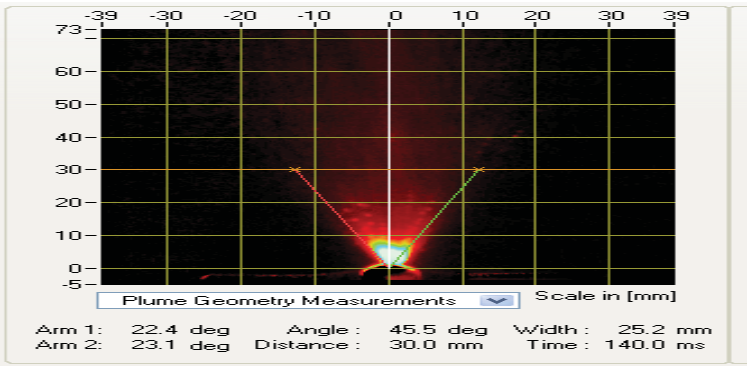
Description	**Test**	**Reference product**
Total Labelled Metered Sprays	120 sprays after priming	120 sprays after priming
Number of Primes (before the first-time use)	10 times or until a fine spray appears	10 times or until a fine spray appears
Total Sprays	130 (Includes 10 primes beforefirst time use)	130 (Includes 10 primes before first time use)
Number of Test/Reference Units	10 units from each batch	10 units from each lot
Spray Number	**Testing/Activity to be performed**	**Testing/Activitytobe performed**
1 to 10	Priming	Priming
11 to 13	Spray pattern @ 30mm	Spray pattern @ 30mm
14 to 15	Fire down	Fire down
16 to 18	Spray pattern @ 60mm	Spray pattern @ 60mm

B: Beginning life stage

Plume geometry[1,,4,5,6,7]

Plume geometry test is used to characterize and quantify the shape of emitted spray plume from side view. The test will be performed at the beginning life stage of a product container. Spray view instrument is used to measure the plume geometry parameter, itcapturesthe fully developed spray plume at a certain time with respect to Plume width, plume angle and plume height.

Plume geometry Shape: Image captured from google



Design

Tablet 2: Test and Reference Product] for Plume Geometry (B Life stage).

Description	**Test**	**Reference product**
Total Labelled Metered Sprays	120 sprays after priming	120 sprays after priming
Number of Primes (before the first-time use)	10 times or until a fine sprayappears	10 times or until a fine spray appears
Total Sprays	130 (Includes 10 primes before first time use)	130 (Includes 10 primes before first time use)
Number of Test/ReferenceUnits	10 units from each lot	10 units from each lot
Spray Number	**Testing/Activity to be performed**	
1 to 10	Priming	Priming
11 to 13	Plume geometry	Plume geometry
14 to 15	Fire down	Fire down
16 to 23	DIS	DIS

Droplet size distribution by laser diffraction [1,2,4,5,6,7]

Droplet size measured by using laser diffraction technique is based on % of light scattered by Malvern spray tec to measure the droplet size distribution. This test is used to quantify the particle size distribution of fully developed plume.

The test shall be conducted at the beginning and end life of spray unit. Droplet size distribution is measured at mean of D_{10}, D_{50}, D_{90} and Span using three consecutive sprays. The nasal sprays droplet size should be in between of 30 µm to 120µm. It is measured at 2 to 7cm at two distance from the actuator orifice. If DSD is measured at 3 cm, the next distance should be more than 3 cm.

The test and reference product should be compared.

The lesser particle size median of 10 µm may travel in to the lungs or higher particles size median of more than 120 µm may get deposited at mucous membrane of the nostril.

Malvern spray tec: Image captured from google

Design

Table 3: Test and Reference Product for Droplet Size Distribution by Laser Diffraction (DSD) (B andE Life stage).

Description	**Test**	**Reference**
Total Labelled Metered Sprays	120 sprays after priming	120 sprays after priming
Number of Primes (before the first-time use)	10 times or until a fine spray appears	10 times or until a fine spray appears
Total Sprays	130 (Includes 10 primes before first time use)	130 (Includes 10 primes before first time use)
Number of Test/Reference Units	10 units from each batch/lot	10 units from each lot
Spray Number	**Testing/Activity to be performed**	**Testing/Activity to be performed**
1 to 10	Priming	Priming
11 to 13	DSD @ 3 cm distance from the actuator orifice	DSD @ 3 cm distance from the actuator orifice
14 to 15	Fire down	Fire down
16 to 18	DSD @ 6 cm distance from the actuator orifice	DSD @ 6 cm distance from the actuator orifice
19 to 122	Fire down	Fire down
123 to 125	DSD @ 6 cm distance from the actuator orifice	DSD @ 6 cm distance from the actuator orifice
126 to 127	Fire down	Fire down
128 to 130	DSD @ 3 cm distance from the actuator orifice	DSD @ 3 cm distance from the actuator orifice

DIS: Drug in small particles B: Beginning life stage E: End life stage

Drug in small particles/droplets [1.4 5 6 7]

The test used to quantify the amount of drug present in fine droplets help us to find the amount of active moiety administrated to the targeted site. This test shall be performed by ACI (Anderson cascade impactor) as per USP< 601>.The flow rate should be maintained at 15Lpm for optimum performance of the spray unit. This test is performed at beginning of the life cycle of the spray unit. 10 Actuations per cycle should be considered for measurement using ACI apparatus.

The drug droplets are classified as below

Group-1: > 9 µm (Expansion Chamber +Nosepiece, inlet cone)

Group-2: < 9 µm (Stage 2 MOC)

Group-3: Mass balance

Group-4: Expansion chamber plus Nose piece.

The assay per one actuation must lie in range of 85.0%-115.0%.

Design

Table 4: Test and Reference Product] for drug in small particles (B Life stage) and DIS (B Life stage).

Description	**RLD**	**Test**
Total Labelled Metered Sprays	120 sprays after priming	120 sprays after priming
Number of Primes (before the first-time use)	10 times or until a fine spray appears	10 times or until a fine spray appears
Total Sprays	130 (Includes 10 primes before first time use)	130 (Includes 10 primes before first time use)
Number of Test/Reference Units	10 units from each batch/lot	10 units from each batch/lot
Spray Number	**Testing/Activity to be performed**	**Testing/Activity to be performed**
1 to 10	Priming	Priming
11 to 20	Drug in small particles	Drug in small particles
21-to 30	Fire down	Fire down

ACI

Images captured from google

Cascade Impactor with Expansion Chamber

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Conflict of Interest or declare none

No conflict interests

Abbreviations

SAC-Single actuation content

FDA-Food and drug Administration

BE-Bio Equivalence

HPLC-High pressure liquid chromatography

PBE-POP Bio equivalence

B Life Stage-Begin life stage.

E Life Stage-End life stage

DIS-Drug in small particles.

DSD-Droplet size distribution

ACI-Anderson cascade impactor

MOC-Micro-orifice collector

RLD-Reference listed drug.

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