The Inhalation Ad Hoc Advisory Panel for the *USP* Performance Tests of Inhalation Dosage Forms

Vivian A. Gray (Co-Chair), Anthony J. Hickey, PhD, DSc (Co-Chair), Patrick Balmer, PhD, Neal M. Davies, PhD, RPh, Craig Dunbar, PhD, Thomas S. Foster, PharmD (Chair, Biopharmaceutics Expert Committee), Bo L. Olsson, PhD, Masahiro Sakagami, PhD, Vinod P. Shah, PhD (Scientific Liaison), Michael J. Smurthwaite, BSc, John M. Veranth, PhD, and Kahkashan Zaidi, PhD[*]

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ABSTRACT The *US Pharmacopeia* (*USP*) contains standards for tests, procedures, and acceptance criteria for inhalation dosage forms that are administered orally and intranasally. Product quality and performance tests are concerned primarily with the assessment of drug delivery and deposition in the respiratory tract. This *Stimuli* article evaluates the scientific rationale, if any, for in vitro dissolution tests for inhalation dosage forms. Studies that determine the profiles and kinetics of dissolution for inhaled therapeutics have been performed, but a literature review could not find compelling evidence suggesting that such dissolution testing is kinetically and/or clinically crucial for currently approved inhalation drug products. Even so, because of the possible development of novel inhalation products with modified or controlled dissolution and release, a *USP* standard for assessing dissolution of inhalation dosage forms may be considered in the future if scientifically warranted.

INTRODUCTION

This *Stimuli* article provides information about ongoing activities relevant to *USP* performance tests for inhalation dosage forms. The activities are proceeding in the Advisory Panels originally formed in connection with the Council of Experts Biopharmaceutics Expert Committee and the Aerosols Expert Committee during the 2006–2007 period. This *Stimuli* article represents a consensus of the Inhalation Ad Hoc Advisory Panel of the 2005–2010 cycle for *USP* performance tests for inhalation dosage forms.

BACKGROUND

Inhalation dosage forms are quite common and are well accepted in the treatment of local nasal and lung diseases such as allergic rhinitis and asthma. Moreover, following the 2006 approval of inhalable insulin by the Food and Drug Administration (FDA), the pulmonary route is receiving considerable attention as a portal for the delivery of macromolecular proteins and peptides to the systemic circulation. Generally, dosage forms can be categorized based on the region of the body to which the active pharmaceutical ingredient (API) is first delivered by the dosage forms (*1*). In this context, the lung and nose are assigned for inhalation dosage forms as the first tier, as shown in *Figure 1*. The second tier is a grouping of the formulations based on physical forms such as gases, liquids, and solids. These include medical gas, liquid and powder nasal sprays, and aerosols from nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs). Finally, the type of the API dissolution or release from the formulation constitutes the third tier, yet only concerning certain products delivering and/or depositing the APIs in semi-solid and solid forms. Regulatory and compendial test procedures for inhalation dosage forms have been developed to ensure products' optimal quality and performance. The numerous quality control tests applied to inhaled dosage forms appear—at least at the present time—to characterize adequately the products' in vivo or clinical performance. These are described below and are published in the Physical Tests and Determinations section of the General Chapters in *USP,* particularly in *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ and *Uniformity of Dosage Units* ⟨905⟩ (*2*).

[*] Correspondence should be addressed to: Kahkashan Zaidi, PhD, Senior Scientist, Documentary Standards Development, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8269; kxz@usp.org.

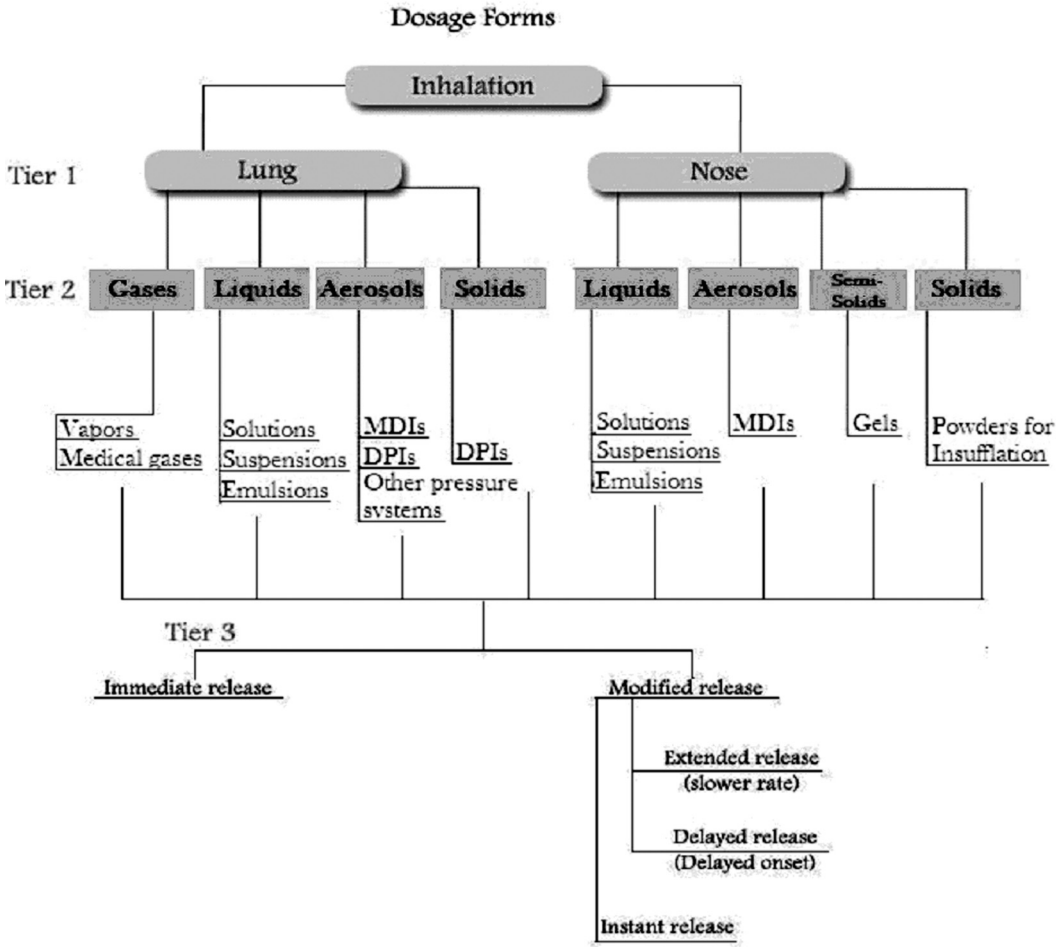

Figure 1. Categories and Tiers of Inhalation Dosage Forms.

Product Quality Tests. Product quality tests are intended to assess attributes such as identification, dose content uniformity, pH, minimum fill, alcohol content, water content, leachables, impurities, and microbial limits to verify the quality of product attributes that could affect drug product performance with respect to lung or nasal delivery and deposition.

Product Performance Tests. Product performance tests are designed to assess inhalation products, primarily with respect to lung or nasal delivery and deposition. Such tests include delivered dose, aerodynamic particle size distribution, droplet size, plume geometry, and spray pattern. Currently developed performance tests do not include the assessment of drug dissolution and/or release following delivery and deposition, which may potentially (as is the case with many solid oral dosage forms) affect the clinical performance of drug products.

BIOPHARMACEUTICAL CONSIDERATION: DISSOLUTION

Dissolution testing is a well-established aspect of oral dosage form product performance testing, especially for solid oral dosage forms, because APIs for these drug products must be dissolved to permit absorption and thus therapeutic action. Some early work with digitalis alkaloids, chloramphenicol, tetracyclines, phenylbutazone, and prednisone alerted manufacturers and regulatory agencies about the need to use dissolution testing to ensure proper in vivo performance of these and other products and has led to the requirement for dissolution testing of other products in *USP* (*3–10*). This early work provided clear evidence that dissolution of certain products was critically linked to in vivo performance. In vitro dissolution tests for solid oral dosage forms are often used to guide formulation and product development as well as to ensure quality control during product manufacture, for example, in establishing in vitro–in vivo correlations between innovator

and generic products and/or demonstrating equivalence after certain changes in drug product formulation and manufacturing (*11*).

Moreover, as manufacturers began to manipulate drug release via modified or controlled release mechanisms they have sought to achieve additional therapeutic benefits, e.g., less frequent dosing, prolonged duration of action, and/or reduced incidences of adverse effects. Dissolution testing has been crucial in helping formulators characterize the dissolution profiles of modified-release solid oral dosage forms and also has become a key regulatory tool. Several *USP* General Chapters have played a central role in these developments, including *Dissolution* ⟨711⟩, *Drug Release* ⟨724⟩, *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩, and, most recently, *The Dissolution Procedure: Development and Validation* ⟨1092⟩ (*2*).

For inhalation drug products, the first and most critical step in clinical performance involves the delivery of the API from the container or package and its deposition in the nose or lung. If the particles are too large or too small they will not reach or be deposited within the appropriate target organs. Because of this limitation for most conventional inhaler products (e.g., MDIs and DPIs), only a minor portion of the drug emitted from a unit-dose dispenser can be deposited within the target organ. This may be a primary reason that the current *USP* test procedures for inhalation products have not addressed product performance and instead typically have focused on delivered dose and aerodynamic particle size distribution. Nevertheless, before they can be available for absorption and therapeutic actions, particles of inhaled therapeutics must be dissolved in a limited volume of the fluids that line the respiratory tracts. Indeed, two of the most popular inhalation dosage forms are MDIs and DPIs that target the lung, and both are likely to deliver APIs onto the lung surface in a solid or semi-solid form, thereby requiring dissolution prior to lung uptake or absorption. Evidence has suggested that mean absorption times of different small molecular weight solutes may range from a few minutes to hours (*4*). This hypothetically suggests that for some drugs in certain inhalation dosage forms the kinetics of dissolution is crucial because it determines the rate of absorption and thus therapeutic activity. In theory, dissolution kinetics can be manipulated and engineered, even for small particles generated from inhalation dosage forms, if formulators change solubility, specific surface area, particle shape, surface structure, crystal habit, or other factors. Formulators also have access to novel formulation techniques including liposomes, polymeric micelles, and microspheres (*12*).

A counterargument suggests that inhaled particles are so small that their dissolution rate may be rapid because of their large surface area to weight ratios. Because the dissolution conditions for inhaled particles and aerosols are not known with certainty even though they may affect drug actions on lung and other tissues, as well as drug disposition (i.e., absorption), the Inhalation Ad Hoc Advisory Panel was called upon to assess the importance or necessity of dissolution test procedures for inhalation dosage forms as a possible performance test. At this point the Inhalation Advisory Panel does not officially advocate a dissolution performance test.

THEORY OF DISSOLUTION

Dissolution is defined as the process by which a solid enters a solvent in solution, and the process can be kinetically controlled by the affinity between the solid and solvent (i.e., interfacial solid-to-liquid reaction) and/or diffusion of the dissolved solid from the solid surface across the aqueous diffusion boundary layer. Accordingly, phase transfer kinetics is generally described by a mass transfer–based equation or more commonly by the Noyes–Whitney equation:

$$dM/dt = kS \times (C_s - C_b) \qquad [1]$$

$$dM/dt = DS/h \times (C_s - C_b) \qquad [2]$$

where dM/dt is the dissolution rate, k is the mass transfer coefficient, S is the surface area of dissolution, C_s is the solubility in the bulk phase, C_b is the concentration of dissolved solid in bulk phase at time t, D is the diffusion coefficient, and h is the thickness of the aqueous diffusion boundary (or stagnant or unstirred) layer. The dissolution rate of drug particles is determined by the rate at which solvent–solid forces of attraction overcome the cohesive forces present in the solid. The rate at which a substance dissolves in a liquid to form a solution is governed by physical parameters such as surface area of the substance at a given time during the process of dissolution, the shape of the substance, the characteristics of the solid–liquid interface, and the solubility of the substance in liquid. Hence, dissolution is a specific heterogeneous reaction that results in a mass transfer as a net effect between the escape and deposition of solute molecules at a solid surface.

Dissolution assumes a stagnant or unstirred layer of solvent is present at the solid–liquid interface. The mass transport or diffusion of solute through the unstirred layer is accomplished by simple molecular diffusion in a steady-state fashion following Fick's law of diffusion. Once the drug has passed the stagnant layer the solute is then mixed quickly by convection and diffusion in the bulk of the liquid. The Noyes–Whitney equation derived from the diffusion layer theory can be used to explain the different variables that can affect the rates of dissolution in solids. This dissolution process is most frequently described in the form of a dissolution profile of a solid oral dosage form obtained by use of a dissolution testing system (see ⟨711⟩). For oral dosage forms a dissolution test may be predictive of systemic bioavailability in certain cases. Because systemic bioavailability may be clinically important, dissolution may be a meaningful performance test.

Dissolution Test Procedures for Inhalation Dosage Forms: Challenges and Concerns

Ideally, a dissolution test procedure for inhaled drug particles—if such a procedure were necessary—would assess or predict the dissolution profiles or kinetics of the fluids that line the respiratory tracts upon which drugs are deposited during aerosolized delivery. Such procedure(s) should be well designed and validated to ensure that they can identify the equivalence of or differences between the dissolution performance of dosage forms and products. However, several experimental difficulties exist: e.g., dissolution procedures preferably would attempt to sample delivered particles that reach the respiratory tracts—not the entire formulations. This

would likely require collection of the API fraction before the performance of the dissolution test. Moreover, although the composition of the fluids that line the respiratory tracts is not certain, their volume is approximately 10–20 mL/~100 m^2 of surface, which implies that the system is stagnant rather than well stirred (*13–14*). Because of these physiological data the Inhalation Ad Hoc Advisory Panel conducted a literature search in PubMed and EMBASE from 1970 to 2008 in an attempt to identify dissolution procedures and other information that could assist in the development of dissolution procedures for inhalation dosage forms.

Possible Adaptive Approach Based on Existing USP Procedures

The literature review of dissolution procedures for inhalation dosage forms began with existing *USP* procedures in order to assess the possibility of adapting existing General Chapters for inhalation dosage forms. Essentially, many inhalation products are powders, and therefore a modified flow-through cell system, USP Apparatus 4, may offer opportunities for adaptation and development. Its general experimental set-up is described in detail in USP General Chapters ⟨724⟩ and ⟨711⟩ [USP Apparatus 4 was official in *USP 29,* which is no longer official; Apparatus 4 is not included in ⟨724⟩ in *USP 30,* which is now official. (See *2 Suppl USP* 2005:3578–3583.)]. The apparatus consists of a reservoir and a pump that pushes the dissolution media through a flow-through cell. The media and cell are maintained at 37 °C. The flow-through cell is mounted vertically with a filter system that prevents escape of undissolved particles from the top of the cell. A pump forces the dissolution media at a rate of 2–16 mL/min upward through the flow–through cell, where particles for dissolution are placed, usually on the top of a small bed of glass beads. Several sizes of the standard cell are available, and the whole system can be provided either in an open- or closed-loop configuration. Standardization for use in a Good Manufacturing Practices (GMP) environment would need to be ensured.

Taylor et al. tested USP Apparatus 4 and found it useful in dissolution testing of inhalation dosage forms (*15*). Ipratropium bromide (IpBr), a short-acting anticholinergic bronchodilator with a fair aqueous solubility (>90 mg/mL), was used as a model drug. By spray drying they prepared crystalline IpBr in respirable-sized particles (1.5 µm, mean mass aerodynamic diameter) coated with polylactic acid (PLA) at 1%, 5%, 10%, 15%, 30%, and 50% by weight. Then each of the PLA-coated IpBr particles was subjected to the 22.6 mm USP Apparatus 4 flow-through cell dissolution system for IpBr dissolution and release profile characterization. Dissolution media was pumped through the flow cell at a rate of 5–16 mL/min. *Figure 2* shows that sustained-dissolution and -release properties of IpBr increased with increasing level of PLA coating of IpBr particles. A related pharmacodynamic study in guinea pigs showed increased duration of bronchodilatory effect in the lung when 30% PLA-coated IpBr particles were administered compared to IpBr alone (56.3 and 11.0 min, respectively) (*15*). The adapted USP Apparatus 4 could differentiate in vitro sustained-dissolution or -release properties, which may be of use in the development of formulations in animal models. In the study under discussion, however, the dissolution profiles obtained from this experimental study set-up were obtained from the entire dosage administered and not simply the respirable fraction that entered the site of action.

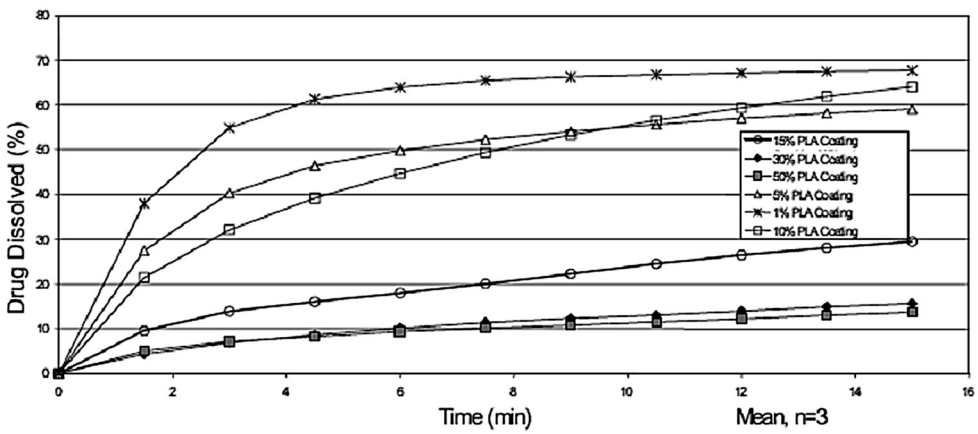

Figure 2. Dissolution Profile of Various PLA-coated IpBr Particles Determined in the Adapted USP Apparatus 4. Reproduced with permission from (*15*).

New Dissolution Approach

Davies and Feddah developed an innovative procedure to assess dissolution profiles and kinetics of inhaled particles collected from MDIs and DPIs (*16*). As shown in *Figure 3*, they used a custom-designed flow-through system similar to USP Apparatus 4. It was novel because it used the Andersen Mark II cascade impactor (USP Apparatus 1 for the assessment of aerodynamic particle size distribution, ⟨601⟩). This apparatus captures drug particles of respirable size only from MDIs and DPIs and collects them on a glass fiber filter in a manner that mimics the action of respiratory tract deposition. The device operates at a flow rate of 60 L/min, which simulates the typical inspiratory flow rate in humans. Following particle collection, investigators mounted the glass fiber filter between two 0.45-µm cellulose acetate membrane filters inside the flow-through cell, which was then subjected to dissolution testing in the system shown in *Figure 3*. The system consisted of a reservoir and HPLC pump for the dissolution media, as well as the flow-through dissolution cell. The media and cell were maintained at 37 °C. The cell was mounted vertically, and the pump delivered the media upwards at 0.7 mL/min. This procedure included an additional unique feature because the dissolution medium was simulated lung lining fluid prepared according to Moss's measurement (*13*). Tested drugs and delivery systems were Flixotide Accuhaler 250 µg fluticasone propionate (Allen and Hanburys, Division of Glaxo Wellcome, NSW, Australia), Pulmicort Turbuhaler 200 µg budesonide (Astra Pharmaceuticals, NSW, Australia), and the MDI Azmacort 200 µg, triamcinolone acetonide (Rhône-Poulenc Rorer Pharmaceuticals Inc., PA, USA), respectively. Their dissolution profiles were shown to differ substantially between the drugs as well as by the use of the simulated lung lining fluid—the addition of spray dried dipalmitoyl-*L*-α-phosphatidylcholine (DPPC) increased solubility of these steroids (*Figure 4*) (*16*). The dissolution profiles were more complex than profiles for drugs whose release is controlled only by their solubility. Notably, this was the first attempt to characterize in the respirable range dissolution profiles of drug particles generated from commercial inhaler products. The procedure employed a relatively lower flow rate (0.7 mL/min) than that commonly used in the USP apparatus, which would potentially create more stagnant conditions in the impactor for dissolution, a situation similar to that in the fluid lining the respiratory tracts.

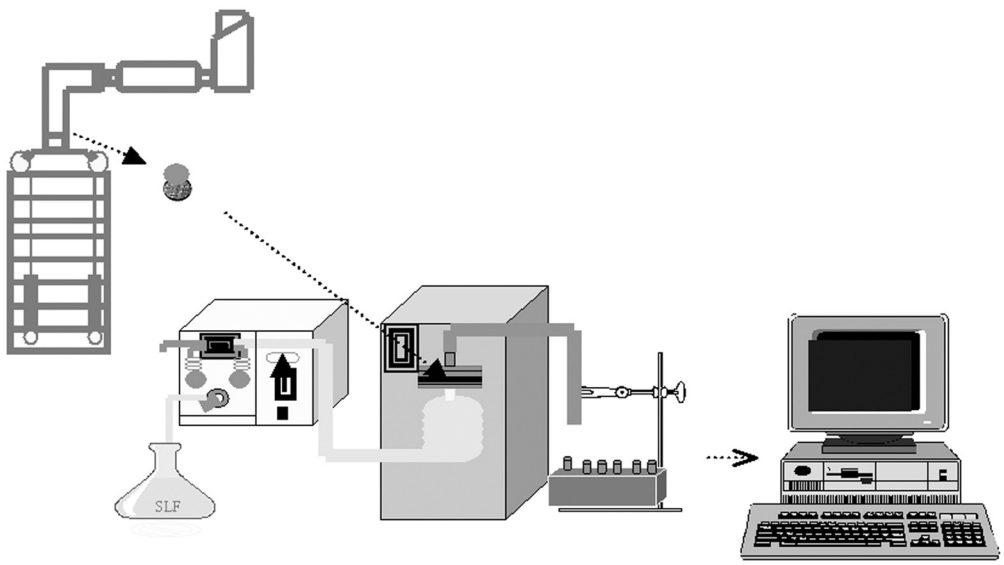

Figure 3. New Dissolution Procedure for Respirable Particles. Reprinted from (*16*) with permission from Elsevier.

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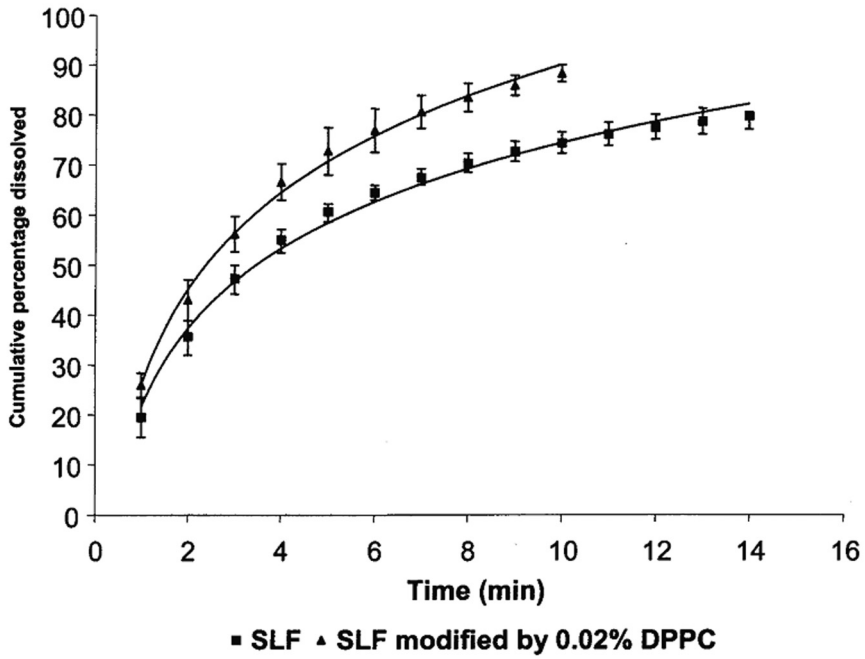

Figure 4. Dissolution profile of triamcinolone acetonide in simulated lung lining fluid and in simulated lung lining fluid modified by 0.02% DPPC. The vertical bars indicate the standard deviation of 5 determinations. Reprinted from (*16*) with permission from Elsevier.

PERSPECTIVES AND CONCLUSIONS

In vivo dissolution may be of some importance during the process of pulmonary drug absorption. For oral aerosol dosage forms a relationship between in vitro dissolution and some relevant parameters of bioavailability may be required before one can predict the bioperformance of aerosols. At this time two cases may be possible:

1. If particle size and thus surface area are the rate-controlling factors for aerosol drug dissolution, manufacturers may need only control particle size and distribution as quality and process control steps during manufacturing and batch release. Such controls may help identify shelf life provided that a relationship between particle size and dissolution has been established.
2. In addition to using cascade impactors to characterize aerosolized drug products, manufacturers may need to conduct dissolution tests for these drug products. The dissolution apparatus could be a flow-through cell that may be modified from USP Apparatus 4. GMPs would be required.

Despite the procedures just described for dissolution testing of inhalation dosage forms, the Inhalation Ad Hoc Advisory Panel reviewed currently approved inhalation products and could not find information that suggests dissolution problems involving fluids that line human respiratory tracts. The Advisory Panel searched several biomedical databases for published pharmaceutical data—including batch-to-batch or product-to-product variation in dissolution that caused variable clinical effects or dissolution rate–determining clinical pharmacokinetics and therapeutic outcomes—but found no adverse dissolution-related outcomes. However, absence of negative outcomes to date cannot predict future findings.

A few quality and performance tests for inhalation dosage forms are available at present. Current *USP* standards for assessing the performance of these drugs involve testing for delivered dose and aerodynamic particle size distribution but do not include dissolution testing. This seems to be the case primarily because drug delivery to, and regional deposition within, the respiratory tract far outweigh dissolution in controlling the effective delivered dose. The Panel's literature review could not identify data associated with dissolution of inhaled therapeutics in terms of pharmacokinetics or clinical performance. Therefore, USP at this point may not need to be concerned about standards for dissolution of inhalation dosage forms, and the importance of dissolution testing may rather be a future consideration if a procedure is developed in industry and then becomes a regulatory concern. Experiments could examine similar inhalation dosage form products with similar particle size distributions to evaluate whether a dissolution test can identify differences in formulation variables. In such cases, dissolution tests could be performed on finished bulk powders as a formulation selection or quality control test (*12*), or more complex methodologies could be adapted to evaluate the dissolution of the delivered dose (*15*). Careful and thorough examinations and validation in the selection of apparatus, media, and sample preparation must be made, especially if one seeks to establish or disprove in vitro–in vivo correlations.

The Inhalation Ad Hoc advisory panel concluded that based on available information and data, the performance test for inhalation dosage form should include 1) uniformity of dose delivered and 2) aerodynamic particle size distribution.

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