

January 8, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2007D-0365

Dear Sirs,

On October 19, 2007, through a *Federal Register* notice, the Food and Drug Administration (FDA) announced the release of a draft Guidance for Industry titled *Use of Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice* (draft Guidance) and called for comments on the draft Guidance. This document provides the comments of the U.S. Pharmacopeia (USP).

Introduction

The intent of the USP Performance test, which is employed for non-solution orally administered drug products, is to ensure continuing equivalence between the clinical trial material on which safety and efficacy conclusions were made and the manufactured article following approval. US regulatory approaches do not require post-approval reconsideration of bioequivalence for drug products, barring post-approval change. Thus, reliance on the USP Performance test becomes a key, if not the sole, means of ensuring consistency in drug product performance both within and among manufacturers over many years of drug product manufacture.

USP General Chapters *Disintegration* <701>, *Dissolution* <711>, and other General Chapters provide general procedures with acceptance criteria, which can then be adapted by manufacturers to specific products. Data arising from the adaptation undergo regulatory review and, if approved, become one of the tests in the private drug product specification. Under law, there is an expectation that these private standards will become public through combined activities of the Secretary and USP. USP recognizes that bioequivalent drug products may have different USP Performance test results and thus allows multiple specific dissolution procedures and associated criteria in a drug product monograph.

The dissolution procedure described in <711> requires an assembly that allows a kinetic measure of drug release over time. Combining effects from the analyst and analytic procedure, the experimental study of drug product dissolution is performed at batch release and also as part of stability studies. The assembly is a complicated mechanical device with many factors that can impact results. In part,

the complexity results from the need to provide some sense of surrogacy for the in vivo condition. For this reason, USP and—until recently FDA—have emphasized the importance of a periodic performance verification test (PVT)* together with careful mechanical calibration to ensure that the combined experimental study yields consistent results.

The draft Guidance argues that only mechanical calibration is needed. Based on substantial research and development efforts in recent years (2–11), USP maintains instead that both PVT and mechanical calibration are critical to the dissolution procedure and that mechanical calibration alone cannot ensure the validity of dissolution results. The dissolution test system consists of the mechanical apparatus (itself composed of several components), the physical environment in which the apparatus exists, the analytic procedure, and the analyst. Mechanical calibration addresses and controls only some of the components of the apparatus. USP has strong evidence, and has so published in the open literature, that other components and variables in the total dissolution test system are major sources of uncertainty and error. Thus, USP maintains that mechanical calibration is a necessary but not sufficient means of ensuring consistency and comparability of measurements obtained with a dissolution test system. By allowing the use of mechanical calibration without a PVT, the draft Guidance substantially weakens the assurance of continuing consistency in the performance of affected drug products over time. Accordingly, USP requests that FDA withdraw the draft Guidance.

USP’s statements in the remainder of this letter are divided into two parts—justification for a combined PVT and mechanical calibration approach (Part I) and commentary on statements in the draft Guidance (Part II).

Part I: Justification for a Combined PVT and Mechanical Calibration Approach

1. Metrology

Fundamental metrology concerns the establishment of measurement units, the realization of measurement standards, and the transfer of traceability from these standards to users in society. As applied to manufacturing, metrology ensures the suitability of measurement instruments, their calibration, and quality control of measurements. In the legal sense of the term, metrology enables regulatory requirements for measurements and measuring instruments for the protection of health, public safety, and the environment, and supports decisions regarding protection of consumers and fair trade. A core concept in metrology is

*General Chapter <711> has been revised, and the term *Apparatus Suitability Test* has been replaced with the term *Performance Verification Test* (1). Although USP reference standard tablets have been referred to as *calibrators*, this is a misnomer. The tablets are not, and cannot, be used for calibration.

traceability, defined as “the property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties” (see the National Institute of Standards and Technology Handbook 143, *State Weights and Measures Laboratories Program Handbook*). The level of traceability establishes the level of comparability of the measurement between results in any and all laboratories conducting the procedure. All USP’s tests and procedures are developed with this objective in mind and form the basis for the legal recognition of USP’s standards of strength, quality, and purity in the adulteration provisions of the Federal Food, Drug, and Cosmetic Act. USP thus works to ensure that manufacturers, for commercial purposes, and FDA, for regulatory purposes, have access to procedures that achieve a high degree of assurance in test results without regard to time and space.[†]

The overarching goal of metrological traceability is the transfer of accuracy (trueness) and precision throughout the measurement “ladder.” The two fundamental transfer agents of this ladder are procedures with specified methods and reference materials (RM). USP’s monograph procedures are frequently grounded in reference materials (official USP Reference Standards), with the understanding that the relationship between the procedure for the measurand (the material being examined) is closely linked to the reference material reflective of that measurand. At times, USP uses informally the terms *vertical standards* for the article under test and *horizontal standards* for the monograph’s procedures. A key example of horizontal documentary and RM standards is the dissolution procedure, described in <711>. There is a metrologic aspect to the dissolution procedure because a concentration is determined and can be traced to the base SI units of mass (kilogram). However, USP notes that the kinetic aspects of the dissolution procedure are not well grounded in metrology; i.e., there is no absolute number from the kinetic study that can be traced to an SI unit. In this regard, the dissolution procedure has the kinetic character of an enzyme assay that yields results in units/mass rather than in SI units alone. This does not mean that such grounding could not be improved, nor does it mean that the procedure is without value. The complex character of an assembly in fact requires careful consideration of horizontal standards to ensure acceptable results.

USP endorses the concept of mechanical calibration (grounded in metrology), conducted at periodic intervals, to ensure that the mechanical components meet specifications and are in a state of control. However, these mechanical checks are

[†]At times, an argument is made that a manufacturer could make its own physical artifact (an in-house reference material standard) for a PVT. Although such standards may work locally, this approach is inconsistent with national and international measurement systems, where comparability and consistency across time and space are essential. Further, this approach is obviously untenable if the goal is to align laboratories among manufacturers and between manufacturers and regulatory laboratories. Finally, the task of developing a reliable and useful reference material tablet is not an easy one and would require much duplication of effort among and within manufacturers.

necessary but not sufficient, because they ignore the chemical and kinetic aspects of the dissolution procedure. This is not unique to dissolution—it is common in most chemical tests. For example, the best-calibrated HPLC still needs systems suitability standards to ensure proper performance within and across laboratories. In one of the most common chemical measurement tests performed, pH, it is not sufficient to ensure only that the electronics of the meter (essentially a voltmeter) are functioning. Rather, there must be assurance that the entire system (the meter, the glass electrode, the counter electrode, the analyst) is performing adequately through the use of pH buffer standard solutions. Traceability, accuracy, and comparability are thus ensured. Hence, USP reference standard tablets used in the PVT help ensure that the complex character of a dissolution assembly, coupled with analyst and analytical procedure, act in concert to yield results within and among laboratories with acceptable accuracy and precision.

USP has established unequivocally that mechanical calibration of a dissolution assembly does not address adequately all factors (e.g., vessel symmetry) that impact dissolution results (5, 8). Recent USP research also leads to the conclusion that the current tolerances and specifications set for mechanical calibration are inadequate and need to be tightened. Even if mechanical calibration could be brought to complete realization (i.e., control of all possible impacting factors through conformance to specified tolerances), a PVT would still be needed to test the system as a whole and in actual use. Control of each factor individually might be possible, but that would not mean that all elements working in concert would yield reproducible and comparable results.

2. ISO Proficiency

In the terminology of the International Organization for Standardization (ISO), USP's chemical reference standard tablets used in a PVT form a proficiency test whereby a laboratory may compare its results to those from other laboratories (12). USP emphasizes the value of these publicly available reference standards that allow a PVT within and among laboratories to ensure that all laboratories achieve similar results in the interests of setting a metrologically sound and publicly derived USP Performance test in the drug product specification.

3. GMPs

Ensuring the quality of data generated by analytical equipment includes an overall approach to equipment quality. Pharmaceutical scientists have long accepted that equipment qualification—installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ)—under the principles of good manufacturing practices (GMPs) should be executed to verify acceptable quality of output from multi-component analytical instrumentation. Although practitioners may debate where in the IQ, OQ, and PQ process individual qualification activities should take place, the fundamental principles are indisputable. Each component of the verification process contributes to the overall

quality of data generated from multi-component analytical instrumentation, and omission of any component will compromise the QA of data (13). Based on its research, USP concludes that mechanical calibration must be coupled with PVT to satisfy GMP requirements for OQ and PQ, respectively.

Part II: Commentary on Guidance Statements

1. USP Prednisone RS Tablets and Stability

Lot O

The draft Guidance misstates USP's reason for widening acceptance criteria for USP Lot O Prednisone Reference Standard Tablets. USP changed the acceptance criteria of Lot O in December 2004 because of the "multiple testing" statistical issue, not because of any stability issues with the material. Historically, the acceptance interval from a collaborative study for USP's RS tablets was determined as $X \pm 2SDr$ where X is the average (assigned value) and SDr is the reproducibility standard deviation for a single determination from the collaborative study. The factor 2 corresponds approximately to 95% coverage and up to a 5% false error rate *per tablet*. Because six tablets are tested, the actual false positive rate is higher than the nominal 5%. USP is now using a 99% confidence interval to resolve this deficiency. A recent USP *Stimuli* article discusses the issue in more detail and postulates a new approach based on ISO principles (14). In this new approach, the PVT might be performed according to a sequential study design that would allow manufacturers with acceptable results to stop with a smaller number of tablets studied but continue if needed.

Lot P

USP Lot P Prednisone Reference Standard Tablets show diminished release over time in Apparatus 2 (<http://www.usp.org/USPNF/notices/prednisoneTabletsErrata.html>, accessed January 02, 2008). To address this matter, USP changed acceptance criteria for Lot P on July 30, 2007, for Apparatus 2. As noted in the Web statement, USP asserts that Lot P is still suitable for a PVT. For proficiency testing the principal concern is that the current acceptance criteria is appropriate to support a manufacturer's PVT, not that the RS tablets exhibit the type of stability in performance characteristics that would be required of a therapeutic article. USP understands that it would be more convenient for industry (and USP) if there were no need to change the acceptance criteria. USP staff is working with formulation experts from the Biopharmaceutics Expert Committee as well as its contract manufacturer for the Prednisone Tablets RS to ensure improved stability of the next lot, Lot Q.

2. Quality of USP Prednisone RS Tablets

FDA has claimed that USP Prednisone RS Tablet exhibit poor quality. The first time this claim came to USP's attention was during presentations by FDA staff at USP's 2004 Annual Science Meeting in Iselin, NJ, and again at meetings of the Advisory Committee for Pharmaceutical Science in May and October 2005. USP refutes the claim based on studies conducted over the past several years (2). USP's Lot P Prednisone RS Tablet exhibits variability that is less than that of commercially marketed therapeutic drug products but about the same as that of FDA's NCDA #2 tablet lot (15, 16).

3. Wide PVT Acceptance Criteria and Tablet Quality

Statements in the draft Guidance misrepresent the basis for the wide acceptance criteria for USP's PVT. This variability arises because the limits are based on the reproducibility variability from USP's collaborative studies, which include a substantial contribution from inter-laboratory variability (3). This substantial variability was observed even though careful mechanical calibration was included in the collaborative study design. Interpretations of such data have suggested that this variability was due to the poor quality of the USP Prednisone RS Tablet. USP research clearly demonstrates that this is not the case and that inter-laboratory—and, at times—intra-laboratory variance is high, findings that in and of themselves argue for the need for the PVT. Thus other factors—not the quality of USP's reference standard tablets—are causing the high degree of variability seen in execution of the dissolution procedure. Rather than challenging the quality of the tablets and the PVT itself, FDA and manufacturers should understand that they are gaining important information that may impact the public health. FDA has stated that wide variability in results can be observed yet a laboratory's results are still within acceptance criteria. This is an important point that merits further consideration. It might be resolved in several ways, e.g., more attention to conduct of the dissolution procedure and more care in selection of laboratories for the collaborative study, both of which could lead to narrowing of the acceptance criteria. USP's publications (see References) provide opportunities to improve execution of the dissolution procedure.

4. Salicylic Acid

USP agrees with the statements in the draft Guidance regarding USP Salicylic Acid RS Tablets. At its May 2007 meeting the Biopharmaceutics Expert Committee recommended discontinuance of this RS tablet at a suitable time. Coincident with this discontinuation, USP expects that the number of Prednisone RS Tablets would increase in accordance with ISO approaches (7).

Summary

In studies cited in this commentary (2–11) and in various internal and external discussions with its Expert Committee members, stakeholders, and others, USP has determined that a PVT performed at periodic intervals, in addition to

mechanical calibration, is required to ensure the integrity and reliability of the dissolution procedure when referenced in the USP Performance test and in private regulatory drug product specifications. FDA has provided no data to support its position in the draft Guidance that mechanical calibration alone is sufficient to ensure the integrity of a dissolution procedure. Much of FDA's opposition to a PVT apparently arises because of erroneous assumptions about the USP Lot P Prednisone RS Tablet. FDA must have come to these conclusions without the benefit of the research in this area done by USP, and USP regrets that the time required for this research and its publication have limited effective dialogue with FDA on the topic. Much of this work is now in the public domain, and the remainder is in press and has been shared with FDA. USP believes that much further work is needed in the immediate future to improve USP's current General Chapters that work to ensure the consistency of drug products and expand them to products other than non-solution orally administered dosage forms. USP also is in accord with an often stated view that new approaches to assess drug product performance in vitro are needed. Thus in the long term, USP envisions an evolved set of approaches to assess drug product performance for all non-solution dosage forms over time following regulatory approval. Although the use of a PVT with some kind of physical article probably will be needed in the short term, these newer approaches—if they can be realized—should offer better public health protection and ease of use for pharmaceutical manufacturers. It will be important not to abandon current approaches that have worked well before new opportunities become available. USP hopes that this work can advance jointly with FDA and welcomes the agency's participation in this effort.

Yours sincerely,

Roger L. Williams, MD
Executive Vice President and
Chief Executive Officer

REFERENCES

1. USP. Interim Revision Announcement. *Dissolution* <711>. *Pharm Forum*. 2007;33(4):626–630.
2. Deng G, Ashley AJ, Brown WE, et al. The USP performance verification test, part I: quality attributes and experimental variables contributing to dissolution variance.” *Pharm Res*. 2008. In press.
3. Glasgow M, Dressman S, Brown WE, et al. The USP performance verification test, part II: collaborative study of USP’s Lot P Prednisone Tablets. *Pharm Res*. 2008. In press.
4. Nithyanandan P, Deng G, Brown W, Manning R, Wahab S. Evaluation of the sensitivity of USP Prednisone Tablets to dissolved gas in the dissolution medium using USP Apparatus 2. *Dissolution Technol*. 2006;13(3)15–18.
5. Eaton J, Deng G, Hauck WW, Brown WE, Manning RG, Wahab S. Perturbation study of dissolution apparatus variables—a design of experiment approach. *Dissolution Technol*. 2007;14(2): 20–26.
6. Liddell MR, Deng G, Hauck WW, Brown WE, Wahab SZ, Manning RG. Evaluation of glass dissolution vessel dimensions and irregularities. *Dissolution Technol*. 2007;14(2):28–33.
7. Hauck WW, Manning RG, Cecil TL, Brown WE, Williams RL. Proposed change to acceptance criteria for dissolution performance verification testing. *Pharm Forum*. 33(3) [May–June 07]:574–579. Reprinted in: *Dissolution Technol*. 2007;14(3):8–12.
8. Hauck WW, Shah VP, Shaw SW, Ueda CT. Reliability and reproducibility of vertical diffusion cells for determining release rates from semisolid dosage forms. *Pharm Res*. 2007;24(11):2018–2024.
9. Liddell M, Deng G, Hauck WW. Dissolution testing variability: effect of using vessels from different commercial sources. *Am Pharm Rev*. 2007;10(6):122–128.
10. Manning RG, Wahab SZ, Brown WE, Hauck WW, Schuber S, Williams RL. Dissolution testing and metrological measurement of quality for solid oral dosage forms. *Pharm Technol*. 2007;31(5):68–74.
11. Deng G, Munoz J, Brown W, Manning R, Wahab S. Frequency-domain vibration measurement and analysis in dissolution testing. Poster presented at: 2007 Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS); November 15, 2007; San Diego, California.

12. ISO. *Standard 5725 Accuracy (Trueness and Precision) of Measurement Methods and Results. Parts 1–6*. Geneva, Switzerland: ISO. 1994.
13. FDA. *ORA Laboratory Procedure. Assuring the Quality of Test Results. ORA-Lab.5.9*. 2007. http://www.fda.gov/ora/science_ref/lm/vol2/section/5_09.pdf. Accessed January 02, 2008.
14. Hauck WW, Manning RG, Cecil TL, Brown WE, Williams RL. Proposed change to acceptance criteria for dissolution performance verification testing. *Pharm Forum*. 2007;33(3):574–579.
15. Nithyanandan P, Hauck WW, Munoz J, Deng G, Brown W, Manning RG, Wahab S. Dissolution Variability: Comparison of Commercial Dosage Forms with US Pharmacopeia Lot P Prednisone Reference Standard Tablets. Submitted to *AAPS PharmSciTech* (2007).
16. Gao Z, Moore T, Smith AP, Doub W, Westenberger B, Buhse L. Gauge repeatability and reproducibility for accessing variability during dissolution testing: a technical note. *AAPS PharmSciTech* 2007;8(4) Article 82