

# USP Responses to Comments on *Stimuli* Article, "Proposed Change to Acceptance Criteria for Dissolution Performance Verification Testing"

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## ABSTRACT

*Pharmacopeial Forum* 33(3) [May–June 2007] included a *Stimuli* article titled "Proposed Change to Acceptance Criteria for Dissolution Performance Verification Testing." This *Stimuli* article proposed changing the form of the acceptance criteria for the Performance Verification Test (PVT) associated with *USP Dissolution* <711> to make the PVT consistent with the International Organization for Standardization's recommendations for proficiency testing. The article elicited five comments, which are abstracted here with USP responses.

## INTRODUCTION

In *Pharmacopeial Forum* 33(3) USP authors published a *Stimuli* article titled "Proposed Change to Acceptance Criteria for Dissolution Performance Verification Testing" (1). This article elicited a number of comments, which are published here with USP responses. Comments have been edited for publication.

### Respondent 1

1. *The fundamental proposal made by USP for the revised acceptance criteria is to test more tablets to overcome tablet variability. It is apparent that there is an issue with the quality of the USP Reference Standard (RS) Tablets. Based on the results of queries to our relevant departments, we have several reports of examples that demonstrate the poor quality of USP RS Tablets.*

USP disagrees with these statements based on data (2, 3). The first reference (2) provides results from subjecting USP Lot P Prednisone RS tablets to the tests, procedures, and acceptance criteria that might be used for a commercial tablet. The data indicate results that are not dissimilar to those required in many USP monographs for drug products legally marketed in the US. The second reference (3) provides an analysis indicating that the contribution of the Prednisone RS Tablet to Performance Verification Test (PVT) variability is low (<4%–5%).

USP believes that the confusion about Prednisone RS Tablet quality has been present for many years and became a focus at meetings of the FDA Advisory Committee on Pharmaceutical Science in May and October 2005. Substantial misinformation about the

PVT and contribution of Prednisone RS Tablets to variability went unaddressed at these meetings. USP hopes that the two publications (2, 3) will dispel some of the misinformation. USP recommends that companies relying on the idea that poor results in the PVT are due to poor quality of the Prednisone RS Tablets should instead consider other explanations (e.g., dissolved gas, 4; perturbation in the dissolution apparatus, 5; and irregularities in the dissolution vessel itself, 6, 7, among other factors that should be investigated and controlled during the dissolution procedure), which is the primary intent of the PVT. In addition, USP has provided a Toolkit (<http://www.usp.org/pdf/EN/dissolutionProcedureToolkit2007-10-04.pdf>, accessed 25 October 2007) to assist manufacturers and other laboratories in this effort.

### Respondent 2

1. *The suggested change of acceptance criteria and focus on the PVT raise some concerns of inconsistency. No other type of analysis/equipment undergoes such a proficiency test.*

USP believes this observation to be generally correct. Historically in the US, FDA, USP and manufacturers have not emphasized proficiency testing for food and drug testing. In other sectors and in some food and drug laboratories elsewhere, proficiency testing occurs and yields useful results. As measurement science advances, the need to ensure that government, compendial, industry, and other laboratories are getting accurate, traceable results with characterization of relevant uncertainties is expected to increase (8, 9). The PVT works in this direction. Among many reasons, the fact that PVT results are disparate between laboratories (see USP's response to Respondent 1, above, and references therein, particularly 3) documents its utility in

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identifying sources of variance and ways to reduce this variance.

2. *A PVT is required only for Apparatus 1, 2, 3, not for 4, 5, 6, and 7.*

USP regrets this situation. USP hopes to advance a concomitant PVT for all apparatus and for all USP performance tests for dosage forms given by any of the five routes of administration (10–13). USP scientists recently published results of their work on a PVT for the vertical diffusion cell (Franz cell) (14). The applied compendial research needed to support the development of a PVT for all apparatus is resource intensive and would proceed faster if there were a combined and sustained government, industry, and compendial effort. The goal of consistently performing dosage form testing within and between manufacturers would seem to be a logical goal of efforts now termed Quality by Design.

3. *Because the PVT includes analyst and equipment, the use of designated service personnel or external vendors causes the PVT to lose all value.*

The respondent is correct that a PVT comprises an assessment of analyst and analytical procedure as well as dissolution apparatus and assembly. USP agrees that a laboratory may lose to its detriment some of the value of the PVT when the latter is conducted by personnel other than the laboratory's regular analysts. For this reason USP recommends that the PVT be performed using the regular laboratory personnel and, regardless who conducts the PVT, that the laboratory's standard procedures be followed. USP does not agree that use of designated service personnel or external vendors causes a PVT to lose all value. The PVT remains an assessment of the assembly, its operating environment, and laboratory procedure. Also, PVT would seem to be a useful way to monitor performance of such designated personnel or external vendors. In addition to the formal PVT itself the USP PVT RS and their externally derived acceptance criteria can be used as a proficiency test as part of training for laboratory personnel.

4. *The Reference Materials supplied by USP in the conduct of a PVT (Official USP Prednisone RS Tablets and Official USP Salicylic Acid RS Tablets) are supposed to be reliable, reproducible, and easy to use. The wide acceptance criteria and recent change in these acceptance criteria do not support that this is always the case.*

This comment speaks to a frequently heard theme that one of the supplied Reference Materials for the PVT, Prednisone RS Tablets, does not have good quality and is the source of failure in laboratories conducting the PVT. This theme is addressed in the USP response to Respondent 1 and references therein. The respondent is correct that the change in acceptance criteria, which occurred on 31 July 2007, signals a

change in the performance of the USP Lot P Prednisone RS Tablet. USP is working diligently to correct this, although USP does not believe that the change negates the value of the tablet's use in the PVT. The task of making a Reference Material that releases at a slow rate (a rapidly releasing Reference Material would be of no value in a dissolution PVT) and that also has requisite sensitivity to factors not readily assessed by mechanical calibration is a challenging one. USP has prepared a public response in this matter available at <http://www.usp.org/USPNF/notices/prednisoneTabletsErrata.html>, accessed 25 October 2007.

### Respondent 3

1. *USP mentioned the power of increasing from 6 to 12 to 18 tablets, but the authors did not provide any power curves or calculations. Are these power calculations available or perhaps contained in one of the references?*

The power results are not currently available. The authors will prepare a summary report for the Biopharmaceutics Expert Committee, and, based on this comment, they intend to make the requested information publicly available. No decision has been made as yet about what form this will take.

2. *As another option, wouldn't a two-stage sampling plan be worth investigating?*

The two-stage suggestion is a good one and will be included in the report as well. The congruence with other dissolution criteria makes it very appealing.

### Respondent 4

*General comment: Rejecting the ISO approach, the respondent calls for focus on performance of an individual apparatus, which is more stringent than a "combined test" that takes into account "Reference Material, medium de-aeration, analyst, laboratory, and the apparatus."*

USP response: This idea has merit, and USP will further consider it.

1. *Requirement for analyst training: A certificate accompanying the USP Prednisone and Salicylic Acid RS Tablets should indicate a requirement for analyst training.*

USP believes that this idea is a good one and merits discussion.

2. *Dissolution medium dissolved air specification: The percent dissolved oxygen should be measured with a calibrated oxygen sensor with specified acceptance criteria measured in vessels after pouring and prior to the conduct of the procedure.*

USP believes that this idea is a good one and merits further discussion.

3. *Replacement RS: If the Prednisone RS Tablet is too sensitive to dissolved air, replacement RS material should be considered.*

USP agrees generally with this response. USP is working on the next lot of Official USP Prednisone RS Tablets—Lot Q—and will attempt to address this comment in the further work.

4. *Sampling filter requirement: Add a filter porosity requirement.*

The Toolkit, Dissolution Procedure: Mechanical Calibration and Performance Verification Test (cited in the response to 1 above) gives the filter type used in the PVT. USP believes that this idea is a good one and merits further discussion.

5. *RS tablet quality control: Reference materials should be tested for hardness, granule particle size, weight, content uniformity, and any other pertinent parameters with defined acceptance criteria relevant to the overall specification.*

USP agrees with the comment. In fact USP and the manufacturer of the RS Tablets test for those quality attributes (2).

6. *Suitability of Apparatus 1 for disintegrating tablets: This should be phased out because disintegrated tablet particles fall through the basket screen, and results depend on how many and how soon particles fall through the screen.*

USP believes this comment has merit and will consider it further.

### Respondent 5

1. *Quality of the RS Tablet.*

See USP's response to Respondent 1 and references therein.

2. *Setting of acceptance criteria from collaborative data: Learning from collaborative studies of USP Lot P RS to set more appropriate specification ranges.*

USP agrees with this comment. The acceptance criteria for any performance standard material will need to be established by analysis of collaborative testing. The collaborative study for Prednisone RS Tablets Lot P was instructive in many ways, and USP expects it to be helpful in planning further collaborative studies (2–7).

3. *Keeping both RS Tablets and adopting the proposals would double the testing. This will be a huge burden on the industry.*

USP agrees with this comment, and a specific vote of the Biopharmaceutics Expert Committee recommended phasing out the Salicylic Acid RS Tablets at the appropriate time.

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