



**Regulatory Update:  
Enhanced Mechanical  
Qualification of the  
Dissolution Apparatus**

Bryan Crist  
Scientific Affairs Manager,  
Agilent Technologies,  
Dissolution Systems

Dissolution Exchange  
WebEx

[Bryan.crist@agilent.com](mailto:Bryan.crist@agilent.com)

# Introduction

The dissolution test has evolved to become a definitive tool used to characterize the performance characteristics of solid oral dosage forms

The dissolution test is remarkably sensitive to the slightest perturbations. As a result, it is critical to isolate the effects of the dissolution tester and the environment from the release characteristics of the dosage form.

Traditionally “calibrators” have been used to determine the acceptance of an apparatus, but is this really the best solution?

# An Overview of In Vitro Dissolution

In vitro dissolution data will be of great importance when assessing changes in production site, manufacturing process, or formulation, and assist in decisions concerning the need for bioavailability studies.

The proper qualification of the apparatus is critical to accurate and precise evaluation of dosage form performance

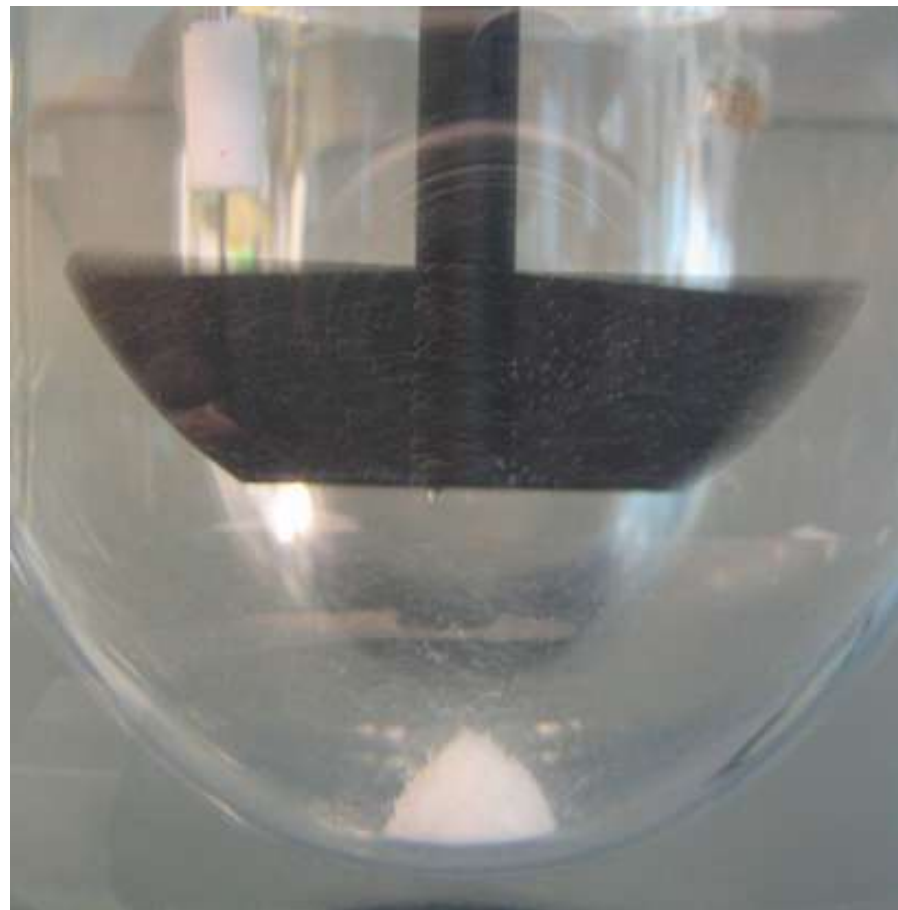


# An Overview of the Dissolution Performance Test

The dissolution apparatus allows the testing of six dosage forms. Each position has:

- An inert hemispheric **vessel**
- A dissolution **solvent** (medium)
- A **rotating spindle** which provides the hydrodynamic flow of the solvent across the surface of the dosage form

The dissolution apparatus must maintain these three components in terms of alignment, stability and isolation from the environment





# BACKGROUND OF PERFORMANCE QUALIFICATION AND ANALYTICAL INSTRUMENT QUALIFICATION (AIQ)

# Background of Performance Qualification

## USP Performance Verification Test (PVT)

- Official since 1978, USP Calibration with Prednisone and Salicylic Acid has been the means of qualifying the dissolution apparatus.
- Initially, the primary purpose was to indicate environmental effects on the apparatus and vibration since most other parameters could be controlled by mechanical measurements
- The original test was called “Calibration” which was not a true indication of the test being performed, later changed to “Performance Verification” (PVT)
- The PVT, has been responsible for detecting problems associated with dissolution apparatus that are found to be within mechanical tolerances

# Background of Performance Qualification

## An Alternative Approach to PVT:

- A Subcommittee on Dissolution Calibration was formed within the Dissolution Subcommittee of the Pharmaceutical Research and Manufacturers (PhRMA) in 1996.
- A collaborative study on perturbation was performed by twelve PhRMA laboratories; the goals were:
  - To evaluate alternative dissolution apparatus suitability test requirements
  - Identify which aspects of calibration add value to the evaluation of bath performance
  - Evaluate non-value added activities performed during dissolution calibration, including the potential elimination of calibrator tablets

# Background of Performance Qualification

## An Alternative Approach to PVT:

- The results of the perturbation study were published in a US Pharmacopeial Forum Stimuli article *Dissolution Calibration: Recommendations for Reduced Chemical Testing and Enhanced Mechanical Calibration*; Vol.26, No.4, 2000; were as follows:
  - Perform enhanced mechanical calibration every three months
  - The use of a calibrator should be maintained until enhanced mechanical calibration is further defined including establishment of a definitive vibration tolerance
  - Eliminate Salicylic Acid Calibrator Tablet



# Background of Performance Qualification

## USP Performance Verification Test (PVT)

As of March 1<sup>st</sup>, 2010, Lot P1I300 became the official USP prednisone calibrator tablet. With the new lot, a new set of acceptance criteria based on both geometric mean and %CV was adopted. The current lot is now lot Q0H398.

In addition to the changes in acceptance criteria, some minor changes to the dissolution test recommendations have occurred

# Background of Performance Qualification

## USP Performance Verification Test (PVT)

Per the new acceptance criteria, the user has the option of either a single-stage test or optional dual-stage test:

- Single-Stage Test – Perform 2 dissolution tests for a total of 12-16 samples.
- Optional Dual-Stage Test – Perform 1 dissolution with tighter acceptance criteria, if first run meets tighter criteria, testing can stop. If test does not meet criteria, perform second run and use overall mean and % CV

# Background of Performance Qualification

Table1. Performance Verification Test (PVT) limits (values apply only to Lot Q0H398)

Apparatus	# of vessels	Single-Stage		Two-Stage			
		GM*	%CV	1 <sup>st</sup> Stage of Two Stages		2 <sup>nd</sup> Stage of Two Stages	
				GM*	%CV	GM*	%CV
1	6	54 - 72	12	57 - 69	9.2	54 - 72	12
	7				9.2		
	8				9.3		
	12			na			
	14			na			
2	6	26 - 38	6.7	27 - 36	4.9	26 - 38	6.5
	7		6.5		4.9		6.3
	8		6.4		5.0		6.3
	12		na				
	14		na				

\* Percent of the labeled amount of prednisone dissolved at 30 minutes at 50-rpm

# Background of Performance Qualification

## Concerns with new USP PVT acceptance criteria:

- Perceived variability with PVT Prednisone tablets
- Difficulty meeting %CV Acceptance Criteria
- Failure investigations did not identify influences from:
  - Poor vessel quality and condition
  - Poor paddle and basket quality and condition
  - Vessel retaining systems failing
  - Unvalidated deaeration techniques
  - Unvalidated automated methods
  - Unvalidated filters

# Background of Performance Qualification

## Initial Concerns with Mechanical Qualification

- Most dissolution apparatus have evolved to precisely control physical parameters, test conditions and alignment to ensure that the release of drug from a dosage form will be determined consistently from one location to another. However, apparatus found around the world are not necessarily equivalent
- Vessels and vessel construction techniques vary tremendously throughout the world
- Present Dissolution Performance Verification testing has revealed problems with dissolution apparatus which are well within mechanical tolerances
- Should Mechanical Qualification alone replace the traditional performance evaluation with the Performance Verification Test (PVT) from the USP?

# Analytical Instrument Qualification

## USP <1058> Analytical Instrument Qualification

### Definition of Performance Qualification (PQ):

- Usually based on the instrument's application and may consist of analyzing known components or standards
- PQ tests may be modular or holistic
- PQ tests should be based on good science and reflect the general intended use of the instrument
- When an instrument fails to meet PQ test specifications, it requires maintenance or repair



# DISSOLUTION MECHANICAL QUALIFICATION GUIDANCE AND STANDARDS

# Dissolution Mechanical Qualification Guidance

## The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)

FDA – Guidance for Industry January 2010

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070350.pdf>

CGMP requires laboratory apparatus be calibrated at suitable intervals in accordance with established written specifications (21 CFR 211.160 (b)(4))



# Dissolution Mechanical Qualification Guidance

## The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 Current Good Manufacturing Practice (CGMP) - Claims:

- Enhanced Mechanical Calibration (MC or MQ) of dissolution apparatus may be used as an alternative to the current *Apparatus Suitability* procedure for Dissolution Apparatus 1 and 2 described in USP <711>
- The MC procedure should specify the frequency at which each calibration step is performed
- Either the USP procedure or an appropriate MC method executed according to a written procedure will satisfy the CGMP requirement for calibration of the laboratory apparatus...
- Regardless of which procedure is used, appropriate measures must be taken to control the following sources of significant variability in dissolution testing: dissolved gases, vibration, and vessel dimensions.

# Dissolution Mechanical Qualification Standards

## Mechanical Qualification of Dissolution Apparatus 1 and 2

US Food and Drug Administration (FDA), DPA-LOP.002, Version 2.0, Effective Date 02 June, 2006

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM142492.pdf>

- Free Download
- First official mechanical qualification procedure

# Dissolution Mechanical Qualification Standards

## Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus

American Society for Testing and Materials, International (ASTM), Designation E 2503-13, Effective 2013

[http://enterprise.astm.org/filtrexx40.cgi?+REDLINE\\_PAGES/E2503.htm](http://enterprise.astm.org/filtrexx40.cgi?+REDLINE_PAGES/E2503.htm)

- Cost: \$32.00 USD
- E2503 is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical Products and is the direct responsibility of Technical Subcommittee E55.03 on General Pharmaceutical Standards

# Mechanical Qualification Standards

## FIP Position Paper on Qualification of Paddle and Basket Dissolution Apparatus

International Pharmaceutical Federation (FIP) Dissolution/Drug Release Special Interest Group, White Paper, AAPS PharmSciTech, 16 July 2009

<http://www.pharmagateway.net/Authenticated.aspx?doi=10.1208/s12249-009-9291-5>

- Requires registration or AAPS membership

# Mechanical Qualification Standards

## FIP Position on Mechanical Qualification

- Recommends mechanical qualification requirements as indicated in the FDA (Draft) Guidance
- If additional system performance information is desired, conduct a performance verification test using either:
  - USP Performance Verification Test with Prednisone Reference Standard Tablets
  - An established in-house reference product
- The use of a specific performance verification test tablet is not recommended at this time

# Mechanical Qualification Standards

## Dissolution Test General Chapter

International Conference on Harmonization (ICH) Topic Q4B Annex 7; For Evaluation and Recommendation of Pharmacopoeial Texts for Use in The ICH Regions, European Medicines Agency (EMA), December 2008

<http://www.emea.europa.eu/pdfs/human/ich/64546908en.pdf>

- Lists conditions of interchangeability of Harmonized Dissolution Test for USP, JP and EP

# Mechanical Qualification Standards

## ICH Q4B Dissolution Test General Chapter

- Cites FDA's endorsement of a rigorous mechanical calibration such as
  - ASTM E2503-07
  - FDA DPA-LOP.002
- When properly executed will satisfy the current good manufacturing practice (CGMP) requirement for dissolution apparatus calibration under US Code of Federal Regulations (CFR) 211.160(b)(4)

# Dissolution Mechanical Qualification Standard Requirements

1. Check vessel, basket and paddle dimensions on receipt or obtain COC
2. Perform maintenance procedures recommended by manufacturer
3. Perform mechanical qualification:
  - At documented intervals (6-month, 3-month, 1-month, weekly) based on risk
  - After apparatus is moved
  - After apparatus is repaired
4. Perform “Operational Checks” at each time of use
5. FDA requires implementation of laboratory controls for significant sources of vibration affecting dissolution testing
  - Vessel quality
  - Deaeration
  - Vibration

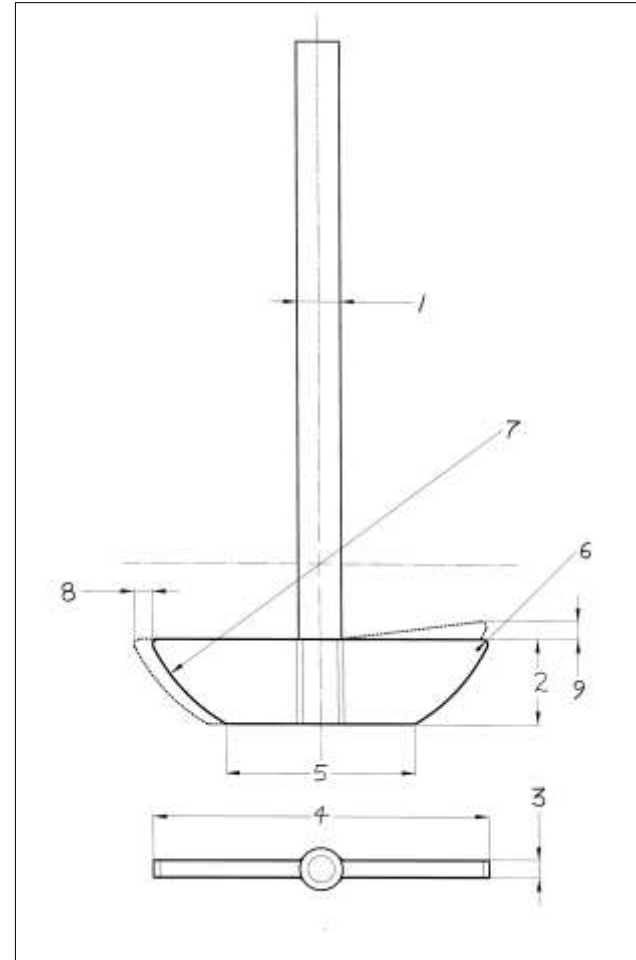


# Dissolution Mechanical Qualification Standard Requirements

Check Dimensions Upon Receipt:

Paddle, Basket/Shaft, and Vessel apparatus components must be verified that they conform with the harmonized standard USP <711> Dissolution (USP, JP, EP)

- Individual measurements for each dimension of each component must be documented
- Certificates of Conformance (COC) may be obtained from Agilent to document conformance.
- Otherwise, measurements must be documented by the end user.



# Dissolution Mechanical Qualification Standard Requirements

Perform Maintenance Procedures:

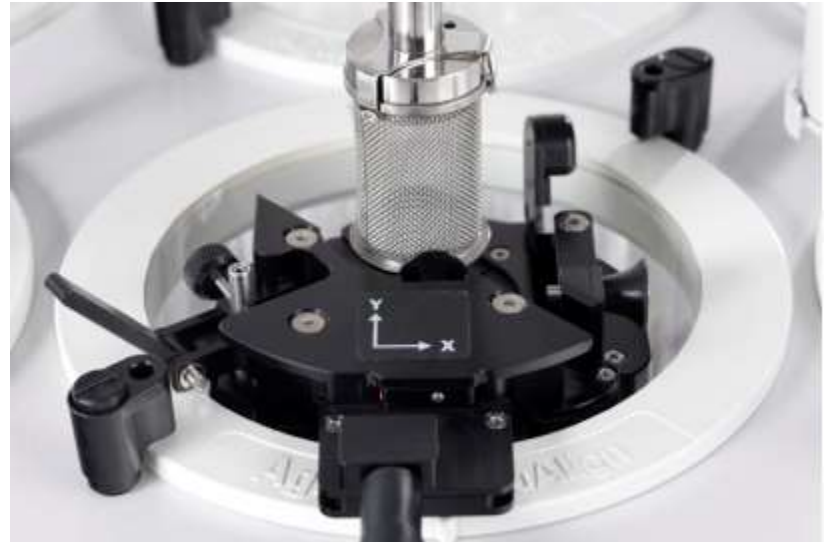
- Lubricate moving parts
- Check belt for wear and proper tension
- Check power cords and cable connections for wear
- Check alignment of belt, pulleys and spindle housing
- Clean water bath, replace tubing if necessary and use algaecide approved for heater/circulators



# Dissolution Mechanical Qualification Standard Requirements

## Mechanical Qualification Requirements:

- Shaft Wobble
- Paddle/Basket Shaft Verticality
- Basket Wobble
- Vessel Centering
- Vessel Verticality
- Paddle/Basket Depth
- Rotational Speed



# Dissolution Mechanical Qualification Specifications and Tolerances

Parameter	ICH Harmonized (USP, JP, EP)	FDA DPA-LOP.002	ASTM E2503-07	USP Toolkit Ver 2.0
Basket and Paddle Depth	25 ± 2 mm	25 ± 2 mm	25 ± 2 mm (or <8%)	23-27 mm
Rotational Speed	± 4% of specified rate	± 2 rpm of target	± 2 rpm or within 2% of target (larger)	± 1 rpm of target
Shaft Wobble	No significant wobble	≤ 1.0 mm total runout	≤ 1.0 mm total runout	≤ 1.0 mm total wobble
Shaft Verticality	Not measured	≤ 0.5° from vertical	Within Bubble	Not measured
Basket Wobble	± 1 mm	≤ 1.0 mm total runout	≤ 1.0 mm total runout	≤ 1.0 mm total wobble

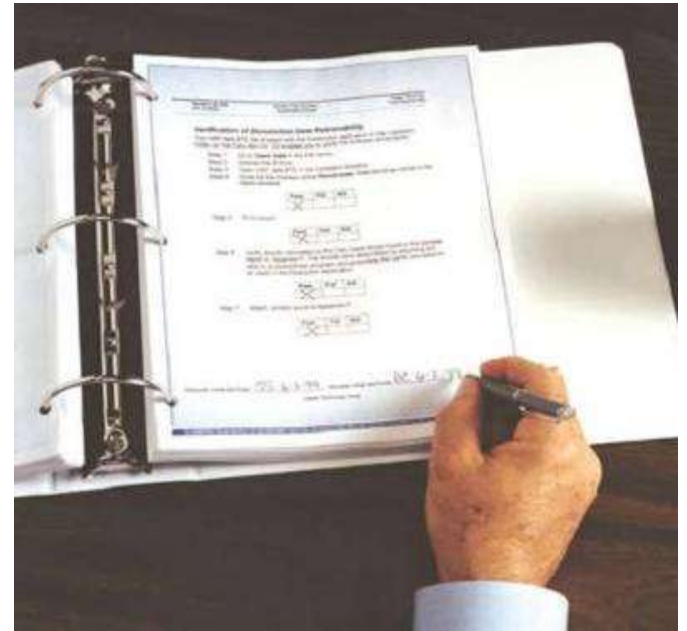
# Dissolution Mechanical Qualification Specifications and Tolerances

Parameter	ICH Harmonized (USP, JP, EP)	FDA DPA-LOP.002	ASTM E2503-07	USP Toolkit Ver 2.0
Vessel/Shaft Centering	NMT 2 mm from center axis	$\leq 1.0$ mm from center line	$\leq 1.0$ mm from center line	NMT 2.0 mm difference (4-90° positions)
Vessel Verticality	Not Measured	$\leq 1.0^\circ$ from vertical (2 - 90° positions)	$\leq 1.0^\circ$ from vertical (2 - 90° positions)	NMT 0.5° from vertical
Vessel Plate Level	Not Measured	Not Measured	Not Measured	NMT 0.5° from horizontal
Performance Verification Test (PVT)	USP Prednisone Tablets RS	Not Measured	Not Measured	USP Prednisone Tablets RS

# Dissolution Mechanical Qualification Standard Requirements

Operational Checks ( document each time of use):

- Basket/shaft examination
- Paddle examination
- Vessel examination
- Vessel Temperature
- Vibration



# Dissolution Mechanical Qualification Standard Requirements

**Basket and Basket Shaft, must be free from:**

- Defects
- Rusting
- Corrosion
- Loose wires
- Clogged mesh openings
- Dented sides or bottom
- Knicks, dents or misshapen appearance
- O-ring are not compliant; three clips required

# Dissolution Mechanical Qualification Standard Requirements

**Paddle Examination**, must be free from:

- Defects
- Rusting
- Corrosion
- Peeling or loose coating
- Knicks, dents or misshapen appearance



# Dissolution Mechanical Qualification Standard Requirements

**Vessel Examination**, must be free from:

- Scratches
- Cracks
- Pits
- Residue
- Surface irregularities

# Dissolution Mechanical Qualification Standard Requirements

**FDA Guidance requires control of significant sources of variability:**

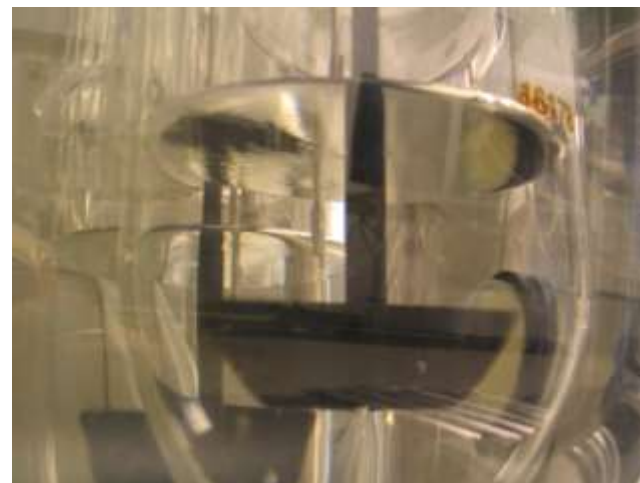
- Dissolved gases - to be removed through a validated deaeration procedure
- Vibration - sources to be eliminated:
  - Shakers, mixers, fume hoods, pumps, centrifuge, radio, etc...
  - Malfunctioning internal components
  - Heater/circulator problems
- Vessel dimensions - conform with cylindrical, circular sides and hemispherical bottom



# Vibration Frequency vs. Displacement



Ripple pattern at 20 Hz



Ripple pattern at 130 Hz

- At 20 Hz the displacement was close to the PhRMA proposal of 0.2 mils (0.0002 inch=0.0051 mm) had no effect on the Prednisone calibrator tablet
- At 130 Hz the displacement was one-tenth of the proposal at 0.02 mils (0.00002 inch = 0.00051 mm) had considerably higher results with two vessel failures.



# PVT OR MQ WHAT IS RIGHT FOR YOUR LABORATORY?

# PVT or MQ

## What Is Right For Your Laboratory?

### PVT Advantages:

- Holistic test with actual controlled tablets
- Conforms closely to USP <1058> Analytical Instrument Qualification, requirement for Performance Qualification
- New USP Acceptance Criteria provides for geometric mean and variability
- Detects issues with Vessel Quality
- Detects environmental issues
- PhRMA studies showed PVT should be maintained until a definitive vibration specification is developed

# PVT or MQ

## What Is Right For Your Laboratory?

### PVT Advantages:

When a PVT failure is observed it is a situation that requires investigation.

The PVT does not tell us exactly what is wrong but if we proceed without resolution, the consequences may be catastrophic!



# PVT or MQ

## What Is Right For Your Laboratory?

### PVT Disadvantages:

- Time – takes days to perform
- Expense:
  - Cost of USP prednisone tablets
  - Cost of USP reference standards
  - Analyst's time away from production
- FDA claims of USP tablet variability



# PVT or MQ

## What Is Right For Your Laboratory?

### MQ Advantages:

- Conforms closely to USP <1058> Analytical Instrument Qualification, requirement for Operational and Performance Qualification
- Simplicity
- Speed – Depending on the qualification instruments; from 20 minutes to a few hours
- Performed more often
- Tighter specifications and tolerances will lead to less mechanical variability





# PVT or MQ

## What Is Right For Your Laboratory?

### MQ Disadvantages:

- Misinterpretation of Certificates of Conformance for components – These are not to be confused with manufacturing conformance certificates which state parts are manufactured according to USP specifications
- Subjectivity of Component Examination at time of use
- Thinking that only mechanical qualification measurements have to be taken more often and not incorporating: PM, Certified Components, Operational Checks and Laboratory Controls
- Enhanced MQ Standards do not account for:
  - Vessel Quality
  - Vibration
  - Deaeration
  - Cumulative Perturbation



# Enhanced MQ Summary

## Primary reason customers in transition to MQ:

- Anticipated savings for time and money
- Anticipated reduction in frequency and intensity of investigations

## Common misconceptions about transition from PVT to MQ:

- Perceived variability in USP Prednisone PVT – cited by FDA
- Requirement for individual component “Certificates of Conformance” is not necessary
- MQ will reduce apparatus variability, however, vessel quality and effects of vibration will not be challenged

# 280-DS Mechanical Qualification System Components



# 280-DS Mechanical Qualification System Vessel Module



Vessel Module (VM) once placed in the vessel will measure:

**Spindle Speed (RPM)**

**Shaft Wobble**

**Basket Wobble**

**Shaft Verticality**

**Vessel Verticality**

**Vessel/Shaft Centering  
(upper and lower)**

**Basket/Paddle height**

# 280-DS Mechanical Qualification System Instrument Module (IM)

The Instrument Module (IM) is placed on the vessel plate to measure:

**Vessel Plate Level**

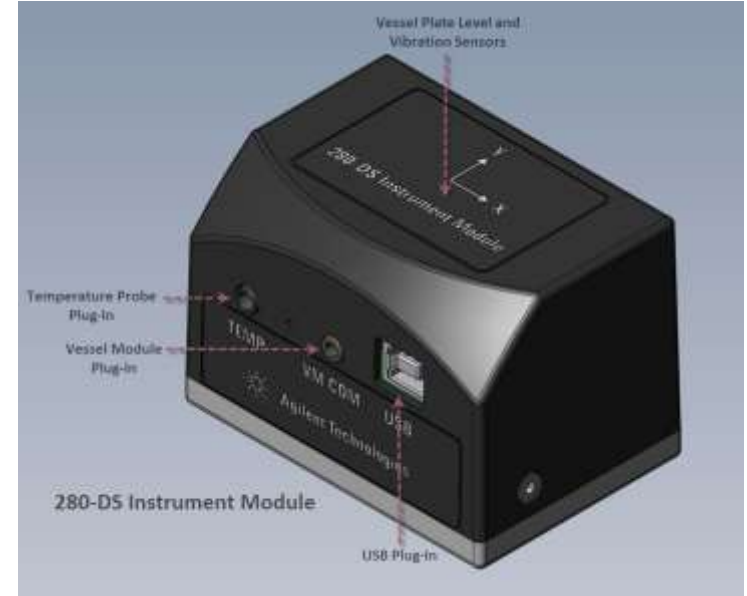
**Vibration**

**Temperature**



# 280-DS Mechanical Qualification System

## How it Works



# 280-DS Mechanical Qualification System

## A Protected Investment



Patent Pending

# The Advantage for MQ

Time Savings (35-min vs 2-days with PVT)

Ease of use allows shorter qualification intervals

Data that helps you pinpoint possible problems

Now have the ability to trend parameter variation over time

No guesswork associated with manual and analog gauges

No standards or tablets to purchase

Provides instant failure investigation information

Reports exact information required by Enhanced MQ Standards







**THANK YOU FOR ATTENDING!**