Point of view: Inconsistency, confusion and lack of consensus due to the USP Chapter <601> update on nasal delivered dose uniformity (DDU) testing

In this opinion article, the author discusses concerns and presents a supporting case study

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In 2022, an update to the United States Pharmacopeia (USP) General Chapter <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests introduced changes to the sampling procedures for Delivered Dose Uniformity (DDU) testing of nasal spray and nasal aerosol products. These revisions, which recommend the use of Dosage Unit Sampling Apparatus (DUSA) tubes for nasal spray testing, have caused concern in the pharmaceutical industry due in part to the additional testing burden needed to respond to this change. Furthermore, the change lacks clinical relevance and does not enhance accuracy and precision in DDU determinations. It has also created confusion, as it is not reflected in the USP monographs and product-specific guidances that the industry follows in product development.

This article reviews the roles of the USP, the United States Food and Drug Administration (FDA) and the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) in shaping the regulatory framework for orally inhaled and nasal drug products (OINDPs) and examines the implications of these recent changes to USP <601>. In addition, a case study (using fluticasone propionate nasal spray) comparing traditional DDU methods to those proposed by the updated USP <601> highlights key issues, such as inconsistencies in sampling procedures, potential sources of error and increased operational costs. These findings underscore the importance of adhering to product-specific monographs and established workflows to ensure regulatory compliance and product quality. The article also highlights the need for clear alignment and consensus across regulatory bodies to prevent confusion and safeguard industry practices [1, 2].

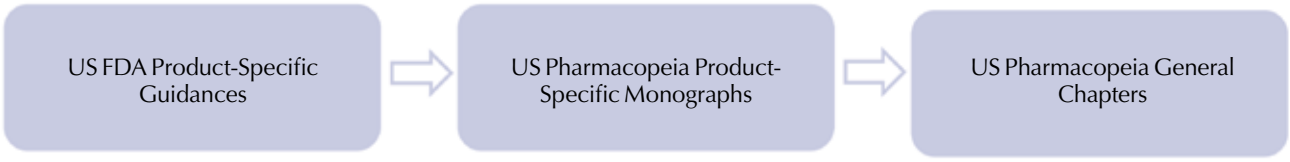
Roles of the FDA, USP and IPAC-RS

To begin, it is important to understand the roles of regulatory bodies and their associated guidance documents and requirements, as well as the part played by non-regulatory groups. While there are multiple, important regulatory organizations in the OINDP industry whose guidelines vary by global region, this article will focus on those in the United States.

- The FDA enforces regulatory compliance for drug products, including OINDPs, ensuring they meet safety, efficacy and quality standards. Their key regulatory documents include Guidances for Industry and Product-Specific Guidance documents, which describe detailed requirements for formulation, testing and submission of drug products.

Figure 1

Hierarchy of guidance documents from the FDA and USP



- The USP provides quality benchmarks and standards for drugs and drug products, including OINDPs, to ensure they meet safety and efficacy requirements. While the USP does not enforce its recommendations or approve drug products, their product-specific monographs and general sampling procedures are instrumental in guiding the industry toward standardizing drug development and manufacturing. USP general chapters explain testing methodology and recommend sampling procedures, but the methods and procedures defined in product-specific USP monographs always take precedence over their general chapters.
- IPAC-RS is a consortium of manufacturers, including those from the OINDP industry, that works closely with both the FDA and USP. IPAC-RS hosts discussions and provides comments that are pivotal in refining USP guidance documents, ensuring they are aligned with the latest scientific and regulatory advancements. This collaborative approach helps maintain the robustness and relevance of USP standards.

By understanding and adhering to input from the FDA, USP and IPAC-RS, manufacturers can navigate the regulatory landscape effectively and work to ensure their OINDPs meet the necessary standards for market approval and patient safety. However, understanding the hierarchy of regulatory documents is essential to successful drug product development. FDA product-specific guidance documents and USP product-specific monographs always supersede general chapters, such as USP <601> (Figure 1).

USP<601>: Its purpose and the DUSA tube update

In 2022, a change was made to USP General Chapter <601> that recommends the use of DUSA tubes for the sample collection of nasal sprays and aerosols. This contradicts other, more specific regulatory guidance documents. Furthermore, the suggested sample collection process imposes physical constraints on the apparatus design and suggested workflow [1, 2].

USP <601> describes testing procedures for OINDP products, primarily regarding delivered dose and particle characteristics. Section A (Delivered Dose Uniformity) describes general sampling procedures, identifying distinct OINDP modalities including Inhalation Aerosols and Inhalation Sprays, Nasal Aerosols and Nasal Sprays, Inhalation Powders, and Nasal Powders. Prior to 2022, USP <601> did not indicate a specific sample collection vessel for nasal sprays and aerosols. Furthermore, no existing product-specific monographs dictate the use of DUSA tubes, but instead recommend use of other collection vessels, most commonly volumetric flasks [2, 3].

In 2023, Proveris Scientific Corporation (Hudson, MA, US) conducted an informal survey of companies in the OINDP market to inquire which sample collection vessel they use for nasal DDU testing and for what purpose. More than 90% of the respondents reported using volumetric flasks, citing reasons such as historical usage, ease of availability, lack of additional consumables and reliable performance.

Several aspects of the nasal spray section of USP <601> remain unclear and potentially contradictory. For example, the recommendation to use specific flow rates during testing conflicts with individual monographs for nasal sprays and aerosol products, which do not specify flow rate parameters for DDU testing. Also, the DDU sampling apparatus in Figure 2 suggests connecting a vacuum during nasal spray and aerosol testing. However, if no flow is required for nasal sprays, attaching a vacuum without flow seems illogical. This requirement also introduces unnecessary steps and increases the potential for human error.

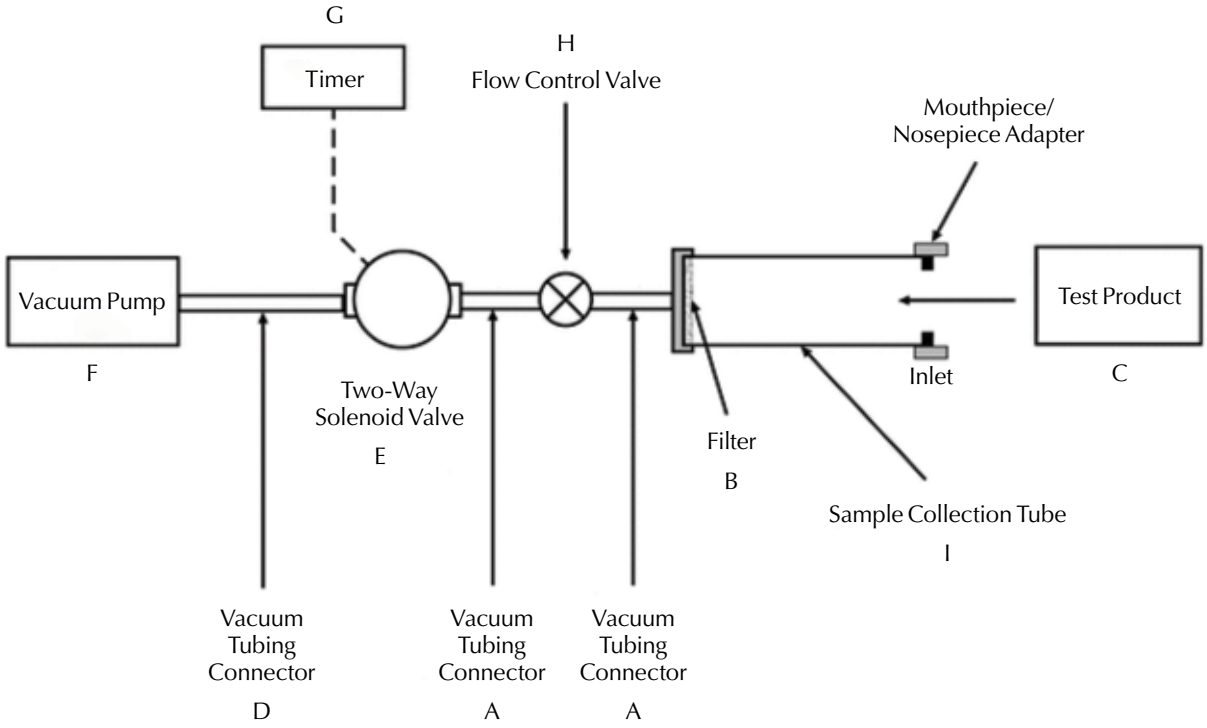
Additionally, the suggested use of a vacuum system with a nosepiece adapter poses risks, as aqueous nasal sprays are typically closed systems. Applying a vacuum could disrupt the seal between the sample collection tube and the device, potentially compromising the sample's integrity and performance. These inconsistencies create confusion and underscore the need for clearer, more practical guidelines for testing nasal spray products.

Case study: A comparison of nasal spray DDU collection methods

To understand workflow and performance differences between Delivered Dose Uniformity collection methods, a study was performed using the currently approved USP monograph for fluticasone propionate nasal spray and the proposed

Figure 2

Diagram from USP <601> Figure 1a: "DDU sampling apparatus for inhalation aerosol, inhalation spray, nasal aerosol, and nasal spray drug products." Republished with permission, [1].



method found in USP <601>. All actuations were performed using a Proveris Scientific Vereo® NSx Automated Actuator. The monograph procedure was followed for Delivered Dose Uniformity method, actuating the device into an inverted 25 mL volumetric flask [2]. The DDU sampling apparatus shown in Figure 2 was used for testing, with and without air flow (28.3 L/min). The study analyzed 3 actuations from 3 fluticasone propionate nasal sprays for each of 3 methods (DUSA with flow, DUSA without flow and traditional volumetric flask), with all sample actuations coming from the beginning of life, after priming. Identical actuation parameters and high-performance liquid chromatography (HPLC) analysis were performed by the same analysts for all samples. The chromatographic method described in the USP monograph for fluticasone propionate nasal spray was used for all sample quantification [2].

To replicate the workflow described in USP <601>, a custom nosepiece adapter was created for testing. This nosepiece adapter, shown in Figure 3, allows for an airtight seal between the nasal spray orifice and the insert while also preventing loss of liquid during vertical actuation. The nosepiece adapter is made of silicone rubber to ensure chemical compatibility with common organic solvents. All actuations were performed in a vertical orientation consistent with traditional nasal spray testing. Vertical automated actuation was enabled using the custom DUSA tube adapter to the Vereo NSx actuator, also shown in Figure 3.

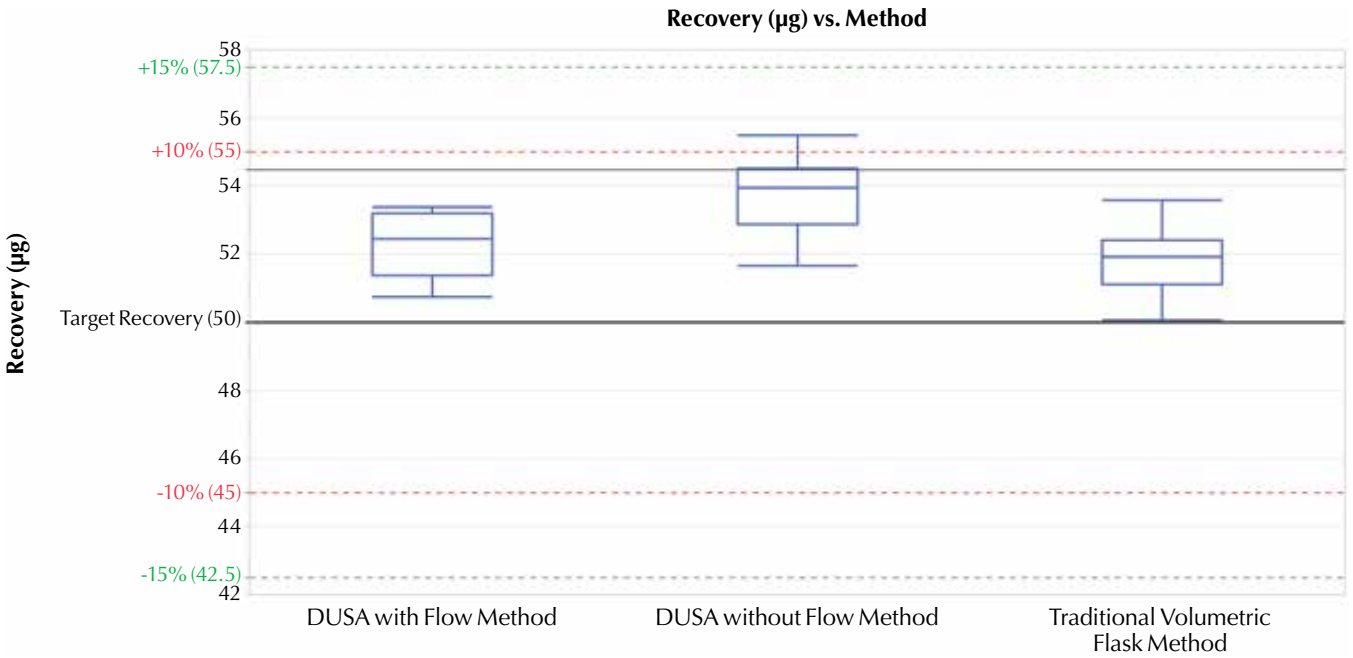
Data presented in Figure 4 showed similar performance across all methods, with the traditional method (volumetric flask) providing values closer to the target than the other determinations. While all products tested exhibited elevated recovery values, the results were all within the acceptable range of +/- 15% of label recovery value.

Figure 3

Proveris Scientific DUSA Nosepiece Adapter (left) and DUSA tube to Proveris Scientific Vereo NSx adapter (right)

Figure 4

Drug recovery results from DDU testing of fluticasone propionate nasal spray under three conditions: DUSA with flow (left), DUSA without flow (middle) and traditional volumetric flask (right)



Workflow comparison: Unnecessary steps can increase risk, testing time and costs

Pharmaceutical regulations are crucial for ensuring the safety and efficacy of therapies, as they provide a framework for consistent product quality and reliability. In a demanding, regulated environment like the pharmaceutical industry, changing Standard Operating Procedures (SOPs) should be approached with caution due to the potential for unforeseen complications, resource allocation issues and varying results. Any modification of SOPs requires sufficient justification, such as a response to an explicit regulatory directive, or the expectation of significant benefits in performance or quality. This principle is particularly relevant for Delivered Dose Uniformity testing of nasal spray products, where the proposed changes in USP <601> not only fail to enhance accuracy or reproducibility, but also introduce potential sources of human error, increase supply costs and require additional time to complete the testing.

The differences in complexity and duration between the workflows of the USP Fluticasone Propionate Nasal Spray monograph and USP <601> are immediately evident. Figure 5 shows a step-by-step comparison of the two methods used in this case study. Each instance where the possibility of human error is introduced is highlighted in red.

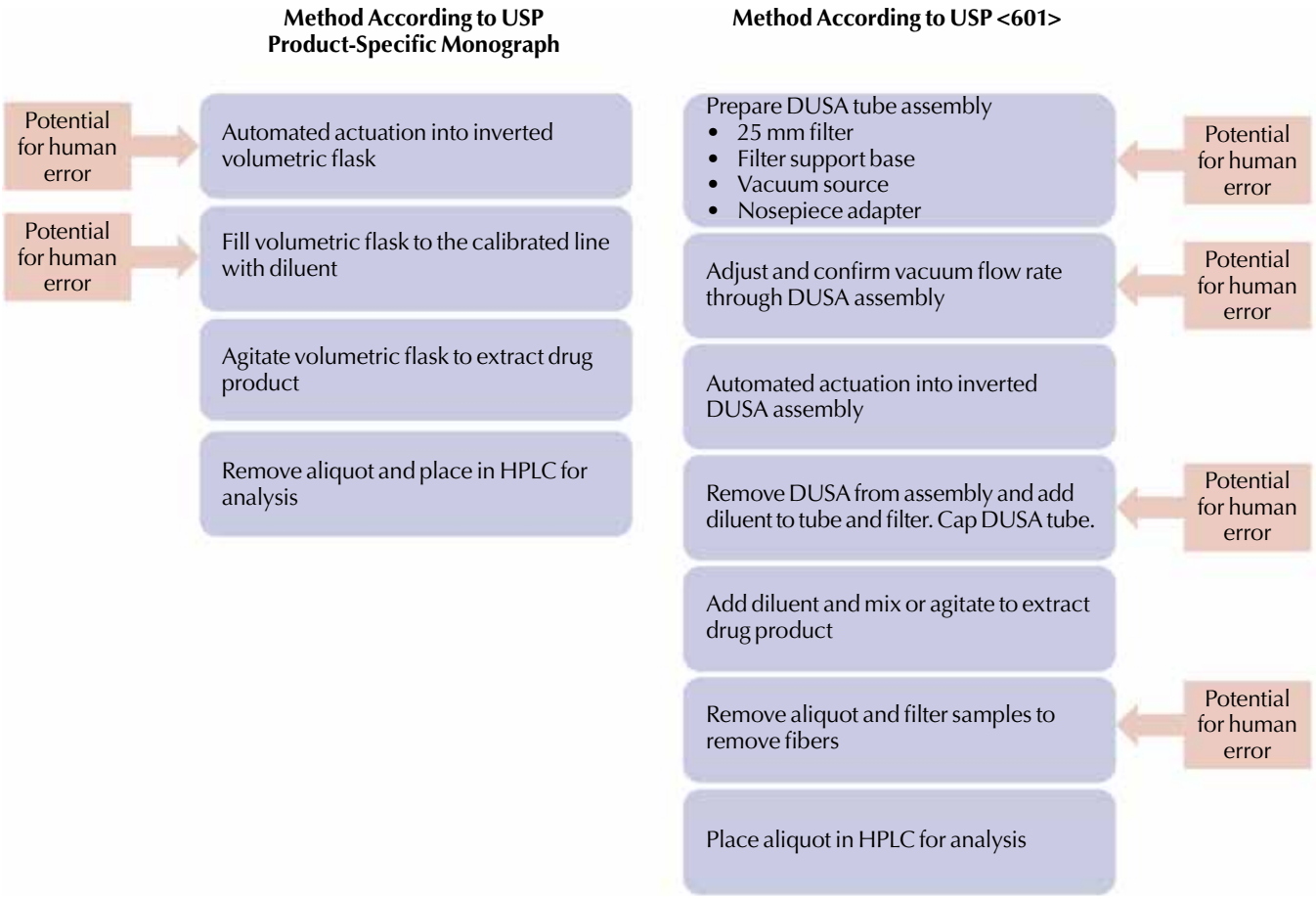
The increased number of steps in the USP <601> workflow also requires more equipment and consumables, inevitably increasing operating costs. In addition to the higher startup costs (including a vacuum system, DUSA tubes, mouthpiece adapters, a flow meter and a DUSA to flow meter adapter), additional consumables are required for each sample.

Table 1 compares the equipment and consumables required for DDU testing according to the USP Fluticasone Propionate Nasal Spray Monograph and according to USP <601>. Some of these materials are low-cost consumables while others require a significant investment, such as DUSA tubes. In addition to costs for materials, following the workflow suggested in USP <601> significantly increases the time required to complete testing and therefore increases analyst time and overall costs.

The principal change in testing due to the use of DUSA tubes is the utilization of air flow to introduce a spray into the DUSA apparatus, which is a closed system. However, this is of little relevance to clinical deposition of sprays in the nasal cavity, which does not provide an airtight enclosure. Use of the DUSA apparatus with flow rate control is necessary for determining the DDU of inhalation aerosols such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs). This is because the fine aerosols emitted ex-actuator/mouthpiece are entrained by the inhalation flow and carried for deposition at target sites in the lower respiratory tract, located at a considerable distance from the site of administration (the mouth). In addition, administration of these aerosols occurs in an essentially closed chamber (mouth to lung). However, aqueous nasal sprays contain much larger droplets and are delivered in the vicinity of the site(s) of action, for which the role of air flow through the nostril has minimal value.

Figure 5

Comparison of the number of testing steps and the potential for human error using either the USP Fluticasone Propionate Nasal Spray monograph and or USP <601>



Reactions from IPAC-RS, the FDA and USP

Just months after the update to USP <601>, IPAC-RS released their comments in a statement, saying, "Care should be made to make it clear that for nasal spray products, a DDU sampling apparatus (traditionally designed for pressurized metered dose inhaler devices) is not required for use in DDU workflows. An appropriate apparatus can be used in place of the DUSA or DDU sampling apparatus using a validated assay. This is in accordance with the language by the FDA in recent product specific guidance documents for nasal spray products." [4, 5].

This IPAC-RS position is also supported by several product-specific guidance documents from the FDA, released since the USP update, which do not allude to any change in sampling procedures involving DDU testing for nasal spray products. The FDA makes the statement, "We recommend a suitable apparatus be used for collecting an emitted dose from a nasal spray." [2, 3]. This highlights the FDA's disregard for the update to nasal DDU testing found in USP <601>, implying that generic manufacturers are not expected to use the apparatus described in that chapter.

In addition to the reaction from IPAC-RS and the FDA's apparent lack of acknowledgment of the update, the USP itself has not explicitly endorsed the use of DUSA tubes for nasal DDU testing. None of the monographs for specific nasal sprays, such as Fluticasone Propionate or Triamcinolone, make any reference to USP <601>. The USP also had the opportunity to include a mention of USP <601> in the updated Fluticasone Propionate monograph, which was released in May 2023, after the update was made to USP <601> in 2022. This suggests that the USP did not intend for the update of USP <601> to alter the product-specific monographs already in place.

The need for continued alignment

Pharmaceutical regulations are essential to producing safe and effective therapies. Changing regulatory standards involves many risks and should be cautiously considered. The FDA, USP and IPAC-RS have worked together for many years, effectively aligning requirements and testing methodologies built on scientific findings and industry consensus. The 2022 update to USP General Chapter <601> fails to add benefits and introduces unnecessary risk and costs. This update represents a lack of alignment where the FDA has not recommended the update

Table 1

Comparison of equipment and consumables required for DDU testing according to USP Fluticasone Propionate Nasal Spray Monograph versus USP <601>.

According to USP Fluticasone Propionate Nasal Spray Monograph	According to USP <601>
Automated actuator system	Automated actuator system
Volumetric flask	Vacuum pump and tubing
	Filter support base
	25 mm filters
	DUSA tubes
	Flow meter
	Pre-HPLC filters
	Nosepiece adapter
	DUSA tube NSx adapter

and IPAC-RS disagrees with the use of DUSA tubes and sampling procedures for nasal drug products.

The confusion caused by this break in collaboration may be managed by following existing procedures that can determine delivered dose from nasal sprays with acceptable precision and accuracy.

While the industry agrees that standardization of nasal dose collection can be a useful regulatory advancement, achieving this should: 1) be based on clear advantage of the update method over the established method, with many years of use in support of both brand and generic nasals sprays and 2) have alignment and clear messaging across regulatory bodies and industry stakeholders, established through open-forum discussions. That alignment should also be reflected in product-specific guidance documents that the industry follows to ensure processes that will be accepted during product submission.

References

1. United States Pharmacopeia: <601>Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests.

2. United States Pharmacopeia Monograph: Fluticasone Propionate Nasal Spray.

3. United States Pharmacopeia Monograph: Budesonide Nasal Spray.

4. United States Food and Drug Administration: Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

5. IPAC-RS Comments on USP "Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests," Confidential Draft, September 13, 2022.

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