Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact Albinus D'Sa at 301-827-9044.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2007
Current Good Manufacturing Practices (CGMP)

Guidance for Industry

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

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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry[1]

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

This draft guidance when finalized will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to aid drug manufacturers (including ancillary testing laboratories) in the use of mechanical calibration as an alternate approach to the use of calibrator tablets in calibrating an apparatus used for dissolution testing. This guidance provides references to information on critical tolerances that should be achieved with mechanical calibration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA's CGMP regulations require that laboratory apparatus be calibrated at suitable intervals in accordance with established written specifications (21 CFR 211.160(b)(4)). Historically, both chemical and mechanical means have been used in calibrating dissolution apparatuses. Since 1978, chemical calibration has been the predominant method of calibration, consistent with Chapter 711 of the *United States Pharmacopeia* (USP), which describes the use of calibrator

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

tablets.[2] Chemical calibration of an apparatus is usually performed, in addition to mechanical calibration, every 6 months. Chemical calibration is also performed if a unit is moved or when there has been a major change made to the instrumentation.

In 1978, a 50-milligram (mg) prednisone tablet (manufactured by Upjohn) and a 300-mg salicylic acid tablet (manufactured by Hoffman LaRoche) became the official USP reference standards for the disintegrating and the non-disintegrating chemical calibration tablets, respectively. Before this time, laboratories solely relied on minimal mechanical calibration standards to make sure their apparatus was set up properly.

Over the years, a 10-mg prednisone tablet has become the official USP disintegrating chemical calibration tablet reference standard (RS). In 1979, CDER's Division of Pharmaceutical Analysis in St. Louis, MO (DPA), discovered a commercially available 10-mg prednisone tablet that was extremely sensitive to dissolved gases in the medium and vessel centering for the paddle method (Apparatus 2). CDER's DPA used this tablet as the in-house calibrator tablet for about 20 years. In 1997, Upjohn discontinued marketing its 50-mg prednisone tablet, which had been the USP disintegrating chemical calibration tablet RS for about 19 years. In 1999, USP replaced the 50-mg prednisone calibrator tablet (in use at that time) with a 10-mg prednisone tablet manufactured at the University of Maryland at Baltimore (UMAB) and similar in formulation to the in-house DPA calibrator tablet.

The use of USP calibration tablets can lead to variability in the dissolution measurement system. Unlike the original DPA 10-mg prednisone tablet, which is stable for over 20 years, the newer USP 10-mg tablet tends to give lower dissolution results with the paddle method and higher results with the basket method over time. Also, acceptance criteria for the prednisone tablet RS (10 mg) are based on a collaborative study and tend to cover a wide range to accommodate data from multiple laboratories (original ranges of 27 to 48 percent for lot O0C056 for Apparatus 2 and 53 to 77 percent for Apparatus 1). Because of stability problems, in December 2004, USP officially changed the limits for this lot to 26 to 47 percent for Apparatus 2 and 51 to 81 percent for Apparatus 1.[3] The newest lot (P0E203) also has wide ranges: 37 to 70 percent for Apparatus 2 and 47 to 82 percent for Apparatus 1. Further, a collaborative study by DPA and the Pharmaceutical Research and Manufacturers of America (PhRMA) has found that the USP Salicylic Acid Tablet is operationally insensitive to perturbations of both USP Apparatus 1 and 2.[4]

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[2] The United States Pharmacopeial Convention, *United States Pharmacopeia 30– National Formulary 25* (2007). The specific method to be used for chemical calibration of dissolution equipment is not in Chapter 711 of the USP. When a bottle of USP calibrator tablets is purchased, the USP sends a sheet that contains the instructions on how to run the test and the acceptance criteria.

[3] See USP Official Dissolution Calibrator Ranges, available on the Internet at http://www.usp.org/referenceStandards/useAndStorage/calibrators.html.

[4] Oates M, Brune S, Gray V, Hippeli K, Kentrup A et al., July-Aug 2000, Dissolution Calibration: Recommendations for Reduced Chemical Testing and Enhanced Mechanical Calibration, Pharmacopeial Forum, 26(4): 1149-1151.

There can also be other sources of variability in the dissolution measurement system. For example, sometimes dissolved gases can cause bubbles to form around a dosage form undergoing testing, which can affect the results of a dissolution test.[5] To eliminate this source of variability, the dissolution medium is degassed. The USP degassing procedure (vacuum filtration at 41°C, then cooling to 37°C before use) can be time-consuming, so some laboratories use an alternative technique such as vacuum degassing with agitation at ambient temperature.[6] The calibrator tablets are sometimes used to ensure sameness between the alternative technique and the USP method for degassing. DPA uses a total dissolved gas meter to accurately measure the amount of total dissolved gas in the medium to ensure adequate degassing.[7]

Because variability of the USP chemical calibration tablets makes it difficult to assess the calibration of dissolution equipment, FDA is providing guidance on mechanical calibration as an alternate approach to calibrating dissolution equipment.

III. RECOMMENDATIONS

Instead of using a calibrator tablet, a firm can use an appropriately rigorous method of mechanical calibration for dissolution Apparatus 1 and 2. An example of an appropriately rigorous mechanical calibration procedure is used by CDER's DPA and is titled *Mechanical Qualification of Dissolution Apparatus 1 and 2*, available on FDA's Web site at http://www.fda.gov/cder/Offices/OTR/default.htm. This procedure describes the mechanical calibration tolerances DPA uses in its laboratories to set up and maintain dissolution apparatuses. Alternatively, a firm can choose another method of mechanical calibration—instead of calibrator tablets—to set up and maintain dissolution equipment, provided the method is sufficiently rigorous.[8]

A compendial product would still need to meet the dissolution requirements for its USP monograph whether mechanical calibration or the USP calibrator tablet approach is used (section 501(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(b)). We believe that this change in calibration methodology, from the use of tablets to rigorous mechanical calibration, will reduce the bias and variation in the measurement system and therefore is an appropriate alternative approach. An appropriately rigorous mechanical calibration method properly

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[5] Other factors that can influence dissolution results include (1) sampling probe size when automatic sampling is used; (2) method of tablet or capsule introduction into medium, including the use of sinkers (devices designed to make tablets or capsules sink to the bottom of the vessel); (3) basket construction (some vendors have *clips* to hold on the basket and others have o-rings); (4) vibration; and (5) accuracy of mechanical calibration procedures.

[6] Moore T, 1996, Dissolution testing: A Fast Efficient Procedure for Degassing Dissolution Medium, Dissolution Technologies, 3(2):3-5.

[7] Gao Z, Moore TW, Doub WH, Westenberger BJ, Buhse LF, 2006, Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter, Journal of Pharmaceutical Science, 95(7): 1606-1613.

[8] See also ASTM E 2503-07, Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus.

107 executed will satisfy the CGMP requirement for dissolution apparatus calibration under §
108 211.160(b)(4).

製薬企業へのガイダンス

溶出装置１と２の機械的機械的校正の使用適用について

－CGMP

追加のコピーは，以下より入手可能です：

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インターネット: http://www.fda.gov/cder/guidance/index.htm

米国保険社会福祉省
食品医薬品局
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2007 年 10 月
CGMP

資料２

強制力のない推奨

ドラフトガイダンス施行を目的としない.

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製薬企業へのガイダンス [1)]

溶出装置１と２の機械的校正の適用について－CGMP

最終的に確認されると，このドラフトガイダンスはこのトピックスに対する FDA の最新の見解を示すことになる．それはいかなる人にも権利をもたらすものではなく，FDA 又は国民を束縛するものではない．他の替わりうるアプローチも，関連する法規や規則上の要求を満たすものであるなら，適用可能である．他のアプローチの適用についてのご相談の希望があれば，このガイダンスの施行に対して責任を負う FDA のスタッフに連絡を取って下さい．もしも適当な FDA のスタッフを特定できなければ，このガイダンスの表題のページに載せてある適当な番号へ電話して下さい．

I 序文

このガイダンスは、製薬企業（属する試験機関を含む）が，溶出試験装置を校正する方法として，カリブレータ錠の使用に換えて，機械的校正の適用を支援するためのものである．このガイダンスは，機械的校正で達成されるべき許容範囲について言及する．

このガイダンスを含む FDA のガイダンス文書は法的強制力を有するものではない．特に規制上のあるいは法的な要求が示されない限り，ガイダンス文書は FDA の現在の考えを示しているのであって，単に推奨事項と見なされるべきものである．ガイダンス文書中に使用される should は，何かが示唆あるいは推奨されることを意味し，要求を意味するものではない．

II 背景

FDA の CGMP 規則は，試験室の装置を，確立された規格(21 CFR 211.160(b)(4))に従って適当な間

隔で校正することを要求している．歴史的に，溶出試験装置を校正する方法として，化学的な方法と機械的な方法が使用されてきた．1978 年以降，カリブレーター錠の使用を記述したアメリカ薬局方（USP)の第 711 章に従って，化学的な校正が主流となっていた．[2] 装置の化学的校正は，通常，機械的校正に加えて，6 ヵ月毎に実行されている．もし装置が移動されたり又は装備に大きな変更があったりしたときには化学的校正も実施されている．

1978 年に，50mg のプレドニゾン錠（Upjohn 製）と 300mg のサリチル酸錠（Hoffman LaRoche 製）が，それぞれ崩壊型，非崩壊型のカリブレーター錠として USP 標準品に設定された．これ以前は，試験所は，個別に装置が適切であることを確認するために，最小限の機械的校正に頼っていた．

長年にわたって，10mg のプレドニゾン錠は，USP の崩壊型カリブレーター錠の標準品であった．1979 年に，ミズーリ州セントルイスの CDER の医薬品分析部（DPA）は，パドル法（装置 2）で試験液中の溶存ガスとベッセルの中心度に極めて鋭敏な市販の 10mg のプレドニゾン錠を発見した．CDER の DPA は，およそ 20 年間，この錠剤を内部でのカリベレーター錠として使用していた．1997 年に，Upjohn は 19 年間に渡って USP の崩壊型カリブレータであった 50mg のプレドニゾン錠の供給をやめた．1999 年に，USP は 50mg のプレドニゾン錠を，DPA の内部カリブレーター錠と処方が類似しているボルチモアのメリーランド大学（UMAB）で製造された 10mg のプレドニゾン錠と切り替えた．

USP カリブレータ錠の使用は，溶出試験システムの変動をもたらすことがある．20 年間安定であった最初の DPA の 10mg のプレドニゾン錠と違って，新しい USP 10mg 錠は時間とともにパドル法では低い溶出結果を，そしてバスケット法では高い溶出結果を出す傾向があった．また，プレドニゾン錠標準品（10mg）の許容限度値は，多くの試験室による共同検定に基づいており，多くの試験室から提出されたデータの広い範囲をカバーするように設定されている（LotO0C056 では，装置 2 で 27～48%，装置 1 で 53～77%）．[3] 安定性の問題のため，2004 年 12 月に，USP は装置 2 では 26～47%に，装置 1 では 51～81%まで限度値を変更した．最新の Lot（P0E203）では，装置 2 で 37～70%，装置 1 で 47～82%の広範囲となっている．さらに，DPA と米国研究製薬工業協会（PhRMA）による共同研究で，USP サリチル酸錠が USP 装置 1 と 2 の振動に敏感でないことが明らかになった．[4]

溶出試験の変動の要因は種々考えられる．例えば，時折，溶存ガスが製剤の周りに泡を生じさせ，溶出性の結果に影響を及ぼすことがある．[5] この変動要因を除くために，溶出試験液の脱気を行う．USP 法では，（41°C で減圧濾過後，使用前に 37°C まで冷却する）脱気するのには時間がかかるため，試験所によっては常温で攪拌と真空脱気のような代わりの方法を使用している．[6] カリブレーターは，脱気についての USP 法と替わりの方法間の同一性を確認する手段として使用することができる．DPA は，十分な脱気を保証するために，試験液中の溶存ガスの全量を正確に計るために，全溶存ガスメーターを使っている．

USP カリブレーター錠の変更が溶出試験装置の評価を難しくしているので，FDA は溶出試験装置を校正する代わりのアプローチとして，機械的校正のガイダンスを提供する．

III 推奨

カリブレータ錠を使う代わりに，企業は溶出装置1と2の為の，適切な機械的校正の方法を適用することができる.適切な機械的校正の手順例は,CDERのDPAによって適用されており,*Mechanical Qualification of Dissolution Apparatus 1 and 2* というタイトルが付けられて，http://www.fda.gov/cder/Offices/OTR/default.htm.のFDAのウェブサイト上で見ることができる．この手順には，溶出試験装置を組み立て，維持するために，DPAが使用する機械的校正の許容差を記載している．方法が十分に厳密であるならば，会社は溶出試験装置のセットアップ，メンテナンスに，キャリブレーター錠の替わりに機械的校正を適用しても，充分に有効である．

局方収載品については，今までどおり、機械的校正あるいはUSPキャリブレーター錠のいずれの校正法が使われても，USP各条の溶出試験規格に適合しなくてはならない．(連邦政府の食品医薬品化粧品法（21U.S.C. 351（b）のセクション501（b））．我々は，校正法を，錠剤の使用から適切な機械的校正へ変更することは，測定システムにおける偏りとばらつきを減らすことにつながり，適切な代替アプローチであると信じている．適切な機械的校正は211.160（b）（4）節における溶出試験装置の校正の為のCGMPの要求条件を充分に満たしている．

1) このガイダンスは，FDAのthe Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

2) The United States Pharmacopeial Convention, *United States Pharmacopeia 30– National Formulary 25* (2007). 溶出試験装置のためのカリブレーターの使用方法は，USPの711章には記載されておらず，USPカリブレーターを購入したときにUSPは操作法と許容範囲を記載した文書を添付している．

3) USPの公式なカリブレーター錠の許容範囲は，下記のインターネットHP上で公表されている．http://www.usp.org/referenceStandards/useAndStorage/calibrators.html.

4) Oates M, Brune S, Gray V, Hippeli K, Kentrup A et al., July-Aug 2000, Dissolution Calibration: Recommendations for Reduced Chemical Testing and Enhanced Mechanical Calibration, Pharmacopeial Forum, 26(4): 1149-1151.

5) 溶出試験に影響を及ぼす要因は (1)自動サンプリング装置のプローブの大きさ．(2) 錠剤やカプセルを試験液に入れる方法，シンカーの使用を含む．(3) バスケットの構造(あるメーカーはバスケットに固定用止め金を付けており，他のものではO-リングを有している) (4)振動 (5)機械的校正の精確さ．

6) Moore T, 1996, Dissolution testing: A Fast Efficient Procedure for Degassing Dissolution Medium, Dissolution Technologies, 3(2):3-5.

7) Gao Z, Moore TW, Doub WH, Westenberger BJ, Buhse LF, 2006, Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter, Journal of Pharmaceutical Science, 95(7): 1606-1613.

8) See also ASTM E 2503-07, Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus.

Sections included in this document

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Document History

Version 2 The procedure was modified to allow its use with all of the manufacturer's dissolution equipment at DPA.

Document history					
Version #	**Status (I, R, C)**	**Date Approved**	**Location of Change History**	**Name & Title**	
				Contact	**Approving Official**
1.0	I	November 21, 2005	In Document	James Allgire	Lucinda F. Buhse
2.0	R	May 31, 2006	In Document	James Allgire Chemist, DPA	Lucinda F. Buhse Acting Dir. OTR

Chronologically track the original document and/or approved revisions or cancellations.

(a) Version # of the Document
(b) Status: I = Initial; R = Revision; C = Cancel
(c) Date Approved by the Approving Official
(d) Location of the Change History
(e) Name, Title of Contact/Approving Official: Include the organization abbreviation in the title. The contact may or may not be the author.

1. **Purpose**

The purpose of this document is to establish the setup, mechanical calibration, and operation checks for dissolution Apparatus 1 (Basket) and 2 (Paddle).

2. **Scope/Policy**

This procedure applies to all Apparatus 1 and 2 dissolution equipment at the Division of Pharmaceutical Analysis (DPA).

3. **Responsibilities**

3.1 Analyst

- Check the vessel, basket, and paddle dimensions on receipt.
- Perform the maintenance procedures as per the manufacturer's recommendation.
- Perform the mechanical calibration on receipt, after the instrument is moved, after the instrument is repaired, and six months after the previous calibration. If the instrument is not being used routinely the six month mechanical calibration can be performed before performing the first dissolution test after the six month time interval.
- Perform the operation checks at each time of use.

4. **Background**

The setup, mechanical, and operational checks are used to minimize variability during dissolution testing.

5. **References**

- USP General Chapter <711>
- <1092> The Dissolution Procedure: Development and Validation, Pharmacopeial Forum, 31(5), 2005, p.1463

6. **Procedure**

Wherever possible, tools should be traceable to NIST.

6.1 Apparatus setup

During apparatus setup or after replacement of parts, verify the following dimensions. Certificates of Analysis (COA) or Certificates of Conformity (COC) may be used to document the measurements. Discard any parts that do not meet specifications.

Vessel Dimensions

Use an appropriate measuring device to verify that the vessel dimensions conform to the specifications listed in the USP General Chapter <711> Dissolution. The vessel must have cylindrical sides and a hemispherical bottom which must be smooth and without defects.

Basket Dimensions

Each basket must conform to the dimensions shown in the USP General Chapter <711> Dissolution in Figure 1, Basket Stirring Element. An appropriate measuring device is used to make the measurements.

Paddle Dimensions
Each paddle must conform to the dimensions shown in the USP General Chapter <711> Dissolution in Figure 2. An appropriate measuring device is used to make the measurements.

6.2 Maintenance
Follow the manufacturer's maintenance recommendations and maintenance schedule.

6.3 Mechanical Calibration
Perform the following in the order given for mechanical calibration of each apparatus. Some iteration may be necessary if extensive adjustments are needed. Perform these tests every 6 months or after any repair, move, etc. If the instrument is not in routine use, the mechanical calibration may be performed prior to performing the first dissolution test after the six month interval. Some dissolution instruments require the use of manufacturer's supplied special tools or incorporate automatic mechanical devices to perform the following tests. These may be used provided they follow the general principle of the procedure.

Shaft Wobble
A runout gauge is placed on top of the vessel plate, and the drive module is positioned so that the gauge probe touches the shaft about 2 cm above the top of the paddle blade or basket. The gauge is placed so that the probe slightly presses in on the turning shaft. If a mechanical gauge is used, the gauge's pointer should read slightly more than zero. The pointer will vary from a minimum to a maximum reading, and the difference is called the wobble. The specification is $\leq$1.0 mm total runout.

Paddle and Basket Shaft Verticality
Lower the drive unit to where it would be during an actual dissolution test. If necessary the shaft verticality may be checked with the shafts raised above the drive unit. Place an accurate bubble level on the front edge of each of the shafts. The bubble should be within the lines of the level. Rotate the level 90° so it is on the side of the shaft. The bubble should again be within the lines of the level for each shaft. If the shafts are not vertical adjust the feet of the apparatus until they are vertical.

A digital leveling device may also be used to determine the shaft verticality. The shaft must be $\leq$0.5° from vertical.

Basket Wobble
A runout gauge is placed on top of the vessel plate and the drive unit is positioned so that the gauge probe touches the bottom rim of the basket. The gauge is placed so that the probe slightly presses in on the turning shaft. If a mechanical gauge is used, the gauge's pointer should read slightly more than zero. The pointer will vary from a minimum to a maximum reading and the difference is called the wobble. The specification is $\leq$ 1.0 mm total runout.

Vessel Centering

The vessel plate of an apparatus may warp or bend or the thickness of a vessel lip or centering collar lip may not be perfectly uniform. If either of these occurs, even though the shafts are vertical and the vessel plate is level, the vessel walls may not be vertical.

Use centering tools which measure centering inside the vessel. Two centering tools are used to center the vessels around the paddle or basket shafts and to align the vessels so that their sides are vertical. For the paddle method, the bottom of one centering tool is placed 2 mm above the top of the paddle blade and the bottom of the second centering tool is clamped on the shaft 80 mm above the blade with the probes positioned in the same direction towards the glass vessel wall. For the basket method, the bottom of one centering tool is placed 2 mm above the top of the basket and the bottom of one centering tool is placed 60 mm above the top of the basket with the probes positioned in the same direction towards the glass vessel wall. Carefully lower the shaft and centering tools into the vessels so that the paddle blade or basket bottom is about 2.5 cm above the bottom of the vessel. Manually rotate the shaft slowly and check the centering at both levels. If the vessel is not centered at either level, adjust the vessel to center it. Adjustments can be made by rotating the vessel or the vessel with the centering collar inside the vessel plate, moving the vessel sideways within the vessel plate or placing shims (such as tape) under one side of the lip of the vessel or vessel centering collar. Repeat this process until both bottom and top positions are centered within 1.0 mm from the center line.

An alternative procedure is to use a mechanical or digital centering device that centers the inside of the vessel around the shaft or a surrogate shaft. The centering is measured at two positions inside the vessel in the cylindrical portion, one near the top but below the rim and one just above the bottom portion of the vessel. The shaft or surrogate shaft must be centered within 1.0 mm from the center line.

Vessel Verticality

The vessel verticality can be calculated using the centering measurements and the difference in height between the two measurements or it can be determined using a digital leveling device placed on the inside wall of the vessel. The verticality should be determined at two positions 90° apart. Adjustments can be made by placing shims (such as tape) under one side of the lip of the vessel or vessel centering collar. The vessel must be $\leq 1.0°$ from vertical.

After each vessel has been centered and made vertical, each vessel and vessel plate opening must be numbered and a mark must be placed on the lip of each vessel and on the vessel plate directly next to the mark on the vessel lip. Each vessel must be returned to the same vessel plate opening and positioned in the exact same position inside the vessel plate opening for all future dissolution tests.

Basket and Paddle Depth
The actual distance between the bottom of the vessel and bottom of the basket or paddle is determined. If the depth of the basket/paddle is adjustable, first a depth gauge is used to set the distance between the bottom of the paddle blade or basket and the bottom of the vessel. The depth gauge is set at 25 mm and placed on the bottom of the vessel. Each shaft is raised into the apparatus drive module. The drive unit is then lowered to its operating position. The paddle or basket is then lowered into the vessel until it touches the top of the depth gauge. The shafts are locked into this height. This is repeated for each shaft. The specification is 25 mm ± 2 mm.

Rotational Speed
A tachometer should be used to measure the rotational speed of the paddle or basket. The shafts should be rotating smoothly at ± 2 rpm of the target value.

6.4 Operation
Before each test perform the following:

Basket Examination
Each basket must be visually examined for defects such as rusting, corrosion, wires sticking out beyond the basket, clogged mesh holes or deformed mesh sides.

Paddle Examination
Each paddle must be visually examined for defects such as rusting, corrosion or loose pieces of coating on the paddles (for paddles coated with Teflon or another coating).

Vessel Examination
Each vessel must be free of scratches, cracks, pits and residue.

Vessel Temperature
The temperature of the medium inside each vessel is measured at time of use. The limit is ± 0.5°C of the target temperature. The target temperature is usually 37°C for Apparatus 1 and 2.

Vibration
The USP criteria of: "No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element" is followed.

6.5 Additional Variables

Basket Shafts (Clips versus O rings)
The diagram of the basket stirring element in the USP General Chapter <711> shows that the basket shaft has clips to hold the basket. Some basket shafts have O rings to hold the basket in place instead of clips. The clips change the hydrodynamics of the medium causing slightly increased dissolution results with certain formulations. In order to conform to the USP diagram, DPA chemists must use basket shafts with clips or use detachable basket clips unless the dissolution method states otherwise.

Sinkers
Sinkers are required for capsules that float when the Apparatus 2 (Paddle) method is used. Some commercial sinkers have too many coils that trap the capsule material inside the sinker. DPA

uses sinkers that are recommended by the USP. A detailed procedure on how to make them is in the proposed USP General Chapter <1092> The Dissolution Procedure: Development and Validation, USP Pharmacopeial Forum, 31(5), 2005, p. 1463. If a method states to use a particular commercially available sinker, the DPA chemist must use the specified sinker.

7. Records

The date, analyst, dissolution vessels' manufacturer, and the dissolution apparatus's manufacturer, model number, and serial number will be recorded on the appropriate Mechanical Calibration Report Sheet (see Attachment A and B) along with the appropriate observations. The completed report sheet will be placed in the report sheet folder for that apparatus. Each dissolution apparatus will have its own report sheet folder.

8. Glossary

Not Applicable

9. Attachments

Attachment A - Mechanical Calibration Report Sheet--Apparatus 1 (Basket)
Attachment B - Mechanical Calibration Report Sheet--Apparatus 2 (Paddle)

Signatures
Approving Official's Signature:

BJ Westenberger_____ 6/1/06
Benjamin J Westenberger, Deputy Director Date

LF Buhse_____ 6/1/06
Lucinda F Buhse, Director Date

Attachment B

PADDLE APPARATUS QUALIFICATION REPORT SHEET

Date _____ Analyst _____

Dissolution Apparatus: Manufacturer _____ Model #_____ Serial #_____ Dissolution Vessels: Manufacturer _____

MECHANICAL CALIBRATION REPORT SHEET -- APPARATUS 2 (PADDLE)

Calibration Parameter	Point of Measurement	Results & Comments	Tools Used	Specifications
Shaft wobble	2 cm above top of paddle blade	1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____		≤ 1.0 mm total runout
Shaft verticality	Along shaft	Record results at 2 points that are 90° apart. Shaft is vertical: (Y/N) Shaft1 Pt1:_____ Pt2:_____ Shaft2 Pt1:_____ Pt2:_____ Shaft3 Pt1:_____ Pt2:_____ Shaft4 Pt1:_____ Pt2:_____ Shaft5 Pt1:_____ Pt2:_____ Shaft6 Pt1:_____ Pt2:_____		Bubble must be with-in the lines of bubble level ≤ 0.5° from vertical
Vessel/Shaft centering	Step 1: Measured lower position Step 2: Measured upper position	Step 1: 1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ Step 2: 1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____		≤1.0 mm from centerline
Vessel verticality	Straight portion of vessel at two places 90° apart	1. _____ 2. _____		≤1.0 ° from vertical
Height check/Paddle depth	Paddle bottom	1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____		25 ± 2 mm
Rotational speed		50 rpm _____ 100 rpm _____		± 2 rpm