

Nasal Spray Device Integrity Testing

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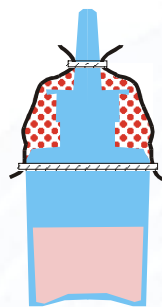
1 Introduction

The FDA Guidance Nasal Spray and Inhalation Solutions, Suspensions, and Spray Drug Products (IV.L) includes microbial requirements: “For device-metered, aqueous-based inhalation spray drug products, studies should be performed to demonstrate the appropriate microbiological quality through the life of the reservoir and during the period of reservoir use. Such testing could assess the ability of the container closure system to prevent microbial ingress into the formulation”. This implies that microbial quality has to be demonstrated under conditions that reflect the physical conditions of regular use (dry challenge of ventilation and wet challenge of tip seal). According to the FDA Guidance Container and Closure Integrity Testing in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (draft) “a container and closure integrity test may replace the 21 CFR 610.12 sterility test or USP <71> sterility test (or their equivalent) in a stability program”.

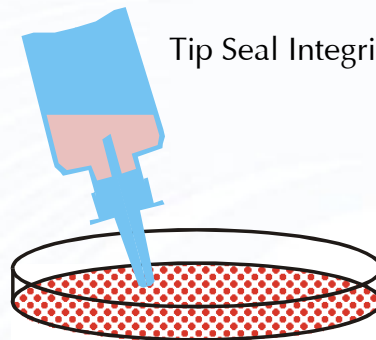
In order to meet the above standards various attempts have been made. Although adequate validation and compatibility with the specific product being tested, may be questioned. The frequently applied protocol “Testing and assessment of preservative free nasal sprays” of Prof. Wiedemann, Germany (1998) is testing the late microbial status of devices only, and this test is focussed on the integrity of the tip opening only. The microbial challenge of devices, takes place without any protective cap on the dispensing tip after inoculation, and thus does not reflect the conditions of regular use.

To get an expressive, reproducible result regarding the microbial robustness of the tested dispensing systems we suggest to split-up the test setup into two procedures:

Closure and Ventilation
Integrity Test



Tip Seal Integrity Test



The Tip Seal Integrity Test that we have established is more likely to simulate the situation during regular application of nasal devices: The microbial status on day 1 to 5 (or later) of the microbial challenge is assessed. The concentration of the challenging bacterial suspension is corrected to 10^7 /ml. With a higher concentration the risk of not challenging the very small residual drop at the dispensing tip is reduced. The incubation temperature is adjusted to a higher degree which also can be reached under conditions of regular use (i.e. keeping in trouser pocket). The incubation is performed with the protective cap placed on the pump system as it would during normal patient usage.

To assure the reproducibility of the Closure and Ventilation Integrity Test first an artificial dust was developed. Unfortunately, the challenge organism for routine filter assays *Brevundimonas diminuta* is not suited for dry microbial challenges. Therefore dry spores of *Bacillus subtilis* (see USP <71>) are used. In addition, similar to dust particles that are present during regular use, dust-sized inert particles are prepared as dry carriers. Spores loosely attached to these carriers function as a model for environmental bacteria that will ingress into the formulation if the nasal device does not have a sterile barrier. The artificial dust simulates the situation during application of nasal devices. Second a simple application of the artificial dust is established with a latex sleeve covering the complete ventilation and closure system.

2 Justification

The first part of the procedure (Tip Seal Integrity Test) is designed to evaluate the tip seal of nasal spray devices in maintaining a mechanical barrier to prevent microbial ingress into the formulation. In order to get detailed information about the properties of the device tips, a regular use challenge (including wiping of tip) and a severe challenge (without wiping of tip) are applied.

The other part of the procedure (Closure and Ventilation Integrity Test) is designed to evaluate the closure and ventilation in maintaining a sterile barrier and in preventing microbial ingress into the container and thereby into the formulation.

3 Definitions

- Latex sleeve: Combination of cut latex tubing, mounted with cable ties or equivalent and one Luer adapter. Item to cover all critical parts of a dispensing system (see pictures, order@qualis-laboratorium.com).
- Artificial dust: Dry inert powder with antistatic properties (spheres of 2-10 μm) containing $10^8 - 10^9$ dry bacillus spores per gram of the preparation (order@qualis-laboratorium.com).

4 Concept of Materials and methods

In order to test the integrity of the tip seal of nasal spray devices against microbial contamination of the formulation during application, a bacterial suspension is applied. The dispensing systems are dipped with the nasal tip downwards into the suspension, the system is actuated and released in the suspension. After 4 hours the tip is tested for initial microbial integrity under regular in-use conditions (including wiping of tip). Thereafter the dispensing systems are challenged severely (without wiping of tip) over a period of 5 days or longer (bacterial growth in container).

In order to test the integrity of all moving and porous parts of nasal spray devices against microbial contamination of the formulation, an artificial dust with bacterial spores is applied. A syringe filter allows pressure equalization during actuation (see picture).

Therefore a latex sleeve is mounted around the critical parts of the devices and is used to keep the spores close to all potential entry sites. Then the dispensing system with the artificial dust under the latex sleeve is vortexed once and actuated and released five times. This cycle is repeated until half of the container volume is dispensed. The device is then incubated and checked for “visual evidence of growth” (USP <71>) in the container.



5 Interpretation of results

The tested system meets the requirements of the tip seal integrity test, if no bacteria in dose during the regular use challenge and no bacterial ingress into the container during severe challenge are observed. When microbial growth is observed in at least one container of one batch and growth is confirmed microscopically (see USP <71>) the batch does not meet the requirement of this tip seal integrity test. If the tested system meets both requirements the sample is considered to have a valid tip seal integrity.

The tested system meets the requirements of the closure and ventilation integrity test, if the containers of all challenged dispensing systems remain clear until the end of the incubation time. In this case the batch is considered to have a valid ventilation and closure integrity.

A sample complies microbial specifications of the FDA Guidance “Nasal Spray and Inhalation Solutions, Suspensions, and Spray Drug Products” (chapter IV.L), if both tests (SOP codes: tsit-1e.doc and cvit-1e.doc) were performed with 3 times 20 dispensing devices of the same batch each and microbial ingress into the formulation of the sample was successfully prevented.

6 Literature

United States Pharmacopeia <71> Sterility Tests,
<http://www.usp.org>

United States Pharmacopeia <61> Microbial Limits Test,
<http://www.usp.org>

Pharmacopoe Europeae, Deutscher Apothekerverlag, Stuttgart

FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation
<http://www.fda.gov/cder/guidance/index.htm>

FDA Draft Guidance for Industry, Guidance Container and Closure Integrity Testing in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
<http://www.fda.gov/cder/guidance/index.htm>

Wiedemann, B. and Kratz, B.; Deutsche Apotheker Zeitung, 1998, 7:41-45

7 Recources

The complete Methods are part of the quality management handbook of the Qualis Laboratorium GmbH and will be send by mail on demand.