Uniformity of delivered dose of nasal preparations

This general chapter applies to certain preparations for nasal administration that are supplied in containers intended to deliver defined doses of the active substance(s) for nasal administration. For the purpose of the pharmacopoeia the container closure system/delivery device for a nasal preparation is referred to as a container.

Uniformity of delivered dose of a multidose container must be ensured within a container (i.e., "*intra*-") and between containers (i.e., "*inter*-"). For single dose nasal preparations, the inter-container test must be performed.

Procedures and sampling schemes both for combined intra- and inter-container testing and for separate testing are acceptable, if justified and authorized. Separate intra- and inter-container testing is not required when combined intra- and inter-container testing is performed. In addition to the following combined or separate intra- and inter-container testing procedures, other testing procedures are acceptable, if justified and authorized.

An example of a combined intra- and inter-container sampling scheme is to take 10 containers and collect the first dose from 3 containers, the middle dose from 4 containers and the last dose from 3 containers and then determine the delivered dose.

For all tests, prepare and use the container as directed in the instructions to the patient. If necessary, before and between dose collections, store the containers to discharge electrostatic charges.

For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

1. Intra-container testing

1.1. Metered-dose nasal sprays

1.1.1. Apparatus

Use an apparatus capable of quantitatively collecting the delivered dose. At the very minimum, the following aspects should be taken into consideration when selecting an apparatus: actuation direction (vertical or tilted), connection between container and apparatus, sampling efficacy, need for an airflow system, venting of collection apparatus and mode of actuation.

1.1.2. Procedure

Unless otherwise prescribed or justified and authorized, perform 10 determinations of the delivered dose by collecting the first 3 doses, the middle 4 doses and the last 3 doses from a single container using the procedure described below.

Unless otherwise prescribed in the instructions to the patient discharge the first delivery to waste. Then connect the container to the apparatus. Discharge the contents into the apparatus until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance as the delivered dose.

Repeat the procedure for an additional 2 doses using the same container.

Discharge the container to waste until (n/2) + 1 deliveries remain, where n is the number of deliveries stated on the label. Collect 4 doses using the procedure described above.

Discharge the container to waste until 3 doses remain. Collect these 3 remaining doses using the procedure described above.

For metered-dose nasal sprays that are solutions, if justified and authorized the uniformity of delivered dose can be replaced by the test for uniformity of delivered mass (i.e. there is a relationship between the amount of active substance sprayed and the change in container weight). Following the procedure described above, replace the determination of delivered dose with the determination of the delivered mass by weighing the container before and after discharging the container at each step calculating the difference between the two masses.

1.1.3. Evaluation

The uniformity of delivered dose is evaluated on the basis of the average value of the 10 delivered doses and their individual results. Since tolerance of the uniformity of delivered dose required for a nasal preparation is different depending on the kind of active ingredients, its content, delivered dose and dosage form, the appropriate tolerance range should be set for each product.

1.2 Metered-dose nasal powders

1.2.1. Apparatus

Use an apparatus capable of quantitatively collecting the delivered dose. At the very minimum, the following aspects should be taken into consideration when selecting an apparatus: actuation direction (vertical or tilted), connection between container and apparatus, sampling efficacy, need for an airflow system, venting of collection apparatus and mode of actuation.

1.2.2. Procedure

Unless otherwise prescribed or justified and authorized, perform 10 determinations of the delivered dose by collecting the first 3 doses, the middle 4 doses and the last 3 doses from a single container using the procedure described below.

Unless otherwise prescribed in the instructions to the patient discharge the first delivery to waste. Then connect the container to the apparatus using an adapter. Discharge the contents into the apparatus until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance as delivered dose.

Repeat the procedure for an additional 2 doses using the same container.

Discharge the container to waste until (n/2) + 1 deliveries remain, where n is the number of deliveries stated on the label. Collect 4 doses using the procedure described above.

Discharge the container to waste until 3 doses remain. Collect these 3 remaining doses using the procedure described above.

1.2.3. Evaluation

The uniformity of delivered dose is evaluated on the basis of the average value of the 10 delivered doses and their individual results. Since tolerance of the uniformity of delivered dose required for a nasal preparation is different depending on the kind of active ingredients, its content, delivered dose and dosage form, the appropriate tolerance range should be set for each product.

2. Inter-container testing

Inter-container testing is to be conducted for preparations for nasal administration supplied in single dose and multi-dose containers. A suitable apparatus, experimental set-up, and evaluation procedure are described in section 1. Intra-container testing.

An example of a suitable inter-container testing scheme is to take 10 containers and collect the first dose from each container and then determine the delivered dose.

Alternatively, the combined intra- and inter-container sampling scheme or other inter-container testing procedures are acceptable, if justified and authorized.