AGILENT TECHNOLOGIES
PRACTICAL SOLUTIONS NEWSLETTER
Volume 12, Issue 2

In This Issue:

Transition to Enhanced Mechanical Qualification: The Template

Making the transition to ASTM and FDA-approved enhanced Mechanical Qualification (MQ) procedures from the USP Performance Verification Test (PVT) is much more than simply taking a few additional mechanical parameter measurements with tighter tolerances. Agilent created the following template as a guide to ensure you have all the details on the requirements. It is not as simple as eliminating Prednisone, but each of the suggested practices must be established in the transition to enhanced MQ to ensure dissolution apparatus integrity.

1. Verification of Dissolution Components

a. Measure/verify the dimensions of the vessels, baskets, and paddles upon receipt. Component measurement and/or verification of a certificate "ensure the components are appropriate for use[1]."

b. Ensure your Certificate of Analysis or Conformance (COA/COC) includes measurements of each serialized component with appropriately documented measuring devices for the critical parameters outlined in USP <711>. A Declaration of Manufacturing Conformity certificate, without the individual component measurements or reference to a specific serial number, will not support the FDA or ASTM MQ guidance requirements.

2. Vital Dissolution Standard Operating Procedures (SOPs)

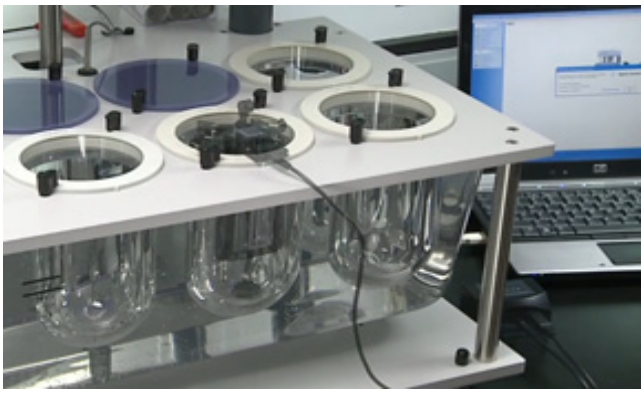
a. Operational Checklist - establish an ongoing evaluation procedure for component integrity, to be implemented prior to and each time the dissolution apparatus is used. Include the following details:

1. Inspect vessels, paddles, basket shafts and paddles[2], ensuring cleanliness and proper working condition.
2. Verify vessel temperature and monitor environment for influences of vibration.
3. Train dissolution analysts on procedure and MQ guidance for proper compliance.

Continued on p. 2

b. Preventative Maintenance Schedule - develop, implement and document the procedure based on recommendations of the dissolution apparatus manufacturer, defining the frequency based on usage.
   1. Perform at 6- or 12-month intervals or based on a number of spindle hours.
   2. Verify the entire apparatus is evaluated, inspecting all parts are in proper working condition.
   3. Replace parts or components with compromised integrity to avoid a future performance issue.

3. Enhanced Physical Parameter Measurements and Tolerances



a. Verify the following measurements adhere to the tolerance guidelines, with instructions on performing these measurements in the ASTM Implementation Guidance[2] and Agilent's MQ implementation white paper[3].
   1. Basket/paddle depth: 25 ± 2 mm
   2. Rotational speed: within 2% or ± 2 RPM of target, whichever is larger
   3. Shaft wobble: ≤ 1.0 mm total runout
   4. Shaft verticality: ≤ 0.5° from vertical
   5. Basket wobble: ≤ 1.0 mm total runout
   6. Vessel-to-shaft centering: ≤ 1.0 mm from center line
   7. Vessel verticality: ≤ 1.0° from vertical at each point

b. Ensure that the position of the measurements conform to the requirements of the enhanced MQ procedures:
   1. Shaft wobble: verify paddle and basket shaft wobble measurements in addition to basket wobble.
   2. Vessel verticality: measure in two locations on the vessel wall, 90° apart.
   3. Shaft verticality: verify that each shaft is vertical at two locations 90° apart
   4. Vessel-to-shaft centering at 2 positions - one near the top but below the vessel rim and one just above the bottom portion of the vessel

4. Control of Significant Sources of Variability

a. Vessel Quality
   1. Acquire and install quality vessels to avoid variation in dissolution results caused by vessel imperfections.
   2. It is recommended to use the same supplier for dissolution vessels at all active vessel locations.
   3. Review COA/COCs for minimal variability of USP tolerances. Consider molded dissolution vessels to minimize variation, where applicable.
   4. Continually monitor and document vessel condition for scratches, cracks and residue buildup.

b. Vibration
   1. Place apparatus in an environment free from sources of vibration. Though the USP/FDA/ICH/FIP do not offer tolerances for vibration, it may have a significant impact on dissolution test results.
   2. Obtain baseline vibration measurements and periodically check to monitor change over time to ensure the vibration level of the environment remains suitable.

c. Dissolved Gases
   1. Define, validate, and control degassing procedures for dissolution media to eliminate variability. This should be performed as a part of testing SOPs with any dissolved gasses that cause test interference.
   2. Gently pour media and begin the test as soon as possible following vessel filling to avoid reaeration.

References

1. E 2503-07 Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus; ASTM International; April 2007.

2. Implementation Guidance for American Society for Testing and Materials (ASTM) E 2503-07 "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus." The Open Drug Delivery Journal, 2010, Volume 4.

3. Agilent White Paper: Proper Implementation of Enhanced Mechanical Calibration of Dissolution Apparatus 1 and 2, Boda and Crist, Agilent Technologies, May 2012.

Dissolution Qualification Timeline / Schedule

Physical parameter verification of the dissolution apparatus has always been required before performing dissolution tests and periodically as part of Performance Qualification testing. One of the advantages of enhanced Mechanical Qualification (MQ) implementation is time savings. From a user perspective, these MQ measurements may be performed in considerably less time which allows them to be performed more often. Once the procedure is firmly integrated into your laboratory routine, it provides less downtime and scheduling issues. The time savings can be significant with these hours, or even days, now available that used to be filled with Prednisone testing and analysis.

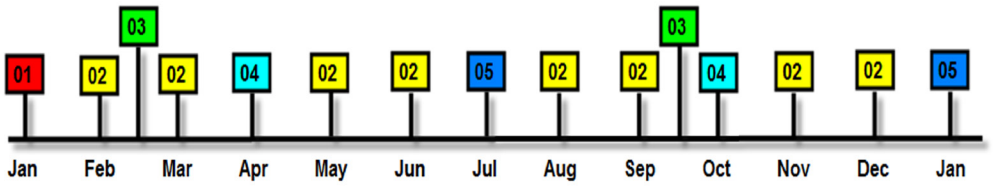
Let's explore how even greater efficiency and reduced instrument downtime can be achieved. We'll examine how some intermittent procedures and monitoring can be inserted into the routine care and maintenance of the dissolution equipment to prevent foreseeable issues and help with future failure investigations.

The timeline displayed below offers one example of how incorporating periodic evaluations – daily, weekly, monthly, or quarterly – between traditional qualifications can lessen the likelihood of problems related to your dissolution instruments. Due to the ability to reduce measurement time and its software trending feature, Agilent's **280-DS Mechanical Qualification System (MQS)** has been used to illustrate this concept. With routine measurement and trending, the laboratory may see a problem before a parameter is out of specification. For instance, steadily increasing paddle wobble measurements from month to month could be corrected before becoming an out-of-specification (OOS) result.

The example timeline consists of an IQ/OQ/PQ (where PQ = USP PVT) performed during initial qualification. Although the PVT is no longer required if it has been replaced by full implementation of MQ, it is still used by some dissolution laboratories during initial installation along with MQ as part of a hybrid approach. Over the next 12 months, several shorter procedures are in place to consistently monitor instrument performance and ensure apparatus integrity:

- **Initial**: IQ/OQ/PQ
- **Daily** (or at time of use): Accessory examination per ASTM E2503-07 guidelines. Verify any physical parameter as a check in only minutes.
- **Monthly**: Abbreviated physical measurements; wobble for paddle, basket shaft and basket along with vessel table level using the 280-DS, takes approximately 20 minutes to perform for both paddles and baskets.
- **Quarterly**: Complete verification of physical parameters using MQ procedure according to ASTM E2503-07; approximately 15-20 minutes per USP Apparatus using the 280-DS MQS.
- **Biannually**: Complete verification of physical parameters using MQ procedures according to ASTM E2503-07; also includes vibration measurement and re-verification of temperature probes; if applicable, auto-sampling instrumentation is inspected and reverified (e.g., volume accuracy); this procedure takes approximately 15-20 minutes per USP Apparatus and an additional 20 for temperature and vibration.
- **Annually**: Biannual procedure plus PM performed by manufacturer.
- **Intermittent**: reverification of critical physical parameters for failure investigation purposes of apparatus installed during unexplained behavior; examination of data trends for the apparatus approximately 15 minutes for complete measurement cycle using 280-DS. Additionally, environmental conditions are reevaluated whenever new instrumentation is added to the bench to ensure that the level and vibration parameters have remained unchanged.

The MQ procedure allows for a robust evaluation schedule to exist with a very manageable time commitment. When coupled with the 280-DS MQS and data trending capability of the software, problems can be proactively addressed and failure investigations improved dramatically. This is just one example of how you may schedule your dissolution qualifications – for additional advice, chat with your peers on the **Dissolution Discussion Group (DDG)** or ask our in-house experts on the **Dissolution Exchange**.



01 Initial instrument qualification: IQ, OQ and USP PVT (2-3 days)

02 Abbreviated MQ: Shaft/Vessel Verticality, Centering, Height, Wobble, Vessel Table Level for Paddles and/or Baskets (20 minutes)

03 FAILURE INVESTIGATION - All physical parameters verified for one apparatus only (15 minutes)

04 Mechanical Qualification (MQ) for Paddles and Baskets according to ASTM E2503-07 (30 minutes)

05 MQ for Paddles and Baskets according to ASTM E2503-07 plus vibration, temperature probes and sampler, if applicable (45 minutes)

MQ Survey Results

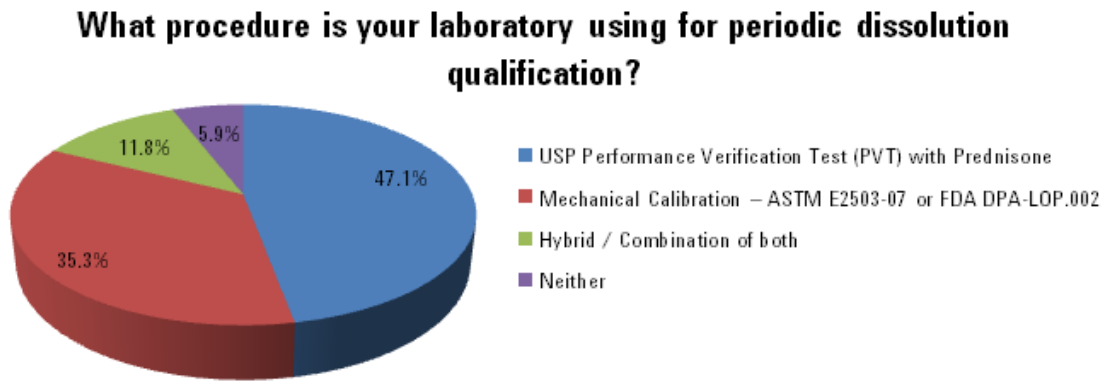
Agilent surveyed the attendees from its recent MQ seminars and asked for their input on some of the key aspects of dissolution qualification. Here's what they said:

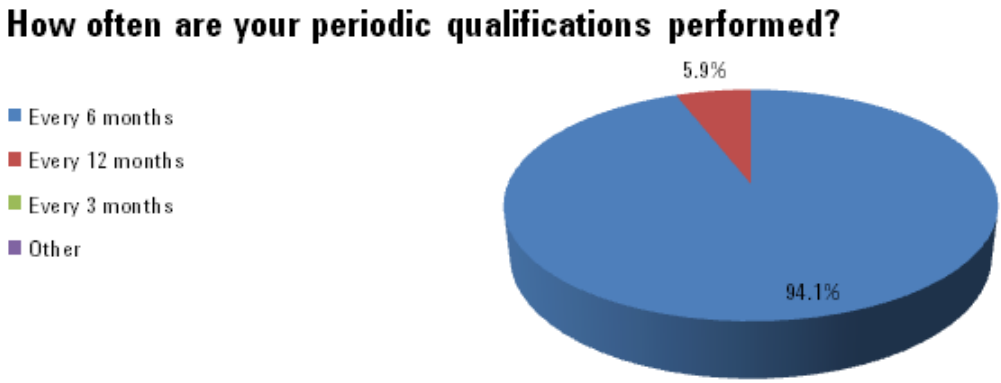
When considering changes to the dissolution qualification schedule, what are or have been your biggest hurdles to overcome? *	
Risk assessment: will the new process effectively identify problems	53%
Understanding of Regulations / Compliance	53%
Financial analysis / Justification	47%
Change Control process	47%
Implementation	24%

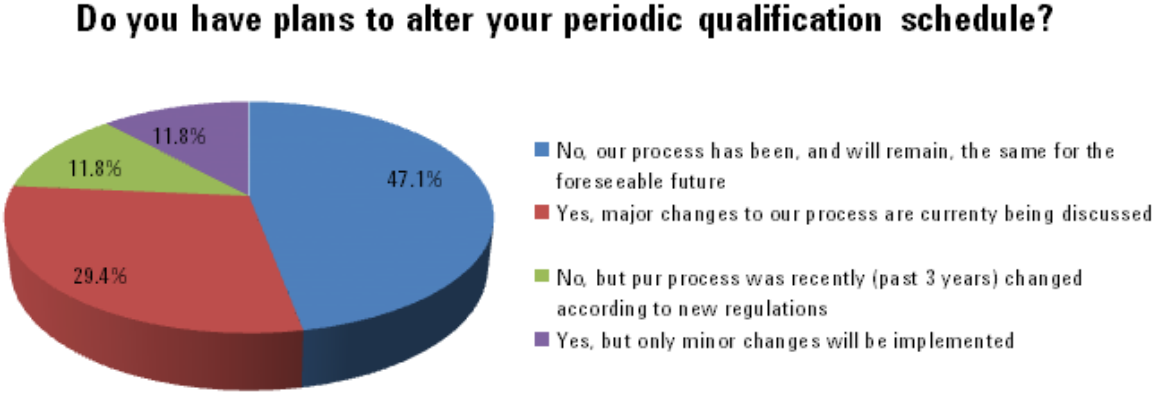
* Participants were asked, if applicable, to enter multiple answers.

What are the key factors that drive changes to your Dissolution qualification schedule? *	
Regulatory compliance	77%
Time savings / Productivity	71%
Budget / Cost savings	41%
Continuous improvement	41%
Specifications / Tolerances of procedures	35%

* Participants were asked, if applicable, to enter multiple answers.







Mechanical Qualification Guidance Summary

One reason that many dissolution laboratories are hesitant to change their qualification procedure is due to a lack of understanding of the position(s) taken by various worldwide agencies. The following table provides a brief summary and helpful links to describe some recent guidance:

Agency	Statement (Excerpt)
International Conference on Harmonisation (ICH)	"An appropriately rigorous mechanical calibration method, when properly executed, should satisfy the current good manufacturing practice (CGMP) requirement for dissolution apparatus calibration under § 211.160(b)(4) of Title 21 of the Code of Federal Regulations." **Reference**: International Conference on Harmonisation ICH Guideline Q4B Annex 7 (R2) For Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions on Dissolution Test – General Chapter; European Medicines Agency, September 2010:
International Pharmaceutical Federation (FIP)	"...the FIP Dissolution/Drug Release SIG recommends that the qualification of a dissolution test instrument should be performed following the calibration requirements as indicated in the FDA (draft) guidance. If additional system performance information is desired, a performance verification test using US Pharmacopeia Reference Standard tablet or an established in-house reference product can be conducted. Any strict requirement on the use of a specific performance verification test tablet is not recommended at this time." **Reference**: FIP Position Paper on Qualification of Paddle and Basket Dissolution Apparatus
United States Food and Drug Administration (FDA)	"This guidance recommends that an enhanced MC procedure (such as the one recommended in this guidance) can be used as an alternative to the current Apparatus Suitability procedure for Dissolution Apparatus 1 and 2 described in USP General Chapter <711> Dissolution. Regardless of whether the enhanced MC procedure or Apparatus Suitability procedure is used, the guidance also recommends that appropriate measures be taken to control the following sources of significant variability in dissolution testing: dissolved gases, vibration, and vessel dimensions." **Reference**: FDA Guidance for Industry: The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP): FDA Guidance for Industry: The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)
United States Pharmacopiea (USP)	"Analytical instrumental qualification (AIQ), which includes installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), is widely accepted. For dissolution assemblies, the mechanical calibration steps in this guide should satisfy OQ and parts of IQ. PQ may be satisfied by a performance verification test (PVT), in support of which USP makes available official USP Prednisone Reference Standard Tablets." **Reference**: USP Dissolution Toolkit Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and Apparatus 2 Version 2.0 March 22, 2010
World Health Organization (WHO)	"Periodically verify the performance of the equipment[3] utilizing an appropriate mechanical procedure or reference tablet." [3] For example, use the mechanical process described in International Standard procedure ASTM 2503-07 or reference tablets such as those available from United States Pharmacopeia Convention Inc., every 6-12 months for each individual system. **Reference**: 5.5 Dissolution Test for Solid Oral Dosage Forms, Revised Draft Proposal; World Health Organization, July 2012

Dissolution 1-on-1: In-depth Training in a Self-paced Environment

The training and education of pharmaceutical chemists and analysts is a vital component of regulatory compliance that helps to ensure the safety of our pharmaceutical drugs. While there are many courses available to teach HPLC and UV analytical techniques, an analyst often learns dissolution techniques primarily by working alongside another analyst. This method of training points out the important need for standardized dissolution training to ensure that all analysts are capable of conducting accurate and reliable testing in a demanding laboratory environment.

To make it easier for analysts to get up-to-date dissolution training, Agilent recently launched a newly updated version of **Dissolution 1-on-1**, its industry-leading, self-paced training course on the **Dissolution Exchange**. This comprehensive online course is free and can serve as a training resource for new analysts or as a refresher for experienced dissolution chemists, technicians, reviewers, and metrologists.

This in-depth course provides six chapters of information as well as a reference section and a comprehensive glossary of terms. It incorporates many updates including the latest industry changes regarding dissolution apparatus qualification, plus an introduction to dissolution testing. The course covers:

Foreword

1. Introduction to Dissolution Testing

2. The Dissolution Apparatus - Anatomy

3. Critical Physical Parameters

4. Performing the Dissolution Test

5. Dissolution Apparatus Qualification

6. Dissolution and Automation

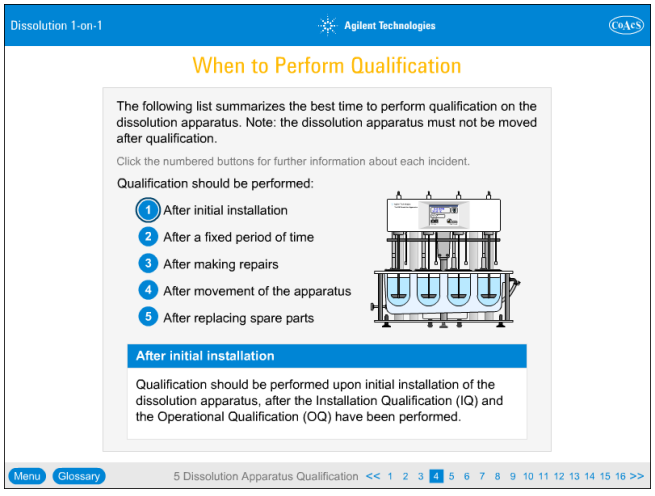
7. Reference Information

Information on Assessment and Certification

This globally-accessible resource is highly interactive and is an easy to navigate learning experience. Simply register once and you'll gain access to a wealth of information to support your dissolution testing training needs for a long time to come.

Agilent has also partnered with CoAcS, Ltd. to produce a comprehensive assessment package that you can purchase to test analysts on the course material. This testing package allows you to identify managers by site or department that can in turn identify those that need training and assessment. The training package offers up to three opportunities for successful completion, at which time the user and his manager receive confirmation of satisfactory completion. Training packages are managed and tracked online for your convenience.

Be sure to **take a tour** of the course to learn more. Or contact your Agilent Representative today for detailed information on our training resources.



Enhancer Cell and the new USP chapter <1724> Semisolid Drug Products – Performance Tests

The Enhancer Cell has been used by pharmaceutical industry for the evaluation of ointments, creams, gels and even selection of transdermal components for nearly 20 years. It is now contained as a performance test for semisolid dosage forms in the First Supplement to USP 36-NF 31, Official August 1, 2013 as the "Immersion Cell Apparatus, Model A".

The new USP chapter provides detailed theory on diffusion cell performance testing with a variety of apparatus but it highlights immersion cell apparatus specifications and tolerances based on the Agilent **Enhancer Cell** and the small volume adapter kit based on a 200-mL flat bottom vessel and mini paddle. The Agilent Enhancer Cell and adapter kit fits seamlessly in the Agilent **708-DS** as well as all previous instruments manufactured by Varian and VanKel. See the example 708-DS Enhancer Cell Conversion Kit details below.

For information on Agilent's adapter kits for previous versions of dissolution apparatus such as the 7000 or 7025 V-Series Dissolution Apparatus, **contact the Dissolution Hotline**. We also have **a video available** that illustrates proper Agilent Enhancer Cell setup and technique.

PN	Description	Quantity
12-6368	TruAlign vessel conversion kit, 100/200 mL	6 or 8
12-5170	TruAlign vessel, flat bottom, 200 mL	6 or 8
13-3608	Mini paddle, lower interchangeable, electropolished stainless steel	6 or 8
12-4000	Enhancer Cell, 4 cm^2 surface area membrane	6 or 8
12-4020	Alignment tool, for 4 cm^2 Enhancer Cell	1
12-4015	Adjustment tool, for all Enhancer Cell sizes (Alternate sizes available)	1

Compendial Updates

Provided by:
Margareth R. C. Marques and
William Brown – U. S. Pharmacopeia

In an attempt to keep you abreast of any changes to the USP, we've invited Margareth Marques and Will Brown from the USP to provide an update.

Note: These are opinions and interpretations of the authors, and are not necessarily the official viewpoints of the USP

Updates on USP Activities Related to Dissolution, Disintegration, and Drug Release

All revisions and updates to any USP monographs or general chapters are published in Pharmacopeial Forum (PF) for a 90-days period for public comments. Pharmacopeial Forum is **available free of charge**. The revisions are downloaded into the site every two months. This site allows search by key word and by monograph and general chapter titles. The online offering gives Pharmacopeial Forum from volume 28 (Jan – Feb 2002) to the present.

Semisolid Drug Products Performance Tests

The new USP general chapter <1724> Semisolid Drug Products – Performance Tests is going to be official in the First Supplement to USP 36 on August 1, 2013. This chapter covers the equipments (vertical diffusion cell, immersion cell, and cell for USP Apparatus 4) and the procedures that can be used to evaluate the drug release from semisolid drug products such as creams, ointments, gels and lotions. Currently, this test is not used routinely for batch release but is an important tool during product development and for post-approval changes (see FDA Guidance for Industry – Nonsterile Semisolid Dosage Forms – Scale-up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and In Vivo bioequivalence Documentation).

Development and Validation of Dissolution Tests

The USP general chapter <1092> The Dissolution Procedure: Development and Validation is under review and a revision is being finalized for presentation in Pharmacopeial Forum. The revised chapter will expand on the information currently provided for method development and validation and will add sections on automation, the analytical finish, and acceptance criteria including interpretation of results. Tentatively, the In Process Revision proposal is targeted at PF 39(5) [Sept-Oct 2013].

Continued on p. 8

Drug Release <724>

When the USP general chapter <711> Dissolution was harmonized with the European Pharmacopoeia (EP) and the Japanese Pharmacopoeia (JP), parts of the USP general chapter <724> Drug Release were transferred to <711> Dissolution but the chapter <724> is not harmonized with EP and JP.

This chapter is being completely rewritten in a more user-friendly way. The drawings of some of the equipments described in this chapter are being updated to better reflect what is commercially available. Also, new accessories are being added to the text. The new version of the chapter will be published in PF 39(4) for public comments.

Dissolution Testing of Capsules

The new USP general chapter <1094> Liquid-filled Capsules – Dissolution Testing and Quality Attributes was published in PF 38(1). After this publication comments were received saying that most of the content of the chapter is applicable to all types of capsules. As consequence of these comments, the chapter was completely revised to include all types of capsules (hard or soft, gelatin or starch or cellulose derivatives) and all types of capsule fill (liquid, semisolid or solid). This chapter discusses the influence of capsule shell composition, capsule fill formulation, storage conditions, etc. on the dissolution behavior of capsules. Also, it contains information on the dissolution testing conditions to be used with capsules with particular emphasis on the use of enzymes with gelatin capsules with cross-linking. The new revised version of the chapter will be published in PF 39(3).

Dissolution <711>

The USP general chapter <711> Dissolution contains a paragraph allowing the use of enzymes when gelatin capsules and gelatin-coated tablets do not conform to the dissolution specification. The chapter recommends the use of pepsin for dissolution media with a pH of less than 6.8 and of pancreatin for media with a pH of 6.8 or greater. The text in the chapter presents some challenges:

1. It does not relate the dissolution failure with the presence of cross-linking in the gelatin. The user can assume that the enzymes can be used for any type of failure, even those not related to gelatin cross-linking;
2. Pepsin has an acceptable activity only up to pH around 4 and pancreatin with media with pH above 6.8. There is no enzyme recommended for the gap in this pH range. Also, the chapter does not give any guidance for dissolution media containing surfactants. Pepsin and pancreatin are not compatible with some types of surfactants.

To address all these issues, USP created an expert panel that is evaluating possible alternatives and modifications in the two-tier dissolution testing of cross-linked gelatin capsules. A revision to the USP general chapter <711> Dissolution, together with the rational for the modifications, will be published in a future issue of PF. Please, contact **Margareth Marques** for more information.

The descriptions of dissolution apparatus given in general chapter <711> Dissolution differ from the enhanced mechanical calibration specifications and information provided in the USP Dissolution **toolkit** and by the FDA guidance, ***The use of mechanical calibration of dissolution apparatus 1 and 2—current good manufacturing practice (cGMP)***. Opportunities for incorporating some of the enhanced mechanical calibration specifications into the general chapter are being explored by the General Chapters Dosage Forms Expert Committee. The Committee recognizes their responsibility to avoid unilateral revision of this harmonized general chapter. Therefore, in addition to the public comment process provided by Pharmacopeial Forum, any revision will be through the processes of the Pharmacopeial Discussion Group (European Pharmacopoeia, Japanese Pharmacopoeia, and USP).

Workshop Dissolution Testing of Capsules

A workshop to discuss all the aspects of the dissolution testing of any types of capsules, including dietary supplements, will be held at the USP headquarters in Rockville, MD, USA on March 24 – 25, 2014. The program and instructions for registration **will be available** in the near future.

Updates on USP Activities Related to Dissolution, Disintegration, and Drug Release

All revisions and updates to any USP monographs or general chapters are published in Pharmacopeial Forum (PF) for a 90-day period for public comments. Pharmacopeial Forum is **available free of charge** online. The revisions are downloaded into the site every two months. This site allows search by keyword and by monograph and general chapter titles. Pharmacopeial Forum has been available online since volume 28 (Jan – Feb 2002).

Ophthalmic Products

In the current version of USP there is only one chapter for ophthalmic products, <771> *Ophthalmic Ointments*. This chapter is out of date and addresses only ophthalmic ointments. This chapter is being revised to include a discussion of all dosage forms that can be applied to the eye. The revised chapter will incorporate the quality tests appropriate for ophthalmic products and it is being named <771> *Ophthalmic Products – Quality Tests*. The text of the general chapter <751> *Metal Particles in Ophthalmic Ointments* has been transferred to <771> under *Particulate and Foreign Matter* and its content has been updated. Therefore, the chapter <751> is being deleted. As a consequence of this change, all monographs for ophthalmic ointments are being revised with the deletion of the reference to chapter <751> and to other chapters included in the new version of <771>. In place of the deleted references, a new reference, *Other requirements – meets the requirements under <771> Ophthalmic Preparations – Quality Tests* will be added.

A new general chapter, <1771> *Ophthalmic Preparations – Performance Tests*, discussing dissolution and drug release testing for ophthalmic products has been developed. The new chapter discusses some of the apparatus and conditions that could be use.

Both chapters and a Stimuli article, with more information on ophthalmic dosage forms, are going to be published in PF 39(5). The deadline to send comments to **Margareth Marques** is November 30, 2013.

Workshop Ophthalmic Products

A workshop to discuss the new USP general chapters and other topics related to ophthalmic products, including dissolution and drug release, is going to be held at the USP headquarters in Rockville, MD, USA on Oct 21-22, 2013. The program and instructions for registration are **available online**. Please, **contact Margareth Marques** for more information.

Workshop Dissolution Testing of Capsules

A workshop to discuss all aspects of the dissolution testing of any types of capsules, including dietary supplements, will be held at the USP headquarters in Rockville, MD, USA on March 24 – 25, 2014. The program and instructions for registration will be **available online** in the near future. Please, **contact Margareth Marques** for more information.

Tablet Splitting

A new general chapter, <705> Quality Attributes of Tablets Labeled as Having a Functional Score, has been developed. The new general chapter gives specifications for tablets with labeling approved by the FDA under the Guidance for Industry, Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. Dissolution testing of split tablets from immediate release and extended release products is included as part of the new general chapter.

The new chapter and a Stimuli article, explaining the proposed requirements, will be published in PF 39(4), available online July 2013. The deadline to **send comments to Will Brown** is September 30, 2013.

Learn more:

www.agilent.com/lifesciences/dissolution

Printed in the U.S.A., August 14, 2013
5991-2822EN