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IPAC-RS Comments on the USP Stim. Article *"Testing the In Vitro Product Performance of Inhalation and Nasal Drug Products: Views of the USP Expert Panel"* [Pharm.Forum 48(5) September 2022]

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/) carefully reviewed and discussed the USP Stim. Article "*Testing the In Vitro Product Performance of Inhalation and Nasal Drug Products: Views of the USP Expert Panel*" [Pharm.Forum 48(5), published September 2022], and would like to offer the following comments.

IPAC-RS is an international association of companies that develop and manufacture orally inhaled and nasal drug products (OINDPs). IPAC-RS seeks to advance the science, and especially the regulatory science, of OINDPs, through joint research, consensus building, development of best practices, and collaborations among stakeholders. Current member companies of IPAC-RS are listed here. The comments provided below represent the consensus of all members.

Due to the numerous concerns described below, IPAC-RS strongly recommends that USP retract the Stim. Article, to prevent any further dissemination of erroneous information and misunderstandings. As currently written, the Stim. Article has the potential to set a precedent that does not align with current scientific literature and additional sources in the field of in-vitro testing of orally inhaled and nasal drug products (both brand-named and generic). The fundamental aims of the Stim. Article are unclear. It is also not clear what the final recommendations from the Expert Panel are with respect to the methods itemized in the Stim. Article, and if they are intended for compendial use. If USP decides to proceed with this effort, we strongly recommend a coordinated process with additional experts in the field to yield an informed review/gap-analysis, prior to issuing any recommendations.

In addition to these major comments, IPAC-RS members noticed numerous editorial inconsistencies, which are not included here but would need to be addressed if the Stim. Article were to be revised.

Abbreviations:

API	Active Pharmaceutical Ingredient
APSD	Aerodynamic Particle Size distribution
CI	Cascade Impaction
DDU	Delivered Dose Uniformity
IVIVC/R	In-Vivo In-Vitro Correlation/Relationship
MDRS	Morphologically-Directed Raman Spectroscopy
OINDP	Orally Inhaled and/or Nasal Drug Product
OIP	Orally Inhaled Product
RDD	Respiratory Drug Delivery (see proceedings at **RDD Online**)

General Comments:

1. We appreciate USP's desire to stay abreast of advances in OINDP performance testing, and indeed to identify opportunities to refine pharmacopeial recommendations in this highly specialized field. That said, we must be clear that this Stim. Article falls well short of its stated goals. **We recommend the article be retracted from *Pharm. Forum*.** In its present state the article propagates misconceptions and misinformation, which has the potential to reverse progress in the field and indeed to cast doubt on the scientific and regulatory authority of the USP. As reflected in the individual comments provided below, most of the topics visited by the authors are treated in a cursory manner, and numerous points made in the article are inconsistent with the experiences of the drug development community and indeed with the scientific literature. If the USP decides to proceed with this effort, we strongly recommend that USP engage the experts required to yield an informed review/gap-analysis, prior to issuing any recommendations.

2. In June 2021, USP provided notice that USP and the Small Molecules 5 Expert Committee intended to revise multiple inhalation drug product monographs to remove the performance quality tests. Specifically, the Expert Committee intended to remove both the *Aerodynamic Size Distribution* test, also known as *Particle Size Distribution by Cascade Impaction* test, and the *Delivered Dose Uniformity* test from the pertinent monographs (See Inhalation Drug Product Monographs: Removal of Performance Tests | USP-NF (uspnf.com)). That action was due, in part, to the FDA suggestion that the inclusion of detailed performance tests in inhalation drug product monographs added a regulatory burden that potentially impeded the approval of generic drug products already in development. The current Sim. Article appears to be at odds with these aims.

3. The Stim. Article refers to current DDU and APSD methods and their originally intended use to ensure product quality, stating that they lack clinical relevance. Please note, however, that while currently existing methods cannot serve as surrogates of clinical outcomes, they are simple, highly sensitive/discriminatory, robust, reproducible and cost-effective, and as such they have a useful role to play in a product's lifecycle, from early screening, development, and control. While advanced modifications to existing methods (realistic throats, breath profiles, etc.) and additional complimentary techniques (such as dissolution, MDRS, and in-silico modelling) can help to bridge the understanding gap between in-vitro and clinical outcomes, they do introduce additional complexity, variability, and cost. Replacing existing methods in <601> with these new methods could have profound consequences for all stakeholders. It is highly recommended that existing methods be retained in <601> for quality control purposes, as they remain fit for purpose and ideally suited to this application. An informational chapter (similar to <1601>, <1602>, <1603> and <1604>) would be the most helpful way to propose advanced methods and to assist stakeholders in improving the clinical relevance of in-vitro tests in support of bioequivalence studies.
4. Among the stated objectives of the Stim. Article in Pharm. Forum 48(5) are an *evaluation of the current compendial product performance tests* and a *gap analysis of the current status of product performance testing in USP.* To this end, the subcommittee should also address the status of cascade impaction metrics commonly used for quality control of OIPs. There is a growing body of literature demonstrating that Stage Groupings and Fine Particle Dose each struggle to make batch-disposition decisions based on differences in inhaler performance. Fine Particle Dose is redundant with impactor-sized mass and is thus remarkably insensitive to changes in the aerodynamic size of the emitted aerosol. Stage Groupings also struggle to control changes in aerodynamic size, and the multiplicity introduced via their conventional application significantly degrades the user's decision-making ability. In each case, despite a tremendous investment in testing, control of product performance is limited by the choice of metric. This is a significant fundamental concern, highly relevant to practitioners of the in-vitro performance tests purportedly assessed in this document. Failure to acknowledge and address these known

gaps (and indeed the available alternatives) in favor of trendier topics diminishes the credibility of this assessment.

5. The premise of the discussion on the performance testing for inhalation and nasal drug products appears to be that compendial methods should be driven by an IVIVC/R. While this may be an ideal, it needs to be accepted that the primary purpose of a compendial method is to provide quality control. It is proposed that the existing compendial methods are fit for that purpose and that differences observed in the *in-vitro* results using such methods are likely larger than the corresponding impact on the clinical endpoint.
6. The overall message of the Stim. Article seems to be that current compendial tests are not fit for purpose. For those working with these products on a regular basis, experience shows that the tests are discriminatory and broadly serve their purpose as they are. It would seem sensible to maintain this but provide guidance on methodology for better understanding or characterization of the product rather than for product release.
7. Within the article, MDRS is only discussed in the context of nasal product assessment. MDRS should also be considered for broader application (i.e., other OINDP dosage forms) to ensure that any future recommendations for development tools (not product release etc.) are reasonably comprehensive.
8. The Stim. Article does not clearly identify if the proposed methodologies are intended to be applied for one-time characterization, or routine quality control, or to demonstrate bioequivalence, or all of the above. As such, this article will cause major confusion for sponsors and inspectors alike, and will proliferate misinterpretations of the various tests, with long-ranging negative consequences for all developers of inhaled and nasal drug products.
9. The Stim. Article references over 40 nasal cast models made with various processes. Guidance should be provided on selection and validation of these models before their incorporation into the USP. Clarification is also needed if nasal cast models will need validation for in-vivo testing.
10. Key dissolution method attributes should be provided to guide appropriate methodology.
11. As nasal powders are growing in scope, clarification of methodology should be included—especially in the context of DDU.

12. MDRS limitations include the inability to measure particles below 1 µm, which may have impact in in-vivo absorption as listed in Table 3. One recommendation could be to use an orthogonal technique such as dissolution.
13. Spray Pattern remains an objective tool to detect device/formulation flaws at a production level.
14. It is not clear what the final recommendations are from the Expert Panel with respect to the methods for compendial use. It's unclear from the document what the fundamental aims of the article are. There appears to be a discussion in relation to tests that will effectively become mandatory, and also aspects that would form part of the general information chapters. It is not apparent which tests / approaches would fit into which category, and so the 'worst case' is that some extremely challenging methodologies would require to be verified / validated, which is currently not possible because no standard approaches exist for a number of methods. If the expectation is that the discussed tests will be shown to be predictive of in-vivo data, how could that be verified in the compendial sense? The goal of the Stim. Article is unclear.
15. It would be much easier (and much less time consuming) to provide comments on this Stim. Article if it were possible to cut/paste text directly from the pdf to the comment document. The "UNOFFICIAL CONTENT" watermark on the document makes this impossible and therefore anyone contributing comments has to manually transcribe any original text they wish to reference. If the subcommittee can find a way to avoid this in future Stimuli Articles, it might help them receive feedback from a broader audience. Numbering the pages (and possibly even the lines) would be another helpful addition.

Specific Comments:

Page numbers refer to the pdf version downloaded from USP–NF/PF (uspnf.com)

Location	***Original Language***	**Comment**	**Comment Type**
Page 1 Current USP Framework & Scope	*Chapter <601> has most widely been recognized and used to assess drug delivery to, and deposition within, the lung and nose from the products.*	This statement implies the acceptance of in-vitro / in-vivo relationships for these tests as described in the pharmacopeia, which is not the case. There is very little evidence of correlations between APSDs as determined by cascade impaction and "drug delivery to, and deposition within, the lung". USP should be careful not to casually propagate this misconception.	Supports Retraction
Pages 1-2 Current USP Framework and Scope	*Chapters …<1601>, …<1602>, …<1603> and …<1604> are informational.*	Is <1604> part of the current USP framework? Our understanding is that this was a proposed chapter for the future, and that it was in the midst of significant revision. It is confusing to the reader if this is portrayed as part of the current framework, but then cannot be located for review.	Supports Retraction
Page 3 Gap analysis In-vivo predictive lung and nose delivery testing	*Moreover, no patients inhale drug aerosols at a fixed inspiratory flow rate, as used in the DDU and APSD measurements*	This statement contains a factual error. For DPIs, APSD testing is generally not actually tested at a "fixed inspiratory flow rate". It is widely acknowledged that there is a "rise time" associated with a given CI method, and that the flow rate is changing as the dose is aerosolized and drawn into the impactor. This topic was recently reviewed in remarkable depth by Ruzycki *et. al.*: *Adv. Drug Del. Rev.* 189 (2022) 114518.	Supports Retraction

Page 3 Gap analysis In-vivo predictive lung and nose delivery testing	*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.*	We take issue with the vague and unsupported claim that the in-vivo predictive measurements "are useful." What does this mean, and what support is there for this claim? If there is insufficient in-vivo data to assess the in-vitro/in-vivo correlation, how can we know whether the in-vitro portion is "useful." The "la*ck of relevant in-vivo human data*" is not for the lack of trying. Efforts to establish IVIVCs for inhaled and nasal drugs have been pursued by many groups, for many years, and discussed in multiple publications (which, however, the authors seem to be unaware of).	Supports Retraction
Page 4 Table 2	*In-vivo predictive aerosol drug release/dissolution test is to be rationalized and established.*	We find this recommendation confusing. If aerosol dissolution testing has yet to be rationalized, why does the subcommittee recommend that such testing be established?	Supports Retraction
Page 4 Gap Analysis	*Besides, in-vivo-relevant inspiratory/breathing flow was not incorporated in the majority of the studies…* *And* *…with use of the in-vivo relevant inspiratory/breathing profile*	In our experience, the use of realistic breath flow profiles has no discernable impact on nasal cast deposition. This observation is consistent with expectations given the size of the particles/droplets, their velocity, and the ability of inspiratory/expiratory breaths to bypass the nostril in use. This is also consistent with referenced article 27 (Guo 2005), which explicitly concludes: "Changes in breathing profiles did not affect aerosol deposition in this nose model."	Supports Retraction
Gap analysis for nasal drug products.		It is clearly understood that APSD measurements for nasal sprays are intended to measure the fine particle fraction as an undesirable characteristic to be controlled. In this context, it is questionable whether the use of in-vivo relevant models would significantly improve the quality of the measurement.	Revision
Table 2		In table 2, A clearer distinction should be made for each of the dosage forms, and a more specific gap analysis made for each.	Major Revision
Tables 2 and 3		Tables 2 and 3 are incredibly cumbersome to read. The purpose of a table is generally to facilitate communication, but the bizarre formatting asks a lot of the reader. This is simply the wrong format for communicating this information to readers.	Revision

Page 4	*Alternatively, nasal cast models can be used*	Please clarify the use of a pre-separator with use of casts or realistic nasal models. Current methodology employs an induction port and pre-separator	Major Revision
Page 5	*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*	Please include a flowrate of 0 LPM (i.e. no flow rate) in this section. This is to account for when a patient is unconscious or simply retaining his/her breath	Revision
Page 5 Fast Particle/Droplet size testing		There seems to be a pre-existing bias against non-CI methods. Far more attention is paid to the shortcomings of laser diffraction-based particle sizing than to those of APSD determination by inertial impaction. Most people who test inhaled products recognize laser diffraction as a powerful surrogate for inertial impaction. Cascade impactor methods are notoriously error-prone and labor intensive. Consequently, CI yields a variable, low-resolution approximation of the APSD from a tiny sample size. Moreover, without adequate characterization of the rise time, meaningful interpretation of inertial impactor stage cut-off diameters is tricky at best. So why does this assessment only list the negatives associated with laser diffraction?	Major Revision
Page 6 Spray Pattern and Plume Geometry Testing	*A nasal spray product with a wider plume angle resulted in greater deposition in the anterior region… 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).*	We would encourage the authors to consider whether highlighting just two articles with apparently contradictory findings offers a good representation of what is known about the impact of plume geometry on regional deposition.	Supports Retraction

Page 6 Spray Pattern and Plume Geometry Testing	*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.*	If this comment refers to references 26 and 27, the experimental portions of each manuscript actually provide much of this detail. We would encourage the authors to make sure that this comment is a fair reflection of these two works.	Supports Retraction
Page 6 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 nose…*	This is factually incorrect. The in-vitro performance tests for OINDPs in USP-NF do not characterize delivery to the lung and nose, but instead are used as product quality control tests.	Supports Retraction
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;*	This implies the acceptance of in-vitro / in-vivo relationships for these tests as described in the pharmacopeia, which is not the case.	Supports Retraction
Section 2 Page 7 Fast Particle/Droplet Size Testing	*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.*	This sentence lacks logic. If these "size distributions are not for the assessments of …delivery and deposition", how can they have anything to say about "uptake/absorption, and local and systemic outcomes"? For a patient taking the drug, its uptake, absorption and outcomes surely begin with, and depend on, delivery and deposition?	Supports Retraction

Section 4 drug release / dissolution testing Page 8 in-vitro dissolution	*No release/dissolution method has been endorsed for compendial use as of yet.*	As the Stim. Article itself shows, there are so many methods and so much variability in experimental conditions that extracting usable information is exceedingly challenging. The presentation needs to be better organized in any future revision/re-write. A Pharm. Forum article is expected to recommend what would be the next step. The Stim. Article seems to suggest that in-vivo predictive dissolution would be the next step but that is misleading because there are currently no good, standardized or generally applicable dissolution methods to characterize API and its formulation.	Major Revision
Section 4 drug release / dissolution testing	*Even so, as our knowledge is limited with respect to the relationship between aerosol drug release….compendial use (Table 2).*	The drug dissolution has been mentioned. However, in-vivo predictive deposition should have far more impact to clinical outcome and safety issue than the dissolution.	Major Revision
5. in-vitro product performance and PBPK modeling page 8 line 5 from the bottom	*Thus have no implication to clinical performance due to a lack of established IVIVC or IVIVR.*	DDU and APSD have some implication to in-vivo performance or in-vivo – in-vitro correlation/relation. What is missing in IVIVC and IVIVR in inhalation space is "how patient inhales the product (in DPI case)" -- this creates an enormous difference in drug delivered into the lung. This should be mentioned in IVIVC/IVIVR. Additionally, there is "a lack of established IVIVC or IVIVR" because there is no really proven method to predict or observe how much and where drug product/particles would be delivered into the lung. Without validated methods, IVIVC and IVIVR cannot be established.	Major Revision
In-vitro Product Performance and PBPK Modeling	*however, use of the parameter sets derived from the compendial DDU and APSD measurements has yet to be reported.*	This is not true. For example, see the following reference: Per Bäckman and Bo Olsson, RDD 2020: "Pulmonary Drug Dissolution, Regional Retention and Systemic Absorption: Understanding their Interactions Through Mechanistic Modeling"	Supports Retraction