dx.doi.org/10.14227/DT310424P162

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Testing the In Vitro Product Performance of Inhalation and Nasal Drug Products: Views of the USP Expert Panel

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ABSTRACT

While inhalation and nasal drug products are available as various different drug-device combination products for the treatments of local and systemic diseases, their compendial performance testing has concerned with only delivered dose uniformity (DDU) and aerodynamic particle/droplet size distribution (APSD). This *Stimuli* article presents the views of the USP Expert Panel on New Advancements in Product Performance Testing (EP-NAPPT), providing the gap analysis and the recommendations for in vitro product performance testing for these local and systemic drug- device combination products. The gap analysis identified the following performance testing areas to be improved: 1) in vivo-predictive lung and nose delivery testing; 2) fast particle/droplet size testing; 3) spray pattern and plume geometry testing; 4) drug release/dissolution testing; and 5) in vitro product performance and physiologically based pharmacokinetic (PBPK) modeling. Recommendations were then made to each area for identification of testing needs and improved in vivo prediction.

INTRODUCTION

Science and technology in pharmaceutical product development continue to evolve, and many innovative and complex dosage forms have been approved for therapeutic use in patients. Considering the prohibitive costs of drug therapies in many diseases, demand for therapeutically equivalent generic products is also rising. Therefore, careful timely assessments, periodic reviews, and updates are essential to ensure that product performance tests in the USP are sufficient and relevant to support regulatory approvals of such new and generic drug products. As overviewed in the introductory article (*1*), the USP Expert Panel on New Advancements in Product Performance Testing (EP-NAPPT) has been charged to: 1) evaluate current compendial product performance tests; 2) conduct a gap analysis of the current status of product performance testing in USP; and 3) provide recommendations for the adaption of product performance tests and the development of innovative approaches.

Accordingly, the Inhalation and Nasal Drug Product Subcommittee of the EP-NAPPT presents this *Stimuli* article as the fourth article in the series, concerning in vitro product performance testing for inhalation and nasal drug products. The article describes the current USP framework and scope, the recent efforts by the Inhalation and Nasal Drug Product Subcommittee on the USP General Chapters Dosage Forms Expert Committee, EP-NAPPT's gap analysis for the USP product performance testing, and the subcommittee's recommendations.

CURRENT USP FRAMEWORK AND SCOPE

As listed in Table 1, *USP–NF* includes several general chapters on inhalation and nasal drug products (*2*). *Inhalation and Nasal Drug Products— General Information and Product Quality Tests* <5> (*3*) clarifies different types and names of the products and describes their general product quality tests (e.g., identification, assay, content uniformity, leachables, elemental impurities, impurities and degradation products, foreign particulate matter, water and co-solvent content, spray pattern, plume geometry, valve/pump delivery, net fill weight, leak rate, and microbial limits). *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* <601> (*4*) describes the performance quality tests of these drug-device combination products, specifically limited to delivered dose uniformity (DDU) and aerodynamic particle/droplet size distribution (APSD). Chapter <601> (*4*) has most widely been recognized and used to assess drug delivery to, and deposition within, the lung and the nose from the products. *Topical Aerosols* <603> (*5*) concerns drug aerosol products for topical delivery to sites other than lung or nose, such as skin, and thus, is not for inhalation and nasal drug products. The other applicable chapters, *Propellants* <602> (*6*) and *Leak Rate* <604> (*7*) concern propellants and leak tests for aerosol containers respectively, and thus are not performance quality tests. Therefore, unlike oral drug products, performance of inhalation and nasal drug products has been thought to depend only on aerosol or spray delivery and deposition, but not on post-delivery and deposition behaviors or events in the lung and the nose, such as drug release and dissolution.

Table 1. USP-NF General Chapters for Inhalation and Nasal Drug Products

Chapter type	Chapter	Title
General Tests and Assays	<5>	Inhalation and Nasal Drug Products—General Information and Product Quality Tests
	<601>	Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests
	<602>	Propellants
	<604>	Leak Rate
General Information Chapters	<1601>	Products for Nebulization—Characterization Tests
	<1602>	Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests
	<1603>	Good Cascade Impactor Practices
	<1604>	Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products

Chapters *Products for Nebulization—Characterization Tests* <1601> (*8*), *Spacers and Valved Holding Chambers Used with Inhalation Aerosols— Characterization Tests* <1602> (*9*), *Good Cascade Impactor Practices* <1603> (*10*), and *Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products* <1604> (*11*) are informational (Table 1). They are useful to assess product quality and performance but are not mandatory for regulatory submissions. Almost identical to its *European Pharmacopoeia* counterpart (*12*), <1601> (*8*) describes the performance tests of products for nebulization, i.e., the measurements of drug delivery rate, DDU, and APSD for aerosol droplets.

Chapter <1602> (*9*) concerns add-on devices used with inhalation aerosols, i.e., spacers and valved holding chambers, and their characterization tests. Chapter <1603> (*10*) is a guide for good cascade impactor practices for quality maintenance; and <1604> (*11*) is a new chapter, currently being drafted, describing how to present APSD measurement data for inhalation drug products. Hence, <1603> (*10*) and <1604> (*11*) both ensure adequate performance testing of APSD described in <601> (*4*).

RECENT EFFORTS BY THE USP INHALATION AND NASAL DOSAGE FORM EXPERT SUBCOMMITTEE

The Inhalation and Nasal Drug Product Subcommittee on the USP General Chapters Dosage Forms Expert Committee has been active in responding to comments made by stakeholders and providing updates and clarifications to the chapters listed in *Table 1* (*13*). Chapter <5> (*3*) has undergone minor changes to its lists for consistency within the *USP–NF*. Chapter <601> (*4*) has had several major revisions, including 1) addition of APSD measurements for nasal aerosols and sprays; 2) removal of Marple-Miller impactor (Apparatus 2) and Multi-Stage Liquid Impinger (Apparatus 4) for APSD measurement; and 3) separation of its data presentation section as <1604> (*13*). Originating in the work by the Product Quality Research Institute (PQRI), <1603> (*10*) was published in 2021 to ensure the maintenance and quality of the cascade impaction equipment. In 2022, <601> (*4*) was revised in *PF* 48(5) (*15*) to provide thorough methodological clarifications in the DDU and APSD measurements including figures and tables. Finally, the joint subcommittee with the USP Statistics Expert Committee is in the process of responding to public comments made to <1604> (*11*) with additional revisions to reflect current FDA practices. Both chapter revisions are expected to appear in the *Pharmacopeial Forum* during 2022 or by the first half of 2023.

GAP ANALYSIS

Inhalation and nasal drug products have now been approved not only for local treatments of lung and nose diseases but also for treatments of systemic diseases, such as diabetes, schizophrenia, Parkinson's disease, migraine, and osteoporosis. Recognizing the need to address gaps in the compendial framework, the EP-NAPPT Inhalation and Nasal Drug Product Subcommittee reviewed these general chapters and their revisions by the USP Expert Subcommittee as well as recent scientific literature on performance testing for inhalation and nasal drug products from a compendial perspective. In addition, the EP-NAPPT Subcommittee also considered the FDA's Generic Drug User Fee Acts Amendments (GDUFA) program and its funding projects to identify more efficient approaches to test bioequivalence (BE) for approval of generic inhalation and nasal drug products (*16*). Following its development by the EP-NAPPT, the Inhalation and Nasal Subcommittee of the USP Expert Committee then reviewed and agreed to this gap analysis.

In Vivo-Predictive Lung and Nose Delivery Testing

For inhalation drug products, the *USP–NF* stipulates only the measurements of DDU and APSD in <601> (*4*) as performance tests (Table 2). In addition to the emitted dose, the total lung dose (TLD) and the fine ("respirable") particle dose (FPD) and/or fraction (FPF) are typically determined from the APSD profiles, alongside the mass median aerodynamic diameter (MMAD) and the measure of spread, e.g., geometric standard deviation (GSD), as described in chapter <1604> (*11*). While these methods were originally intended to ensure product quality, the TLD and FPD or FPF would become clinically meaningful, if predictive of in vivo lung delivery and deposition in humans. However, the 90-degree USP induction port is geometrically far simpler than the internal geometry of the mouth and throat of humans. Moreover, no patients inhale drug aerosols at a fixed inspiratory flow rate, as used in the DDU and APSD measurements (Table 2). Hence, use of in vivo-mimicking mouth-throat (MT) models and/or inspiratory maneuvers (inspiratory flow-time profiles) has been assessed as an alternative to better predict in vivo lung delivery, deposition, and their variations (*17–20*). A variety of "realistic" MT models differing in material and geometry/size (Figure 1) and inspiratory flow profiles of healthy and lung disease [e.g., chronic obstructive pulmonary disease (COPD)] subjects (Figure 2) have been proposed and tested (*18–20*). Even so, improved in vitro-in vivo correlations (IVIVCs) are yet to be formally acknowledged, presumably due to limited and rather imprecise in vivo lung delivery and deposition

Table 2. Gap Analysis and Recommendations by USP EP-NAPPT: USP–NF Performance Tests for Inhalation (Inh.) Drug Products

Dosage Form	Current Performance Test	Limitations of Current Performance Test	Analytical Challenges	Possible Alternatives or Surrogates	Limitations of Possible Alternatives	Recommendations
Inh. aerosol (suspension and solution); and inh. spray	<601> DDU (App- A); APSD (impactor)	• Performance measures (TLD, FPD/FPF, MMAD, and distribution) are not predictive of in vivo lung delivery, deposition, and their variations • Drug release / dissolution is not a subject of performance test[a] • Methods for IVIVC / IVIVR evaluation are not certain	• The USP induction port and the fixed inspiratory flow rate are "not realistic" • In vivo lung delivery and deposition by imaging are highly variable for use in IVIVC / IVIVR • Whether drug release/ dissolution affects in vivo performance is yet to be established[a]	• Use of in vivo-mimicking MT models and inspiratory maneuvers may enable better in vivo prediction • In vivo-relevant respirable aerosol release / dissolution test may enable better prediction of in vivo local and systemic exposure and their changes[a] • Model-based analysis (e.g., PBPK modeling) may be useful to identify critical attributes	• In vivo-predictive performance measures are uncertain • Imprecise in vivo lung delivery and deposition may preclude IVIVC / IVIVR • In vivo predictive release / dissolution test and model-based analysis are work-in-progress; their need is still being debated[a]	• In vivo-predictive MT model and inspiratory flow profiles are to be developed for DDU and APSD tests • In vivo predictive aerosol drug release / dissolution test is to be rationalized and established[a] • Use of the performance measures in modeling and simulation would be a desired goal
Inh. powder	<601> DDU (App-B); APSD (impactor)					
Inh. solution; solution for inh.; (Drug) for inh. solution	<1601> Rate, total mass, and APSD of nebulized aerosols					
Inh. suspension	<1601> Rate, total mass, and APSD of nebulized aerosols; primary PSD					

[a]*Not applicable for Inh. Solution; Solution for Inh.; and [Drug] for Inh. Solution.*

data in humans (Table 2). Scintigraphy-based imaging enables direct assessments of aerosol drug delivery to, and deposition within, the lungs of humans (*21*). However, inter-subject variability of whole and regional lung depositions [e.g., central-to-peripheral (C/P) ratio] is large (up to 80% of relative standard deviations), in part attributed to natural variability of airway geometry (*18, 9, 21*). By contrast, pharmacokinetics (PK)-based prediction of whole and regional lung depositions has been exercised through various PK modeling analyses including physiologically based PK (PBPK) modeling, as discussed in the section below. Even so, such PK model- predicted lung delivery and deposition have yet to be used as reference in vivo human data to validate and establish the methods of in vivo- predictive DDU and APSD measurements. Thus, in vivo-predictive DDU and APSD measurements are useful as in vitro performance tests for inhalation drug products; however, the issue seems to be rather a lack of relevant in vivo human data to properly assess IVIVCs (Table 2).

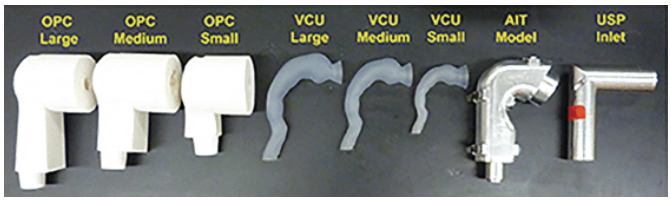

Figure 1. Various "realistic" mouth-throat (MT) models developed to test inhalation drug products, alongside the USP induction port (inlet), for DDU and APSD measurements. OPC, Oropharyngeal Consortium; VCU, Virginia Commonwealth University; AIT, Alberta Idealized Throat. Adapted from (18) with permission of the publisher.

For nasal drug products, DDU and APSD measurements are also performance tests in the *USP–NF* (Table 3). However, it is questionable whether APSD measurements with cascade impactors are valid as a product performance test, recognizing that the majority of particle/droplet size from nasal drug products are ≥10 µm, which exceeds the size measurable with compendial cascade impactors (*22, 23*). Rather, it would assess lung penetration as an off-target, if particles/droplets escaping from nasal deposition accurately enter the cascade impactors. Clearly, however, the 90-degree USP induction port would not capture drugs deposited in the nose; and patients never take drugs from nasal products at a fixed inspiratory/breathing rate (Table 3). Therefore, if the assessment of lung penetration continues to be needed, in vivo-relevant nose-throat models and inspiratory/breathing profiles are to be developed for this cascade impactor-based method. Alternatively, nasal cavity cast models can be used (Table 3). Approximately 40 anatomically relevant nasal cavity cast models that differ in material, modeling process, and geometry/size have in fact been tested by virtue of direct assessments of nasal delivery and deposition from products (*22, 23*). However, to date, no nasal cast model has been endorsed for use in regulation, as IVIVCs remain unproven (*22*). Like lung data, in vivo nasal deposition data in humans are rarely available and, if any, highly variable for use in IVIVC (*22*). Besides, in vivo-relevant inspiratory/breathing flow was not incorporated in the majority of the studies; how to determine and compare whole and regional nasal depositions is uncertain; and the regions of interest within the nasal cavity (e.g., turbinates, maxillary sinuses, and ethmoid regions) for clinical implications are hardly set. Even so, this approach (i.e., a nasal cast model with use of the in vivo-relevant inspiratory/breathing profiles) may be more meaningful as a performance quality test for nasal drug products (Table 3).

Fast Particle/Droplet Size Testing

Use of laser diffractometry (LD) to measure particle/droplet sizes and their distributions is described in <601> for nasal aerosol and spray drug products (Table 3), but

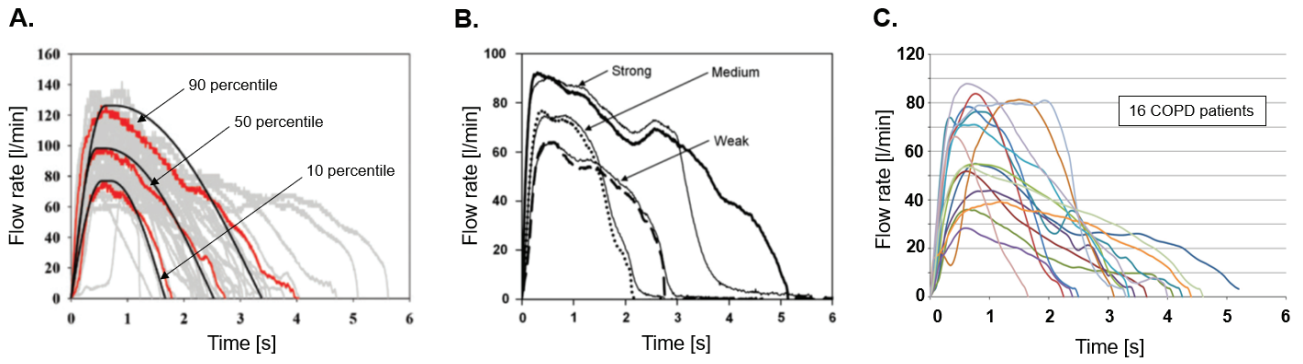

*Figure 2. Selected inspiratory flow rate vs. time profiles used to test inhalation drug products for DDU and APSD measurements. **A.** The 90th, 50th, and 10th percentiles were obtained from 20 healthy adults (18); **B.** "Strong", "Medium", and "Weak" profiles were the 95th, 50th, and 5th percentiles obtained from 74 healthy adults (19); and **C.** each inspiratory profile was obtained from individual COPD patients (20). Although adapted from (18-20) with permission from the publishers, these figures were redrawn by USP, partly since the Subcommittee believed the y-axis ticks on Fig. 2C was mislabeled in (20).*

Table 3. Gap Analysis and Recommendations by USP EP-NAPPT: USP-NF Performance Tests for Nasal Drug Products

Dosage Form	Current Performance Test	Limitations of Current Performance Test	Analytical Challenges	Possible Alternatives or Surrogates	Limitations of Possible Alternatives	Recommendations
Nasal aerosol; nasal spray (suspension and solution)	<601> DDU (App-A); P/DSD[a] (laser diffraction) or APSD (impactor)	• Performance measures (delivered dose, aerosol / droplet size, and distribution) are not predictive of in vivo nose delivery, deposition, and their variations SP-PG[b] is a quality test, but not implicated with performance • Drug release / dissolution is not a subject of performance test[c] • No performance test is listed	• The USP induction port and the fixed inspiratory / breathing flow rate are "not realistic" • In vivo nose delivery and deposition are rarely available and highly variable for use in IVIVC / IVIVR • P/DSD does not measure size of the drug but the formulation[c] • Whether SP-PG and aerosol drug release / dissolution affect in vivo performance is yet to be established	• Use of in vivo-mimicking inlet port and inspiratory / breathing profiles in APSD test may enable better prediction of lung penetration as an off-target • Nasal cast model may enable direct assessments of in vivo nose delivery, deposition, and their variations • MDRS measures drug-specific size and its distribution in nasal suspension, which may be in lieu of a clinical bioequivalence study[c] • SP-PG may be an attribute for in vivo performance • In vivo-relevant drug release / dissolution test may enable better prediction of in vivo local and systemic exposure and their changes[c] • Model- based analysis (e.g., PBPK modeling) may be useful to identify critical attributes	• In vivo predictive performance measures are uncertain • No nasal cast model has been endorsed for use in IVIVC / IVIVR • Imprecise in vivo nose delivery and deposition may preclude IVIVC / IVIVR • MDRS may not be sensitive to the in vivo performance changes; delivery and deposition-dependent outcomes are not examined[c] • SP-PG, in vivo-predictive release / dissolution test and model-based analysis are work- in-progress; their need is still being debated[c]	• In vivo- predictive inlet port and inspiratory / breathing profiles are to be developed for DDU and APSD tests • Nasal cast models need to be examined for regulatory use • MDRS is to be methodologically validated as a performance test[c] • More systematic investigation would be needed to identify critical attributes for nose deposition, including SP-PG • In vivo-predictive release / dissolution test is to be rationalized and established[c] • Use of the performance measures in modeling and simulation would be a desired goal
Nasal powder	<601> DDU (App- B); APSD (impactor)					
Nasal solution	-					

[a]*P/DSD: Particle/droplet size distribution.*
[b]*SP-PG: Spray pattern and plume geometry.*
[c]*Not applicable for nasal spray (solution) and nasal solution.*

not for inhalation drug products (*2*). While the method is much simpler, faster, and less labor-intensive than cascade impaction, careful methodological validation is essential to ensure that the measurements accurately reflect the distribution of drug mass in each size, as delivered to, and deposited within, the lung and the nose (Table 2) (*3, 24, 25*). In reality, however, the method measures the size distributions of particles/droplets that are not necessarily those of drugs due to the possibility of heterogenous drug compositions among the particles/droplets (Table 2 and Table 3). For inhalation aerosols—metered-dose inhalers (MDIs)—drug aerosol particle formation upon actuation is not instantaneous but rather dynamic due to a need for evaporation of propellants and volatile co-solvents (e.g., ethanol), if any. Thus, a location for laser diffraction (LD) sampling from aerosol emission of the products should be rightfully chosen with a proper rationale. Meanwhile, many inhalation powders—dry powder inhalers (DPIs)—formulate physical admixtures of drug and excipients (e.g., lactose); however, size distributions are reported without their distinction, thereby requiring post-sampling data processing to obtain drug-specific size distributions.

Even so, such size distributions are those for the particles/droplets passing through the laser beam, which is just a part of those emitted from the products. Therefore, it is pivotal to ensure that such a partial sampling still represents the entire populations of the particles/droplets for the product. Finally, the LD method measures volume-based size distributions so that APSDs are processed outcomes computed with an assumption of spherical shape and an allocation of a constant density

value, irrespective of particle/droplet size. With all these taken into consideration, the LD method may not be a product performance test in regulation to replace cascade impaction and may rather be suited to screening for formulation and/or device selection during inhalation drug product development. Similar conclusions can also be drawn for the use of other fast size testing methods, such as light scattering, laser Doppler, and time-of-flight methods, although several attempts have been made toward regulatory testing applications (*24, 25*).

For nasal aerosol and spray drug products, the LD method is a *USP–NF* product performance test to measure particle/droplet size distributions "for the delivered plume subsequent to delivery under specified experimental conditions" (*2*). Generally, particle/droplet size distributions are reported with the 10th (D_{10}), 50th (D_{50}), and 90th (D_{90}) percentiles of the cumulative volume-based size distribution, alongside the span of the distribution [$(D_{90} - D_{10})/D_{50}$] and the percentages of particles/droplets in a size <10 µm (to estimate lung penetration) (*2*).

Nevertheless, as is the case for testing inhalation drug products described above, such size distributions may not accurately reflect the distributions of drug mass in each size, especially for suspension aerosol and spray drug products (Table 3) (*24*). Besides, how particle/droplet size distribution and its changes influence regional drug deposition within the nasal cavity and thus, local or systemic therapeutic or adverse outcomes, remain still uncertain (Table 3). After all, particle/droplet size distribution alone is probably not a single independent attribute for regional deposition within the nasal cavity. Spray pattern and plume geometry, orientation/angle and insertion depth of dosing should also be involved as covariates (*24*). Thus, these different measures may need to be systematically understood, with respect to their impact on regional drug deposition within the nasal cavity.

Meanwhile, morphologically directed Raman spectroscopy (MDRS) is an emerging in vitro tool that can be used with suspension nasal spray drug products (*26*). MDRS measures the size and shape of particles in sprayed suspensions using its microscopic component and identifies drug particles by Raman spectra, apart from excipient particles. By so doing, drug-specific particle size distributions can be obtained, potentially as a product performance test (Table 3). Nevertheless, it should be noted that these drug-specific size distributions are not for the assessments of nasal delivery and deposition, but of post-delivery and deposition behaviors/events, such as drug release/dissolution, uptake/absorption, and local and systemic outcomes. The MDRS data were in fact submitted in the abbreviated new drug application (ANDA) for a generic nasal spray product of mometasone furoate suspension in lieu of a comparative clinical BE study (*26*). Subsequently, the FDA revised product-specific guidance for locally acting nasal suspensions, adding recommendations for an alternative approach to BE testing using the MDRS method and other similar advanced methods (*26*). Even so, the MDRS measures drug-specific particle size and its distribution in the entire sprayed formulations, but not those in different droplet sizes sprayed from the product. Hence, the method would not examine delivery-dependent or regional deposition-dependent outcomes, such as local pharmacological actions. Clearly, more experience and evidence would be needed to identify this emerging method for usefulness and thus inclusion as a product performance test for suspension nasal drug products in regulation (Table 3).

Spray Pattern and Plume Geometry Testing

Chapter <5> (*3*) in the *USP–NF* lists spray pattern and plume geometry to assess performance of the delivery system including valve, actuator, and pump, for inhalation and nasal aerosol and spray drug products (*2*). They are characterized by imaging methods with certain outcome measures, such as angle and width of spray plume, and ovality ratio and area of section of spray (*22, 23*). However, like the LD method for size measurements, these outcome measures are based on particles/droplets, but are not necessarily specific to drugs (Table 3). Moreover, these measures have not yet been proven to influence delivery and regional deposition, more than or equivalent to DDU and APSD, especially for inhalation aerosols/sprays. In the *USP–NF*, no general chapter describes the standardized methods for these measurements, although contract-based testing services are commercially available, typically using controlled mechanical actuation and sophisticated imaging analysis. Selection of relevant outcome measures and their acceptance criteria that provide discriminatory capability among products are also in need. Finally, inspiratory/breathing condition is generally absent in these tests, differing from a condition of actual use by patients. In patients, inhalation aerosols/sprays are taken with deep inspiration, and many nasal drug products also recommend inspiration during administration with or without one nostril closed.

For nasal drug products, spray pattern and plume geometry have both been shown to influence regional deposition within the nasal cavity (*21–23, 26*); however,

opinions in the literature differ. A nasal spray product with a wider plume angle (a greater area of spray) resulted in greater deposition in the anterior region of the nasal cast model than that with a narrower plume angle (*27*). On the other hand, wider plume angles paradoxically led to increased posterior nasal deposition for another nasal spray product (*28*). In these studies, however, whether other delivery properties, such as aerosol/spray size and its distribution, and dosing orientation/angle and insertion depth, remained unchanged to properly examine the impact of plume angle is uncertain. In fact, computational fluid dynamics simulation failed to show effects of plume angle on regional deposition within the nasal cavity (*29*). Therefore, it is highly likely that spray pattern and plume geometry are each not a single independent attribute. As discussed above, other delivery properties (aerosol/spray size and its distribution, and dosing orientation/angle and insertion depth) should also be involved as covariates, and therefore, systematic investigation is needed to identify their validity as a product performance test in regulation (Table 3).

Drug Release/Dissolution Testing

In the *USP–NF*, the performance tests for inhalation and nasal drug products are focused on the characterization of drug delivery and deposition from devices to the lung and the nose; and testing of drug release/dissolution is not stipulated, unlike the situation for oral drug products (*2*). To date, no compendial methods are available to test drug release/dissolution for inhalation and nasal drug products (Table 2 and Table 3). In 2008, the Inhalation Ad Hoc Advisory Panel for the USP Performance Tests for Inhalation Dosage Forms concluded through a literature review that compelling evidence suggesting a need for drug release/dissolution tests could not be found (*30*). It was noted though, that a USP standard for assessing drug release/dissolution for inhalation dosage forms may be considered in the future, if scientifically warranted, as a result of the development of novel products with modified or controlled drug release/dissolution (*30*). An interest then emerged in light of the BE assessment for approval of generic inhalation products of locally acting drugs, specifically poorly soluble corticosteroids (*16*). During GDUFA I, FDA supported several research projects to explore in vivo-predictive aerosol particle dissolution test methods for inhalation drug products as potentially more efficient in vitro approaches for BE demonstration (*16*). Attempts and discussions have also been active over the years among scientists and their consortiums and working groups toward the development and establishment of in vitro drug release/dissolution testing for inhalation drug products (*31–34*). Even so, as our knowledge is still limited with respect to the relationship between aerosol drug release/dissolution and clinical therapeutic or safety outcomes, the need and establishment of in vivo-predictive discriminatory drug release/dissolution test methods for inhalation drug products are yet to be substantiated for compendial use (Table 2).

The development of in vitro drug release/dissolution test methods for inhalation drug products is an ongoing research area with an initial focus on poorly soluble inhaled corticosteroids, such as fluticasone propionate (*16, 31–34*). It is important to consider the robustness and validation of the published methodologies that would be required for a standardized performance test method. The design of the test method (e.g., use of whole or "respirable" aerosol particles, or testing under sink or non-sink conditions) and the correlation of its outcome measures with clinical performance measures should be carefully considered as an in vivo-predictive method. Generally, the methods have used either the whole formulated dose or a certain (e.g., "respirable") fraction of the dose collected using cascade impactors or customized deposition/collection apparatus (*31–35*). Modifications were also made for sample introduction to the release/dissolution test systems (e.g., use of aerosol samples collected on filters or direct sample placement in a basket) to ensure reproducible and homogenous dispersion without aggregation or floating (*31–35*). The solvent media for release/dissolution were phosphate buffer, phosphate-buffered saline, or simulated lung lining fluids, and were used with different volumes (*31–35*). Drug release/dissolution of such an aerosolized fraction is recognized to be more likely predictive of in vivo release/dissolution in the lung, although drug aerosol particles with similar aerodynamic size may still exhibit different release/dissolution upon lung deposition due to different particle morphology (*36*). In reality, drug release/dissolution is affected by many factors, such as the size of the particles (as the dissolution rate is inversely related to the radius of the particles; especially for particles within the range of 1.5–10 µm), the drug solubility, the diffusion layer thickness, and the particle shape/morphology. Upon collection, several dissolution test systems have been employed in the literature, such as two-stage impinger, horizontal diffusion cell, static dissolution cell, shaking incubator, paddle dissolution apparatus (USP Apparatus 2), dialysis membranes, flow through cell apparatus (USP Apparatus 4), Transwell system, and Franz cell system and the dissolution model integrated with deposition and cell permeation (*31–35*). Even after this active research, no release/dissolution method has been endorsed for

compendial use as of yet. By contrast, attempts to develop in vivo-predictive release/dissolution tests for nasal drug products are scarce in the literature despite their similar use for poorly soluble corticosteroids.

Nevertheless, similar factors would be expected to be of interest for consideration, while drug release/dissolution of suspension droplets may also need to be assessed for nasal suspension spray products.

Implications of aerosol particle drug release/dissolution for systemic exposure and PK have been shown for poorly soluble corticosteroids; however, their implications for clinical therapeutic and safety outcomes remain unsubstantiated (*16, 31–34*). Hence, given the current advances in local and systemic use of inhalation and nasal drug products, there is an interest in how the GDUFA II program will progress, considering BE testing for approval of generic inhalation drug products. So, whether an in vitro drug release/dissolution test is necessary for these products as well as controlled release products pursued for approval in near future is still formally undecided to date (Table 2 and Table 3).

In Vitro Product Performance and PBPK Modeling

Model-based systemic PK profile analysis has been used to identify critical drug, product, and biological/physiological attributes primarily for systemic actions (e.g., oral drug products). Among several approaches, PBPK modeling is a powerful tool, because its model is physiologically relevant and can incorporate organ-specific parameter sets for healthy subjects or patients with disease, alongside drug properties, delivery, and delivery site-specific biopharmaceutical disposition (*37*). PBPK modeling could also establish a link between in vitro product quality attributes and in vivo clinical performance by IVIVC or relationship (IVIVR). Once this link is verified, critical product quality attributes can be identified to ensure clinical safety and efficacy performances, as expected by product design. Moreover, acceptable variations of such product quality attributes without causing changes in safety and efficacy outcomes could also be examined, which would then in theory enable the establishment of their specifications.

PBPK modeling has been increasingly used for inhalation drug products to understand not only systemic but also local lung exposure of drugs, given that their primary use is for local therapeutic actions (*38–43*). Nevertheless, lung delivery and regional deposition, drug release/dissolution, and lung absorption and disposition for inhalation drug products are highly complex, which makes their interpretations via PBPK modeling extremely challenging, especially for quantitative assessments (Table 2; *38–43*). To date, many different PBPK models have been proposed and all of them have sounded sensible (*38–43*); however, use of the parameter sets derived from the compendial DDU and APSD measurements has yet to be reported. Accordingly, DDU and APSD specifications have been established in most cases, based on the data obtained by experiments with limited batches of the product, from a product quality control perspective, and thus have no implication to clinical performance due to a lack of established IVIVC or IVIVR. Clearly, however, if PBPK modeling could be verified with use of the DDU and/or APSD parameters, DDU and APSD specifications would surely become more meaningful clinically. Likewise, aerosol drug release/dissolution in the lung could be kinetically critical (i.e., rate-limiting), especially for poorly soluble drugs. However, as addressed above, to date, no in vitro drug release/dissolution method has been established to be predictive of in vivo, and thus, incorporation of drug release/dissolution kinetic processes is quite limited in the literature (*42, 43*).

In contrast, support for the use of PBPK modeling for nasal drug products in humans is still scarce in the literature (*44*). However, recognizing that this drug delivery route is used not only for local actions but also for systemic actions, and may notably be used for drug delivery to the brain (*45*), it is predicted that efforts to quantitatively understand critical attributes for efficient local, systemic or brain drug delivery will be increasing through, for example, PBPK modeling (Table 3). Even so, as is the case for inhalation drug products, whether the compendial performance measures (DDU, APSD, and droplet size distribution) and possibly drug release/dissolution measures can be incorporated in such exercises for IVIVC or IVIVR remains uncertain.

Use of PBPK modeling to evaluate bioequivalence and therapeutic equivalence for inhalation and nasal drug products is just on the horizon. While these methodologies have great potential, there are significant knowledge gaps in this area. To address these gaps, FDA has included PBPK modeling in a list of GDUFA science and research policy initiatives since 2020, with a hope to help rationalize critical attributes for product performance and specifications of compendial performance measures (*16*). Thus, there is no doubt that such quantitative rationalization is desired; however, more research should be indispensable, including model verification and sensitivity analysis.

CONCLUSION

Inhalation and nasal drug products are available in a variety of drug-device combination products (e.g., aerosols, sprays, powders, and nebulization) and are approved not only for local treatments of lung and nose diseases, but also for treatments of systemic diseases. At present, DDU and APSD measurements are the performance tests for delivery and deposition in the *USP–NF*. However, the methods are not necessarily in vivo-predictive and, for nasal drug products, may not be valid. Therefore, alternative or additional methods have been exercised, which include delivery and deposition assessments with nasal cavity cast models, fast particle/droplet size measurements (by laser diffraction and MDRS), and spray pattern and plume geometry analyses. Various drug release/dissolution test methods have also been reported as potentially performance tests for inhalation drug products (but not for nasal drug products), with a notion that clinical outcomes of poorly soluble drugs like fluticasone propionate may be compromised due to solubility and/or dissolution after delivery and deposition. Finally, use of PBPK modeling is being extended to inhalation and nasal drug products with a hope to help identify product quality attributes pivotal for local lung or systemic clinical outcomes. This *Stimuli* article is a view of the Inhalation and Nasal Drug Product Subcommittee of the USP EP-NAPPT for each of these product testing methods with a review of the up-to-date knowledge and our recommendations for consideration in compendial use, if and where appropriate. The EP-NAPPT Subcommittee would like to receive valuable comments, suggestions, and opinions from stakeholders to further discuss the outcomes of this review process in the near future.

DISCLAIMER

FDA representatives participated in the USP Expert Panel on New Advancements in Product Performance Testing and in the drafting of this article. FDA's participation in the USP Expert Panel on New Advancements in Product Performance Testing and in drafting this article should not be construed as an endorsement of the approaches outlined in this article. No official support or endorsement by the FDA is intended or should be inferred.

ACKNOWLEDGEMENTS

The authors are grateful to the following members at the USP EP-NAPPT and the Inhalation and Nasal Drug Product Subcommittee on the USP General Chapters Dosage Forms Expert Committee for providing valuable insights, discussions and suggestions to this *Stimuli* article during review: Om Anand (US FDA Office of Pharmaceutical Quality, Maryland, USA); Emmanuel Scheubel (Roche Pharmaceuticals, Basel, Switzerland); Raymond Skwierczynski (Tremeau Pharmaceuticals, Boston, MA, USA); James DeMuth (University of Wisconsin-Madison, Madison, WI, USA); Anthony Hickey (RTI International, Chapel Hill, NC, USA); Jolyon Mitchell (Jolyon Mitchell Inhaler Consulting Services, London, ON, Canada); and Guirag Poochikian (Poochikian Pharma Consulting, Derwood, MD, USA).

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