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Overview of the Activities of the USP Expert Panel on New Advancements in Product Performance Testing

Raymond D. Skwierczynski,[a] Vivian Gray,[b] James De Muth[a]

[a]*USP Expert Panel New Advancements in Product Performance Tests.*

[b]*USP Expert Committee Dosage Forms.*

Correspondence should be addressed to:
Margareth R. C. Marques, Senior Principal Scientist,
Science-General Chapters, US Pharmacopeia,
12601 Twinbrook Parkway, Rockville, MD 20852-1790
email: mrm@usp.org

ABSTRACT

The purpose of this paper is to provide an overview of the activities of the USP Expert Panel on New Advancements in Product Performance testing.

INTRODUCTION

The USP Expert Panel (EP) on New Advancements in Product Performance Testing was created by the 2015–2020 USP Expert Committee on Pharmaceutical Dosage Forms near the end of 2019 to explore new advances in drug product performance testing. The original charge to the EP was to provide recommendations for the adaptation of product performance tests and for the development of innovative approaches applicable to novel dosage forms in *USP* monographs and general chapters, as well as to evaluate current compendial product performance tests (dissolution, disintegration, and drug release) while considering the latest developments in the field. Furthermore, the EP was charged with conducting a gap analysis of USP's status quo regarding performance testing of commercially available drug and dietary supplement dosage forms versus emerging drug delivery systems, and the demand for performance tests applicable to innovative dosage forms. Finally, the EP was required to draft a *Stimuli* article, recommending possible chapter revision(s) and new chapter development. The panel will lead and cooperate with USP staff on the organization of activities for stakeholders' engagement, such as round tables and workshops.

The purpose of this paper is to provide an overview of the article series developed by the EP for pharmaceutical stakeholder and regulator consideration. In doing so, this article will provide a brief history of performance testing and summarize the current state of USP performance testing. The article will describe how the EP was structured to achieve its mandate and will discuss some of the challenges revealed by the aforementioned gap analysis.

HISTORY OF PERFORMANCE TESTING

The Dissolution Test is the most frequently required performance test in the *USP–NF*. It originated in the late 1800s when pill absorption was discovered to be related to dissolution. In 1895, Caspari wrote in a *Treatise on Pharmacy*, "... the composition of compressed tablets should be such that they will readily undergo disintegration and solution in the stomach" (*1*). Only a few years later, in 1897, the Noyes Whitney Equation was published (*2*). As early as the 1930s, experiments with in vitro–in vivo correlations using disintegration were performed and published (*3*). By 1937, tablets had begun to appear as an important dosage form, with disintegration testing found in the British Pharmacopoeia (BP) in 1945 and in the USP in 1950.

During the 1950s, it became known that disintegration was insufficient as evidenced by a *USP–NF* statement that

"disintegration does not imply complete solution of the tablet or even the active ingredient" (*4*).

To ensure drug effectiveness as well as safety, the Kefauver-Harris Drug Amendment was passed in 1962. At that time, the Pharmaceutical Manufacturers Association (PMA) Quality Control Section's Tablet Committee did a survey of 76 products because of concerns that some products disintegrated well but did not absorb. Also, there were product failures noted when the dissolution time was long. The survey found problems in those drugs with solubility less than 30 µg/mL of water—a recommendation was considered that dissolution should be required for drugs with less than 1% solubility instead of disintegration.

During the late 1960s, generic drug approvals were granted, and by 1973, bioequivalence regulations were in place. From the 1960s onward, instrumental analysis with drugs in biological fluid began, and a new generation of pharmaceutical scientists applied physical chemistry to pharmacy (this is attributed to Higuchi) (*5–7*). In 1960, a publication showed that incidence of local irritation and absorption rate of acetylsalicylic acid is a function of its dissolution rate (*8*).

Digoxin tablets were found to have different dissolution rates that were related to differences in plasma levels (*9*). This observation, in 1972, was considered a "game changer" as it was the single most significant medical occurrence of bioavailability problems. At the time, the "Griffin beaker" (a 400-mL beaker with a stirrer) was used for dissolution testing. It was determined that the main culprits for formulation problems were shellac coating and magnesium stearate.

USP scientists began to identify the need for dissolution testing. In 1967, a *USP–NF* Joint Panel on Physiologic Availability was set up to evaluate mechanisms to help assure drug effectiveness. This panel provided the following recommendations:

1. testing to demonstrate the rate at which active ingredients dissolve from the dosage form;
2. the rotating basket would be the most suitable method based on the results of non-disintegrating salicylic acid tablets; and
3. testing should include individual dosage units necessary to ensure uniformity of performance within a batch and should consider high within-lot variability.

A description of the dissolution apparatus known as "Pernarowski's basket" (officially adopted by USP as *Apparatus 1* in 1970) was published in 1967 by the *USP–NF* Joint Panel, although Pernarowski himself claimed that an obscure scientist developed the basket apparatus in Krasnoyarsk, Russia in 1922 (*10*).

PERFORMANCE TEST DEVELOPMENT AND EVOLUTION

The very first water bath was used in 1968 and was a 100-gallon glass-walled container. The equipment was pioneered by what at the time was called the USP Drug Standards Laboratory (DSL). Tim Grady, Bill Hanson, and William Mader were the key scientists who developed the tester currently used today (*11*).

During the 1970s–80s, dissolution test and equipment refinement took place. The *USP–NF* Joint Panel on Physiologic Availability that was established in 1967 advocated for the identification of candidate articles for the first 12 official dissolution tests that used *Apparatus 1* in 1968 (*12*). By the 1970s, there were 12 official *USP* monographs using the basket apparatus. The paddle method (USP *Apparatus 2*) was adopted in 1978. This apparatus was based on the round-bottom organic synthesis flask.

In 1975, regulations began to require bioequivalence and bioavailability with in vitro bioequivalence coming into play. Generic products were the driver for this initiative. Dissolution was seen as the only compendial test that assured the drug would be liberated from the dosage form and available for in vivo absorption.

In 1976, USP in joint leadership with the National Formulary (NF) adopted a new policy that advocated for the inclusion of dissolution tests in all tablet and capsule monographs; however, conditions and specifications were not uniform and sometimes absent. Also, there was a lack of industry cooperation.

By 1980, only about 72 *USP* monographs had dissolution tests. To remedy this situation, in 1975 USP enacted its "First Case" dissolution policy, which was a comprehensive policy for dissolution standards for tablets and capsules, which stated that "all tablet and capsules are subject to a dissolution standard of not less than 75% of label content is dissolved in not more than 45 min in 900-mL water at 37°, *Apparatus 1* (basket) at 100 rpm and *Apparatus 2* (paddle) at 50 rpm for all other cases."

The text of the policy stated, "The public interest warrants no further delay in assuring reliable release of

active ingredients from dosage forms." The policy meant automatic application of "First Case" requirements to every tablet and capsule monograph. All articles were presumed to conform unless USP was notified to the contrary. An earlier specification of 60% dissolution at 20 min was considered but discarded. By 1985, dissolution tests in monographs jumped from 70 to 400, with the majority as "First Case" conditions.

The preface to *USP XXI* (1985) contained the following words: "Experience has demonstrated that where a medically significant difference in bioavailability has been found among supposedly similar articles, a dissolution test has been efficacious in discriminating among these articles." The preface continued as follows—"There is no known medically significant bioinequivalence problem with articles where 75% is dissolved in water at 37° in 45 min." This was when highly soluble and highly permeable drugs were the majority. Eventually this wording was dropped out of the preface.

In the 1990s, the FDA pushed for profile testing: "The value of the dissolution test is significantly enhanced as a function of time with profiles instead of single points" and comparison of dissolution profiles using the F2 equation was introduced (*13*).

During the 1990s, there were several other changes initiated: 1) removal of disks from disintegration; 2) FDA directive stating that chewable tablets and soft gel capsules are no longer exempt from dissolution testing; 3) pooled dissolution instated for multi-component, highly soluble articles with a known track record and methodology included pooling six sample aliquots in one flask; 4) replace 0.1 N HCl media with 0.01 N HCl, viewed as more discriminating media and more environmentally friendly; 5) the FDA began to push for the specifications of 80% in 30 min rather than 75% in 45 min; 6) the FDA began to push for 100 rpm paddle speeds for immediate release products to be reduced to 50 rpm, 75 rpm in some cases; and 7) the FDA discourages use of water as a dissolution medium.

Today dissolution testing is generally recognized as the gold standard for performance testing.

CURRENT STATUS OF USP PERFORMANCE TESTING

USP provides five official chapters on the applicable quality standards for pharmaceutical products based on a taxonomy for the route of administration. These standards are presented in the first five chapters of the *USP–NF*:

<1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests

<2> Oral Drug Products—Product Quality Tests

<3> Topical and Transdermal Products—Product Quality Tests

<4> Mucosal Drug Products—Product Quality Tests

<5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests

Each of these chapters provide product quality tests, such as identification, assay, content uniformity, and impurity testing. Based on the route of administration, each chapter includes additional quality tests. Performance testing that assesses the release and availability of the drug substance from the dosage form is also provided but often in general terms. For example, Oral Drug Products—Product Quality Tests <2> states that Dissolution <711> or Drug Release <724> should be performed to assess the performance of a solid oral dosage form, but details of the test method are not provided. These performance tests have historically served as a quality control test at the time of product release or demonstration of stability over the product's shelf life.

Details of the performance test method and acceptance criteria can usually be found in the specific *USP–NF* monograph, if one exists (*14*). The USP and FDA dissolution databases provide information on the test method conditions (*15*, *16*). Additional *USP* chapters provide some guidance for performance tests for the five routes of administration. These chapters are presented in *Table 1*.

Ophthalmics, which represent a unique class of products, are discussed in *USP* chapters Ophthalmic Preparations—Quality Tests <771> and performance tests currently presented in Ophthalmic Products—Performance Tests <1771>. Performance tests for ophthalmic products are required for those with an extended- release mechanism, usually administered by injection or by a small surgery procedure.

DEVELOPMENT OF THE TACTICAL PLAN TO ACHIEVE THE OBJECTIVES

Members of the EP were recruited from the pharmaceutical industry, academia, and the FDA. A list of EP members and their affiliations is given in *Table 2*. The initial focus of the EP in May 2019 was to discuss emerging trends regarding drug delivery technologies. During subsequent meetings, characterization methods were

Table 1. Current USP Chapters Addressing Quality and Performance Testing

Quality Tests	Performance Tests
<1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests <2> Oral Drug Products—Product Quality Tests <3> Topical and Transdermal Products—Product Quality Tests <4> Mucosal Drug Products—Product Quality Tests <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests	<1001> Performance Test for Parenteral Dosage Forms <701> Disintegration <711> Dissolution <724> Drug Release <1711> Oral Dosage Forms—Performance Tests <1087> Apparent Intrinsic Dissolution-Dissolution Test Procedures for Rotating Disk and Stationary Disks <1088> In vitro and In vivo Evaluation of Oral Dosage Forms <1090> Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution <1092> The Dissolution Procedure: Development and Validation <1094> Capsules—Dissolution and Related Quality Attributes <2040> Disintegration and Dissolution of Dietary Supplements <724> Drug Release <1724> Semisolid Drug Products—Performance Tests <1004> Mucosal Drug Products—Performance Tests <601> Inhalation and Nasal Drug Products Aerosols, Sprays, and Powders—Performance Quality Tests

Table 2. EP Membership and Working Group Assignments

Name	Affiliation	Workgroup Assignments
Om Anand, Ph.D.	FDA, USA	Topicals, Inhalation
Matthew Burke, Ph.D.	GlaxoSmithKline, USA	Parenterals, Nanomaterials
Carrie Coutant, Ph.D.	Eli Lilly & Co., USA	Orals, Cont. Manufacturing
Deirdre Darcy, Ph.D.	Trinity College Dublin, Ireland	Parenterals,* Orals
James E. De Muth, Ph.D.	University of Wisconsin, USA	Topicals, Mucosals, Inhalation
Raafat Fahmy, Ph.D.	FDA, USA	Cont. Manufacturing, Nanomaterials
Nikoletta Fotaki, Ph.D.	University of Bath, UK	Orals,* Inhalation
Andre Hermans, Ph.D.	Merck & Co, Inc., USA	Orals, Cont. Manufacturing
Gregory Hunter, Ph.D.	FDA, USA	Parenterals, Orals
Sandra Klein, Ph.D.	University of Greifswald, Germany	Mucosal,* Parenterals, Orals
Christina Lee, Pharm.D.	FDA, USA	Topicals, Mucosals
Hanlin Li, Ph.D.	Vertex Pharmaceuticals, USA	Cont. Manufacturing,* Orals
Kevin Li, Ph.D.	University of Cincinnati, USA	Topicals, Mucosals
Xujin Lu, Ph.D.	Bristol-Myers Squibb, USA	Cont. Manufacturing, Nanomaterials
John Mauger, Ph.D.	University of Utah, USA	Topical,* Orals
Masahiro Sakagami, Ph.D.	Virginia Commonwealth University, USA	Inhalation,* Mucosals
Emmanuel Scheubel, Ph.D.	F. Hoffmann-La Roche AG, Switzerland	Orals, Inhalation
Vivek Shah, M.S.	SOTAX Corp., USA	Parenterals, Orals
Raymond Skwierczynski, Ph.D.	Tremeau Pharmaceuticals, Inc., USA	Chair, Expert Panel
Matthias Wacker, Ph.D.	National University of Singapore, Singapore	Nanomaterials,* Injections
Kevin Warner, Ph.D.	Alucent Biomedical, Inc., USA	Topical,* Mucosals
Hao Xu, Ph.D.	Zoetis, USA	Parenterals, Topicals, Mucosals

**Working group chair.*

discussed and how these topics would influence how the EP would organize to meet its objectives. In-person meetings were held at USP headquarters in Rockville, MD in October and December 2019. The December meeting followed the workshop "Advancements in In-Vitro Performance Testing of Drug Products" where members heard presentations from USP staff and experts on drug performance testing and received input from stakeholders (*17*). In addition to reviewing information presented at the workshop, the EP discussed emergent technologies in major categories of dosage form performance testing and determined a plan and timeline for incorporating these technologies into a written USP standard.

The primary deliverable from the December 2019 meeting was a tabular framework for the gap analysis. The framework consisted of these points: 1) route of delivery; 2) dosage form; 3) current performance test for each dosage form, its limitations, and analytical challenges; 4) possible alternatives to or surrogates for the current performance test for each dosage form; and 5) recommendations.

It became quickly apparent that the magnitude of the gap analysis and subsequent *Stimuli* article was an enormous task. A decision was made to divide the charge into manageable pieces. Seven working groups were created to discuss and explore current and potential future tests that may be used for pharmaceutical performance tests.

Five of the working groups focused on the five aforementioned routes of administration (parenterals, orals, topical/transdermals, mucosal products, and inhalation and nasal products). Two additional groups were created to look at continuous manufacturing and nanomaterials.

Each EP member was assigned to at least two working groups, so information, thought processes, and designs could be shared amongst the various working groups. Working group assignments and chairs are also presented in *Table 2*.

Each working group was commissioned to complete a gap analysis and subsequent *Stimuli* article for their respective area. This approach provided the flexibility to have as many as seven focused *Stimuli* articles to cover the charge to the EP. Each group was also permitted to adjust the framework of the gap analysis and the format of their *Stimuli* article in order to facilitate public commentary from subject-matter experts and stakeholders who are familiar with the specific route or topic.

STATUS OF STIMULI ARTICLES

The first *Stimuli* article on nanomaterials has already been presented in *PF* 47(6) (*18*). The *Stimuli* article on continuous manufacturing will appear in *PF* 48(4) (*19*). The five working groups on the routes of delivery are progressing with their gap analyses. Publication of their *Stimuli* articles in *PF* is targeted for 2022 and 2023.

There are several common themes and visionary points emerging from the gap analyses. One is the desire to have performance tests be clinically relevant in addition to being discriminatory. Another is the desire to incorporate modeling, such as in vivo-predictive mouth-throat models and inhalation profiles for aerodynamic particle size distribution tests, and the predictive modeling for real-time release during continuous manufacturing.

As was mentioned in the nanomaterials *Stimuli* article, guidance on the selection of appropriate testing methodology, method development, and validation of release assays is needed for nanomaterial dosage forms. A similar gap analysis identified the need for a general systematic method development approach for various injectable dosage forms.

The examples above are not intended to be comprehensive. The details of the current state of performance testing, its gaps, and EP recommendations will, of course, be provided in each *Stimuli* article. The ultimate purpose of these *Stimuli* articles is to provide information to stakeholders and to provide opportunities to discuss and respond to the information and recommendations. Such feedback can range from support of the findings to challenges of their validity or feasibility. All comments are gratefully accepted and will be considered by the EP and the USP Dosage Forms Expert Committee as they work to prepare future standards for drug performance testing. Additional thoughts on the topics are also encouraged.

CONFLICT OF INTEREST STATEMENT

The authors did not declare any perceived or actual conflicts of interest related to the subject matter of this *Stimuli* article. The views presented in this article do not necessarily reflect those of the organizations for which the authors work. No official support or endorsement by these organizations is intended or should be inferred.

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