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Inspiring Excellence

Mechanical Qualification (MQ) for Apparatus 1 and 2

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- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)



- IQ Definition – the documented collection of activities necessary for installing an instrument in the user's environment
- Ensures the equipment and accessories have arrived undamaged and the order is complete
- Verifies that the user environment meets all vendor-specified requirements
- Instrument setup and verifying unit comes on usually completes the procedure



- OQ Definition – collection of basic functionality tests that ensure the instrument operates as intended by the manufacturer and the end user
- Tests performed are specific to the instrument being qualified
- Performed after the IQ or if the instrument undergoes service / modification or is moved to another location
- May be repeated at regular intervals if the instrument does not have a PQ or “calibration”



- PQ Definition – test(s) performed based on the typical on-site application of the instrument
- Performed after the IQ/OQ or at a pre-determined interval (usually every 6 months)
- Dissolution PQ includes the verification of basic physical parameters as well as execution of the PVT
- The USP Performance Verification Test (PVT) requires use of Prednisone and Salicylic Acid
- Used since 1978



Why MQ Now?

- It has long been understood that the physical parameters of dissolution apparatus and their tolerances can have significant impact on the quality of dissolution test results
- Recently, several standard-setting groups such as the FDA, USP and ASTM officially released protocols and recommendations to perform mechanical calibration of dissolution apparatus
- The FDA's draft guidance recommends the use of mechanical calibration for dissolution apparatus "as an alternative to the use of calibrator tablets" (PVT and PQ)



- MQ Definition - measurement and verification of a dissolution apparatus' physical parameters, which impacts the results of a dissolution test
- Newly implemented procedure based on release of guidance from FDA, ASTM
- Executed in place of PQ for dissolution apparatus 1 and 2
- Does not require use of Prednisone or Salicylic Acid tablets



Physical parameter measurements performed on dissolution apparatus:

- Basket/paddle depth
- Shaft wobble
- Shaft verticality
- Basket wobble
- Vessel centering
- Vessel verticality
- Rotational speed (RPM)
- vessel temperature

- Measurement of vessels, baskets, and paddles dimensions (listed in USP General Chapter <711>)
- Regular maintenance schedule for any dissolution apparatus that includes MQ as a part of overall AIQ based on frequency of use or internal quality system requirements
- Daily or prior-to-use examination to:
 - Visually inspect vessels, baskets, paddles for scratches, cracks, residue and rusting
 - Check that vessel temperature is within 0.5° C of target temperature

The FDA draft guidance was issued in October 2007

- Online: <http://www.fda.gov/CDER/GUIDANCE/7232dft.pdf>
- FDA Draft Guidance for Industry: The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (cGMP)
- It recommends the use of “appropriately rigorous methods” for mechanical calibration of dissolution apparatus and specifically references two such methods:
 - FDA - CDER Division of Pharmaceutical Analysis Document # DPA-LOP.002, “Mechanical Qualification of Dissolution Apparatus 1 and 2”
 - ASTM E 2503-07 Standard, “Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus”



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USP Draft Toolkit

- The USP also issued a draft toolkit, which contains a section describing mechanical calibration preceding the section on the PVT
- Dissolution Procedure: Mechanical Calibration and Performance Verification Test; Version 1.0
Draft 5.1 October 4, 2007
<http://www.usp.org/pdf/EN/dissolutionProcedureToolkit2007-10-04.pdf>

Comparison of MQ Tolerances

| Parameter | FDA (DPA-LOP.002) | ASTM (E2503-07) | USP Toolkit, 2.0, includes PVT (Draft) | Current Physical Parameters |
|----------------------------------|------------------------------|---|---|--------------------------------|
| Basket / Paddle Depth | 25 ± 2 mm | 25 ± 2 mm (or within 8% of desired height) | 23-27 mm above bottom of vessel | 25 +/- 2mm |
| Rotational Speed | ± 2 rpm of target | within 2% or ± 2 rpm of stated rate (use larger) | ± 1 rpm of set value | +/- 4% |
| Shaft Wobble | ≤ 1.0 mm total runout | ≤ 1.0 mm total runout | ≤ 1.0 mm total wobble | No significant wobble |
| Shaft Verticality | ≤ 0.5° from vertical | Within bubble | <i>Not measured</i> | <i>Not measured</i> |
| Basket Wobble | ≤ 1.0 mm total runout | ≤ 1.0 mm total runout | ≤ 1.0 mm total wobble | +/- 1.0 mm |
| Vessel Centering | ≤ 1.0 mm from center line | ≤ 1.0 mm from center line | NMT 2.0 mm diff. between smallest/largest measurement | NMT 2mm of center axis |
| Vessel Verticality | ≤ 1.0° from vertical | ≤ 1.0° from vertical at each point | NMT 0.5° from vertical | <i>Not measured</i> |
| Vessel Plate Level | <i>Not measured</i> | <i>Not measured</i> | NMT 0.5° deviation from horizontal | Within bubble |
| Temperature | <i>Not measured</i> | <i>Not measured</i> | NMT 0.2°C difference between set point / meas. | <i>Not Measured</i> |



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Comparison of MQ Procedures – Frequency of Activities

| Parameter | FDA (DPA-LOP.002) | ASTM (E2503-07) | USP Toolkit, 2.0 - includes PVT (Draft) | |
|--|--|--|---|--|
| <i>Operation (before every dissolution test)</i> | Basket Examination | Basket Examination | Basket Examination | |
| | Paddle Examination | Paddle Examination | Paddle Examination | |
| | Vessel Examination | Vessel Examination | Vessel Examination | |
| | Vessel Temperature | Vessel Temperature | Vessel Temperature | |
| | Vibration | Vibration | Vibration | |
| | | | Water Bath | |
| | | | Centering | |
| | | | RPM (single position) | |
| <i>Maintenance</i> | According to manufacturer | Established program; consult manufacturer | Routine maintenance / inspection | |
| <i>Frequency</i> | Upon move, repair or six-month interval | Upon move, repair, or quality system determination | Mechanical- every 3 months; PVT – every 6 months | |

PQ vs. MQ



- Takes less time to perform
- Does not require Calibrator tablets and standards
- Verification of accessory components (baskets, shafts, paddles, vessels) is a critical feature of all mechanical qualification protocols
- The quality of accessory components and their compliance of physical dimensions to USP, EP, and JP are critical factors that affect the performance
- Regular scheduled maintenance required
- No specifications for Vibration



- Time consuming
- Requires use of Calibrator tablets and standards
- Wide specification range and questions regarding stability of Prednisone Tablets
- PQ remains extremely valuable as a holistic test of the performance of a dissolution apparatus
- PQ is able to discern the effects of vessel imperfections and vibrations on the performance of the apparatus



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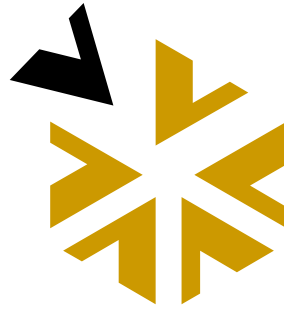
Status of the Pharmaceutical Industry's Position on MQ

- The FDA draft guidance has invited comments and is currently in the process of consideration for issuance of final guidance

Comments?



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