

Performance Tests Toolkit for Orally Inhaled and Nasal Drug Products

I. What is it?

The toolkit considers the types of Performance Tests that may be applicable to Orally Inhaled & Nasal Drug Products (OINDP), either as container closure or delivery system raw materials (used in the manufacture), in-process (part-finished) products or components, or final finished products.

In particular the toolkit considers the final product function of the OINDP – i.e. the method by which the OINDP is intended to give a therapeutic benefit to the user. An OINDP is a pharmaceutical product. The therapeutic (and potential life-saving) benefit that it gives is entirely dependant on the correct functioning and performance.

II. Who is it for?

This document is intended to be used by those seeking a general introduction to the performance tests that may applied to OINDP and the container closure or delivery system components and materials used in their manufacture. It will be specifically of interest to suppliers of components and materials for OINDP.

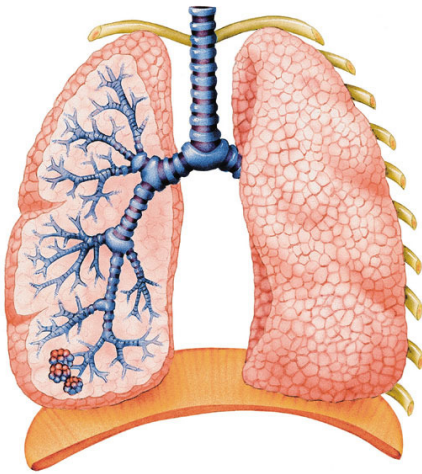
III. Why use it?

To obtain an introduction to performance test requirements for OINDP.
To identify further resources that will enable a deeper understanding of specific topics.

1. Introduction

Orally Inhaled Nasal Drug Products (OINDP) are intended to deliver therapeutic benefit by delivery of a pharmaceutical substance to the lungs (Orally Inhaled) or nasal cavity (Nasal). Both of these routes of administration by OINDP have some common characteristics:

- Delivery of the drug as a specific range of particle sizes, which may be the drug particle alone, or bound to a carrier particle (dry powder), or dissolved or suspended in a liquid droplet
- Targeted deposition to specific membranes, for example specific point of pulmonary tract, specific mucous membrane in the nasal cavity



OINDP are complex products which contain the drug substance with excipients as powder, solution or suspension in a container closure system which may also act as the drug delivery device. There are several types of OINDP such as nasal sprays, the pressurised metered dose inhaler (pMDI), the dry powder inhaler (DPI), nebulizers, and other novel inhaler types, such as Aqueous Droplet Inhalers (ADI). Container closure components used to manufacture OINDP include pumps, valves, cans, bottles, actuators, spray nozzles, spacer devices, dose counting mechanisms. Consideration is also given to the raw materials used to manufacture the container closure components, such as polymer materials used for moulding sub-components, rubber gasket materials used as seals.

Figure 1: Dry Powder Inhaler**Figure 2:** Nasal Spray**Figure 3:** pMDI

Some examples of components and materials (often referred to as Container Closure Components/Materials) used to manufacture these OINDP are listed below (some example images of components may be found in the Appendix #1):

- Pumps
- Valves
- Aluminium or steel cans
- Glass or plastic bottles
- Actuators, spray nozzles, DPI devices
- Blister strips for dry powders
- Spacer devices
- Dose Counting mechanisms
- Polymer materials used for moulding sub-components in the components listed above
- Rubber gasket materials used as seals in the components listed above

It is critical and obligatory to be able to define and demonstrate the performance of the OINDP during clinical trials, i.e., relate the performance to the therapeutic benefit, and to be able to demonstrate that these performance criteria are maintained when the product is used by the patient.

As well as assuring the quality of the OINDP, some of these Performance Tests may also be obligatory to comply with regulatory requirements for the OINDP.

This toolkit provides a general overview of the types of performance tests that may be applicable to OINDP and container closure components.

2. Performance Tests

OINDP may be stated to have some common design characteristics:

1. Contain and protect the pharmaceutical product
2. Control the quantity of each dose
3. Control the drug particle size, direction and rate/flow of the drug product in each dose
4. Be safe for use – present no danger to the user of the OINDP

And it is these 4 characteristics which largely determine the Performance Tests applied to OINDP and the components.

As previously stated, the performance tests assure the quality, safety and the therapeutic effect of the OINDP. Therefore careful consideration should be given to the intended product performance and the critical quality attributes of the container closure component and the OINDP. This will lead to the selection, development, validation and application of the appropriate performance tests required to assure that the product will function as defined, and meet regulatory commitments to verify the performance.

The tests defined in this section may be applied to the individual components, or to the finished OINDP.

However before considering the performance tests applied to finished OINDP and container closure components, it is also necessary to consider the materials used to manufacture the components. The basic physical-mechanical properties (for example hardness, tensile strength, dimensions, surface finish, permeability) may be critical to ensure that the finished OINDP component or product gives the required performance.

Example materials of construction used for components of OINDP are listed in the table below.

MATERIAL TYPE	COMPONENT MANUFACTURED FROM THE MATERIAL	EXAMPLE FUNCTIONAL PERFORMANCE THAT MAY BE IMPACTED
Steel	Springs, containers	Spring force to assure return/reset of mechanisms
Aluminium	Containers, caps, foils	Foil tear/peel strength for blisters in Dry Powder Inhaler
Plastic polymer	Mould complex component shapes	Tensile strength for 'flex' mechanisms
Rubber elastomers	Seals for valves and pumps	Leakage, friction
Glass	Ampoules for Nebulisers Bottles for Nasal Sprays	Strength Light transmittance

Therefore, while this document focuses upon the performance of the OINDP container closure components and products, careful specification and control of the characteristics of the materials of manufacture is essential to assure the intended performance, as well as to avoid quality and safety problems.

2.1 Sealing, Protection

TEST	APPLIED TO	COMMENT
Leakage rate	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules, ADI Spray nozzles	Loss of contents per unit time from the system. Performed at ambient temperature or pressure, or using vacuum, elevated/reduced temperature, programmed cycling
Moisture, air/oxygen or bacteria ingress	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules	Ingress per unit time of moisture or gas or bacteria into the system. Performed at ambient temperature or pressure, or using vacuum, elevated/reduced temperature, programmed cycling
Burst pressure	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules. ADI Spray nozzles	Performed at elevated temperature and/or pressure differential. May be a legal requirement for pressurised OINDP that may be air-freighted
Peel/tear strength	Blister strips, sealing covers	Verify the force required to peel apart two bonded surfaces (e.g., to open a blister of dry powder) or to pierce a material (e.g., foil of a blister of dry powder)

2.2 Quantity of Dose

TEST	APPLIED TO	COMMENT
Dose weight (‘Emitted Dose,’ ‘Shot weight’)	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules, ADI	Verify the consistency of weight in each dose. May be applied to the quantity held in the container/blister, or to the quantity expelled during use of the OINDP
Drug per dose (‘Dose / Spray Content Uniformity’, ‘Dose Through Use’)	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules, ADI	Verify the quantity of drug in each dose. Verify the number of doses in the container. May be applied to the quantity held in the container/blister, or to the quantity expelled during use of the OINDP
Number of doses required to prime or re-prime	pMDI / Valves Nasal spray / Pumps DPI, ADI	Verify the number of doses required to be emitted (wasted) to achieve a full dose (first use, or after a period of non-use)

2.3 Drug Particle Size and Delivery

TEST	APPLIED TO	COMMENT
Particle/Droplet Size Distribution	pMDI / Valves Nasal spray / Pumps DPI / Blister strips Reservoirs, ampoules, ADI	Verify the full range of particle or droplet size distribution in a dose
Fine Particle Fraction/Mass	pMDI Nasal spray DPI, ADI	Verify the amount of drug substance with a particle size distribution as specified.
Spray pattern / cone angle / plume geometry	Nasal sprays. pMDI actuators. ADI (if relevant)	Verify the direction and geometric pattern of the spray at a defined distance from the OINDP
Flow rate / resistance	pMDI DPI Nebuliser, ADI	Verify the flow rate through the OINDP (e.g., through a spray orifice). May be important to assure delivery of the dose, or during manufacturing (filling) of the OINDP
Triggering flow rate	Breath- operated/triggered device (pMDI or DPI, ADI or where applicable)	Verify the flow rate at which the OINDP ‘triggers’ or activates

Figures 4 and 5 provide illustrations of the spray pattern test and particle size distribution test respectively.

Figure 4: Analysis of Spray Cone Angle of a Nasal Spray. Verification of the Spray Cone Angle is necessary to assure that the dose of product will be targeted at the intended site of therapeutic effect (e.g., specific nasal mucosa). Such testing is typically performed as a quality release test on the container closure components (prior to delivery to the OINDP manufacturer) and also on the finished pharmaceutical product by the OINDP manufacturer (prior to delivery to the pharmacy). The illustration shows an example analytical result -- in this instance the analysis is performed using laser scattering technology.

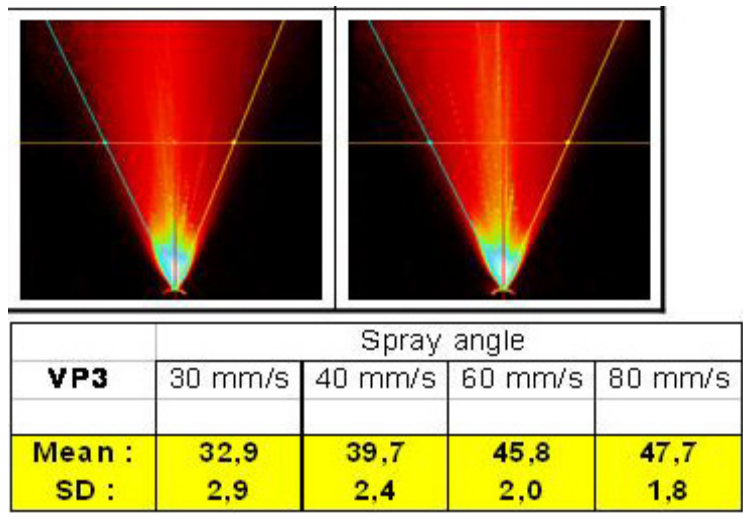
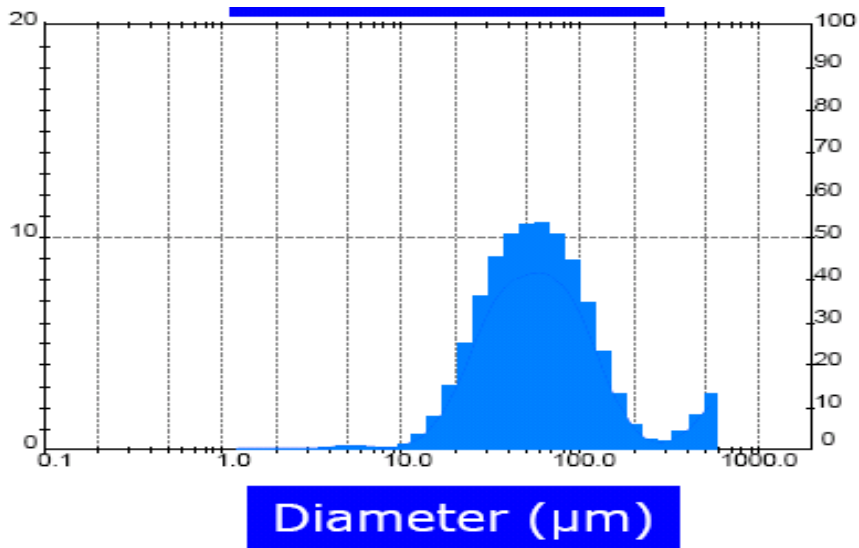


Figure 5: Analysis of Particle Size Distribution. Verification of the distribution of the size of the particles is necessary to assure that particles of the correct size are delivered by the OINDP, since therapeutic effect may be dependant upon this. For example in inhalation therapies where drug particles must be within a very specific range of sizes to penetrate to the deep alveoli of the lungs. As with Spray Cone Angle, Particle Size Distribution will be verified on batches of container closure components and the final drug product. The example below shows an analysis by Laser Scattering equipment. The product will typically be characterised and specified by percent of particles below a specific size, e.g. % of particles less than 10 microns (%<10 μ m).



VP22	%<10 μ m	D(v, 0.1)	D(v, 0.5)	D(v, 0.9)
Mean	0.9	24.3	58.2	164.4
SD	0.2	1.4	6.8	61.2

2.4 Safety

TEST	APPLIED TO	COMMENT
Extractables*	Plastic and rubber materials used to manufacture components. Coatings (e.g., to cans)	Verify the identity and quantity of chemical compounds that can be extracted from a material using an aggressive solvent and conditions
Leachables**	Final drug product.	Verify the identity and quantity of chemical compounds that are extracted from the OINDP container closure components by the drug product under actual use conditions
Residual solvents or substances	Plastic and rubber materials. Coatings (e.g., to cans)	Verify the residual level of solvents or other substances (e.g., detergents, lubricants) used in manufacturing
Bioburden	Components used in manufacture of OINDP. Finished OINDP.	Verify the identity and quantity of bacteria present in the OINDP during its shelf-life Should be performed according to applicable compendial methods
Sterility	OINDP products and components that are sterilised.	May be applicable to aqueous inhalation and nasal products
Particulates	Applied in particular to inhalation products and components (pMDI valves, Dry Powder Inhaler)	Verify the identity and quantity of particulates, fibres etc on the OINDP

*Extractables are chemical compounds that can be extracted from container closure components using appropriate solvents and conditions. The objective of extractables testing is to use the most efficient conditions to extract, identify and quantify the entire level of the chemical compounds in the components (i.e., the maximum quantity that could potentially be extracted).

**Leachables are chemical compounds which leach from container closure components and thus 'contaminate' the drug product. The quantity of leachables in the drug product is likely to be time dependant, and so is measured over the shelf-life of the OINDP. The objective of leachables testing is to verify the actual amounts of chemical compounds (usually a subset of the extractables) that will enter into the drug product.

2.5 Miscellaneous

TEST	APPLIED TO	COMMENT
Counting accuracy	Dose counting mechanisms	Verify the counting accuracy of a Dose Counter (where equipped)
Triggering force and distance	pMDI Nasal spray DPI, ADI	Verify the distance and force required to ‘trigger’ the OINDP or the mechanism of a Dose Counter (where equipped)
Loss on Drying / absorption capacity	Materials used to absorb moisture or gases	Verification of the moisture uptake capacity of materials (may be integrated into the OINDP – e.g. component moulded from a hygroscopic material such as Nylon; or be included in the packaging, e.g. sachet of Silica Gel)
Printing legibility	Dose Counting mechanisms Laser marking or other anti-tamper/anti-counterfeiting marking	Verify the legibility of printing
Weight	Components and finished OINDP	Consistency of weight (of components or finished OINDP)

3. General comments

The performance tests defined above are not an exhaustive list. The tests should be chosen based upon the intended functional performance and critical quality attributes that must be verified. Therefore it may be necessary to develop new tests. Different tests may be applied at different stages (stage of development cycle of the product, in-process or release QC test, monitoring, etc).

Testing may also be applied using specific storage conditions (e.g., elevated or cycled temperature and humidity) to verify the performance (e.g., per ISO 20072) of the OINDP through its intended life cycle or intended expiry date.

Testing may be performed after any specific treatments, sterilization procedures, robustness testing (effect of vibration, dropping, storage in specific orientations) etc to verify that these have no impact on performance.

Testing may be required to verify the propensity of the drug product to adhere to the container closure components, or to verify the effectiveness of special coatings to prevent adhesion.

As stated, some of the tests listed may be defined as minimum requirements by regulatory authorities and international pharmacopoeia, together with minimum acceptance criteria/limits. And these regulatory requirements may also include stipulations regarding the test method, apparatus and test parameters that must be used. Further details can be found in the reference list below, as well as in applicable pharmacopoeia monographs and other standards.

4. References

US - Food and Drug Administration

Container Closure Systems for Packaging Human Drugs and Biologics <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979>.

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products

Europe - EMEA

Pharmaceutical Quality of Inhalation and Nasal Products <http://www.emea.europa.eu/pdfs/human/qwp/4931305en.pdf>

93/42/EEC. Council Directive. *Medical Devices Directive (MDD)* Consolidated Text http://europa.eu.int/eur-lex/en/consleg/pdf/1993/en_1993L0042_do_001.pdf

Plastic Packaging Materials (CPMP/QWP/4359/03) Immediate <http://www.emea.europa.eu/pdfs/human/qwp/435903en.pdf>

Canada

Pharmaceutical Quality of Inhalation and Nasal Products http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/inhalationnas_e.pdf

Other

ICH Q8 Pharmaceutical Development (R2, Step 4, August 2009) <http://www.ich.org/LOB/media/MEDIA4986.pdf>

Safety Thresholds and Best Practices for Extracables and Leachables in Orally Inhaled and Nasal Drug Products. PQRI, 2006 http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

ISO 20072 Aerosol drug delivery device design verification – Requirements and test methods

APPENDIX: EXAMPLES OF OINDP COMPONENTS

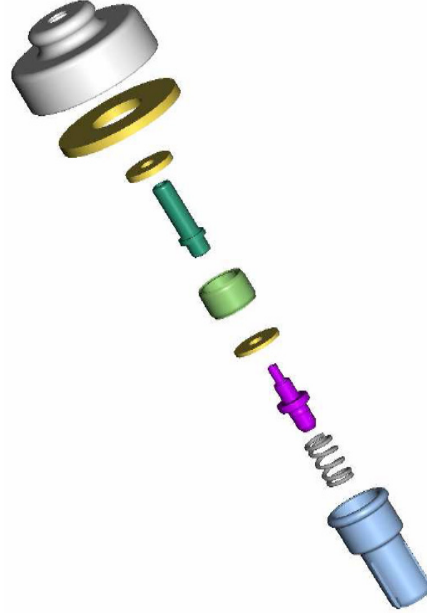


Figure 1. Components of valve for an MDI