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ICH guideline Q4B
Annex 13 to Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bulk Density and Tapped Density of Powders – General Chapter

Step 3

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Comments should be provided using this template. The completed comments form should be sent to ICH@ema.europa.eu

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1. INTRODUCTION

This annex is the result of the Q4B process for the Bulk Density and Tapped Density of Powders General Chapter.

The proposed texts were submitted by the Pharmacopoeial Discussion Group (PDG).

2. Q4B OUTCOME

2.1. Analytical Procedures

The ICH Steering Committee, based on the evaluation by the Q4B Expert Working Group (EWG), recommends that the analytical procedures described in the official pharmacopoeial texts, Ph.Eur. 2.9.34. Bulk Density and Tapped Density of Powders, JP 3.01 Determination of Bulk and Tapped Densities, and USP General Chapter <616> Bulk Density and Tapped Density of Powders, can be used as interchangeable in the ICH regions subject to the following conditions:

2.1.1 For Bulk Density Method 2, the tolerance of the cup volume should be 16.39 ±0.20 milliliters (mL).

2.1.2 For Tapped Density Method 3, the test conditions, including tapping height, should be specified in the results.

2.1.3 For Measures of Powder Compressibility, if V_{10} is used, it should be clearly stated in the results.

2.2. Acceptance Criteria

The texts evaluated did not contain acceptance criteria.

3. TIMING OF ANNEX IMPLEMENTATION

When this annex is implemented (incorporated into the regulatory process at ICH Step 5) in a region, it can be used in that region. Timing might differ for each region.

4. CONSIDERATIONS FOR IMPLEMENTATION

4.1. General Consideration

When sponsors or manufacturers change their existing methods to the implemented Q4B-evaluated pharmacopoeial texts that are referenced in Section 2.1 of this annex, any change notification, variation, and/or prior approval procedures should be handled in accordance with established regional regulatory mechanisms pertaining to compendial changes.

4.2. FDA Consideration

Based on the recommendation above, and with reference to the conditions set forth in this annex, the pharmacopoeial texts referenced in Section 2.1 of this annex can be considered interchangeable. However, FDA might request that a company demonstrate that the chosen method is acceptable and suitable for a specific material or product, irrespective of the origin of the method.

4.3. EU Consideration

For the European Union, regulatory authorities can accept the reference in a marketing authorisation application, renewal or variation application citing the use of the corresponding text from another pharmacopoeia as referenced in Section 2.1, in accordance with the conditions set out in this annex, as

fulfilling the requirements for compliance with the Ph. Eur. Chapter 2.9.34. on the basis of the declaration of interchangeability made above.

4.4. MHLW Consideration

The pharmacopoeial texts referenced in Section 2.1 of this annex can be used as interchangeable in accordance with the conditions set out in this annex. Details of implementation requirements will be provided in the notification by MHLW when this annex is implemented.

4.5. Health Canada Consideration

In Canada any of the pharmacopoeial texts cited in Section 2.1 of this annex and used in accordance with the conditions set out in this annex can be considered interchangeable.

5. REFERENCES USED FOR THE Q4B EVALUATION

5.1 The PDG Stage 5B sign-off document (Rev. 1 – Corr. 1): *Japanese Pharmacopoeial Forum*, Volume 18, number 3 (September 2009).

5.2 The pharmacopoeial references for the Bulk Density and Tapped Density of Powders General Chapter for this annex are:

5.2.1 *European Pharmacopoeia* (Ph. Eur.):
Supplement 6.8 to Ph.Eur. 6th Edition (official July 2010), Bulk Density and Tapped Density of Powders (reference 07/2010:20934)

5.2.2 *Japanese Pharmacopoeia* (JP):
3.01 Determination of Bulk and Tapped Densities as it will appear in the JP Sixteenth Edition (March 31, 2011. The draft English version of the JP text provided by MHLW is appended (see Appendix A).

5.2.3 *United States Pharmacopeia* (USP):
<616> Bulk Density and Tapped Density of Powders, USP 33 Reissue (published April 2010 and official October 1, 2010).

APPENDIX A

Draft JP 16 English Text Provided by MHLW

3.01 Determination of Bulk and Tapped Densities

Change to read:
This determination is harmonized with the European Pharmacopoeia and the U.S. Pharmacopeia. The parts of the text that are not harmonized are marked with symbols (◆ ◆).

◆Determination of Bulk and Tapped Densities is a method to determine the bulk densities of powdered drugs under loose and tapped packing conditions respectively. Loose packing is defined as the state obtained by pouring a powder sample into a vessel without any consolidation, and tapped packing is defined as the state obtained when the vessel containing the powder sample is to be repeatedly dropped a specified distance at a constant drop rate until the apparent volume of sample in the vessel becomes almost constant.◆

Bulk density
The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per milliliter (g/mL) although the international unit is kilogram per cubic meter (1 g/mL = 1000 kg/m^3) because the measurements are made using cylinders. It may also be expressed in grams per cubic centimeter (g/cm^3).

The bulking properties of a powder are dependent upon the preparation, treatment and storage of the sample, i.e. how it was handled. The particles can be packed to have a range of bulk densities and, moreover, the slightest disturbance of the powder bed may result in a changed bulk density. Thus, the bulk density of a powder is often very difficult to measure with good reproducibility and, in reporting the results, it is essential to specify how the determination was made.

The bulk density of a powder is determined by measuring the volume of a known mass of powder sample, that may have been passed through a screen, into a graduated cylinder (Method 1), or by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup (Method 2) or a measuring vessel (Method 3). Method 1 and method 3 are favoured.

Method 1: Measurement in a Graduated Cylinder
Procedure
Pass a quantity of powder sufficient to complete the test through a sieve with apertures greater than or equal to 1.0 mm, if necessary, to break up agglomerates that may have formed during storage; this must be done gently to avoid changing the nature of the material. Into a dry graduated cylinder of 250 mL (readable to 2 mL), gently introduce, without compacting, approximately 100 g of the test sample (m) weighed with 0.1 per cent accuracy. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume (V_0) to the nearest graduated unit. Calculate the bulk density in g per mL by the formula m/V_0. Generally, replicate determinations are desirable for the determination of this property.
If the powder density is too low or too high, such that the test sample has an untapped apparent volume of either more than 250 mL or less than 150 mL, it is not possible to use 100 g of powder sample. Therefore, a different amount of powder has to be selected as test sample, such that its untapped apparent volume is 150 mL to 250 mL (apparent volume greater than or equal to 60 per cent of the total volume of the cylinder); the mass of the test sample is specified in the expression of results.

For test samples having an apparent volume between 50 mL and 100 mL a 100 mL cylinder readable to 1 mL can be used; the volume of the cylinder is specified in the expression of results.

Method 2: Measurement in a Volumeter

Apparatus

The apparatus [1] (Figure 3.01-1) consists of a top funnel fitted with a 1.0 mm screen. The funnel is mounted over a baffle box containing four glass baffle plates over which the powder slides and bounces as it passes. At the bottom of the baffle box is a funnel that collects the powder and allows it to pour into a cup mounted directly below it. The cup may be cylindrical (25.00 ± 0.05 mL volume with an inside diameter of 30.00 ± 2.00 mm) or a square (16.39 ± 0.20 mL volume with inside dimensions of 25.4 ± 0.076 mm).

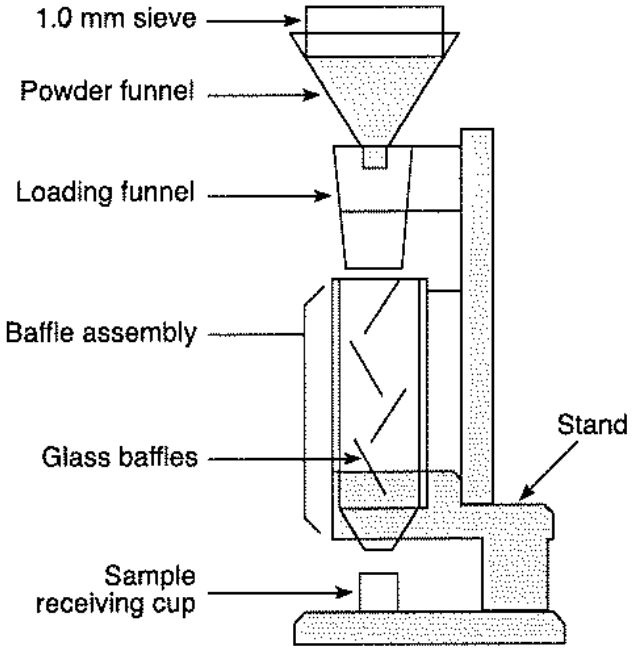

Figure 3.01-1. Volumeter

Procedure

Allow an excess of powder to flow through the apparatus into the sample receiving cup until it overflows, using a minimum of 25 cm^3 of powder with the square cup and 35 cm^3 of powder with the cylindrical cup. Carefully, scrape excess powder from the top of the cup by smoothly moving the edge of the blade of spatula perpendicular to and in contact with the top surface of the cup, taking care to keep the spatula perpendicular to prevent packing or removal of powder from the cup. Remove any material from the side of the cup and determine the mass (m) of the powder to the nearest 0.1 per cent. Calculate the bulk density in g per mL by the formula m/V_0 in which V_0 is the volume of the cup and record the average of 3 determinations using 3 different powder samples.

Method 3: Measurement in a Vessel

Apparatus

The apparatus consists of a 100 mL cylindrical vessel of stainless steel with dimensions as specified in Figure 3.01-2.

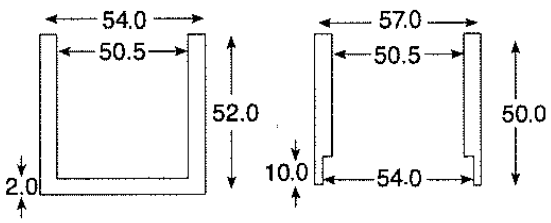

Figure 3.01-2. Measuring vessel (left) and cap (right)
Dimensions in mm

[1] The apparatus (the Scott Volumeter) conforms to the dimensions in ASTM 329 90.

Procedure
Pass a quantity of powder sufficient to complete the test through a 1.0 mm sieve, if necessary, to break up agglomerates that may have formed during storage and allow the obtained sample to flow freely into the measuring vessel until it overflows. Carefully scrape the excess powder from the top of the vessel as described for Method 2. Determine the mass (m_0) of the powder to the nearest 0.1 per cent by subtraction of the previously determined mass of the empty measuring vessel. Calculate the bulk density (g/mL) by the formula $m_0/100$ and record the average of 3 determinations using 3 different powder samples.

Tapped density
The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample.
The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop, under its own mass, a specified distance by either of 3 methods as described below. Devices that rotate the cylinder or vessel during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Method 1
Apparatus
The apparatus (Figure 3.01-3) consists of the following:

- a 250 mL graduated cylinder (readable to 2 mL) with a mass of 220 ± 44 g.
- a settling apparatus capable of producing, in 1 min, either nominally 250 ± 15 taps from a height of 3 ± 0.2 mm, or nominally 300 ± 15 taps from a height of 14 ± 2 mm. The support for the graduated cylinder, with its holder, has a mass of 450 ± 10 g.

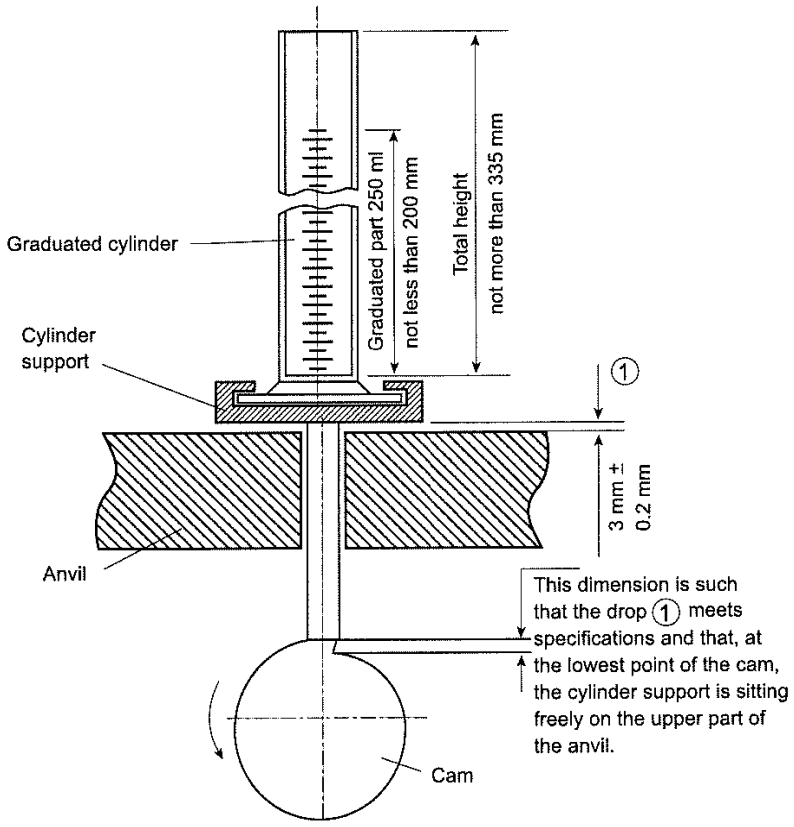

Figure 3.01-3.

Procedure
Proceed as described above for the determination of the bulk volume (V_0).
Secure the cylinder in the holder. Carry out 10,500 and 1250 taps on the same powder sample and read the corresponding volumes V_{10}, V_{500} and V_{1250} to the nearest graduated unit. If the difference between V_{500} and V_{1250} is less than 2 mL, V_{1250} is the tapped volume. If the difference between V_{500} and V_{1250} exceeds 2 mL, repeat in increments such as 1250 taps, until the difference between succeeding measurements is less than 2 mL. Fewer taps may be appropriate for some powders, when validated. Calculate the tapped density (g/mL) using the formula m/V_f in which V_f is the final tapped volume. Generally, replicate determinations are desirable for the determination of this property. Specify the drop height with the results.
If it is not possible to use a 100 g test sample, use a reduced amount and a suitable 100 mL graduated cylinder (readable to 1 mL) weighing 130 ± 16 g and mounted on a holder weighing 240 ± 12 g. The modified test conditions are specified in the expression of the results.

Method 2
Procedure
Proceed as directed under Method 1 except that the mechanical tester provides a fixed drop of 3 ± 0.2 mm at a nominal rate of 250 taps per minute.

Method 3
Procedure
Proceed as described in the method for measuring the bulk density using the measuring vessel equipped with the cap shown in Figure 3.01-2. The measuring vessel with the cap is lifted 50-60 times per minute by the use of a suitable tapped density tester. Carry out 200 taps, remove the cap and carefully scrape excess powder from the top of the measuring vessel as described in Method 3 for measuring the bulk density. Repeat the procedure using 400 taps. If the difference between the 2 masses obtained after 200 and 400 taps exceeds 2 per cent, carry out a test using 200 additional taps until the difference between succeeding measurements is less than 2 per cent. Calculate the tapped density (g/mL) using the formula $m_f/100$ where m_f is the mass of powder in the measuring vessel. Record the average of 3 determinations using 3 different powder samples. The test conditions including tapping height are specified in the expression of the results.

Measures of powder compressibility
Because the interparticulate interactions influencing the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow, for example the Compressibility Index or the Hausner Ratio.
The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed as described above. As such, they are measures of the powder ability to settle and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

Compressibility Index:

$$100 (V_0 - V_f) / V_0$$

V_0: unsettled apparent volume
V_f: final tapped volume

Hausner Ratio:

$$V_0 / V_f$$

Depending on the material, the compressibility index can be determined using V_{10} instead of V_0. If V_{10} is used, it is clearly stated in the results.