Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

Annex 3: Test for Particulate Contamination: Subvisible Particles General Chapter

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For questions regarding this draft document contact (CDER) Robert King 301-796-1242, or (CBER) Christopher Joneckis 301-435-5681.

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Draft Consensus Guideline

Q4B - Annex 3

Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

ON

Test for Particulate Contamination: Sub-Visible Particles

Current Step 2 Version
Dated November 1, 2007

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Q4B -- Annex 3

Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

ON

Test for Particulate Contamination: Sub-Visible Particles

ICH Consensus Guideline

Released for Consultation on November 1, 2007, at *Step 2* of the ICH Process

1. Introduction

This annex is the result of the Q4B process for Test for Particulate Contamination: Sub-Visible Particles. 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 official pharmacopoeial texts, Ph.Eur. 20919 Particulate Contamination: Sub-visible Particles, JP 6.07 Insoluble Particulate Matter Test for Injections, and USP <788> Particulate Matter in Injections General Chapter can be used as interchangeable in the ICH regions given the following:

2.1.1 Instrument calibration and system suitability measurements should follow regional GMP requirements.

2.2. Acceptance Criteria

Except for nominal 100-milliliter (mL) parenteral products, the acceptance criteria are interchangeable. At the 100-mL nominal volume, the criteria specified in JP are more stringent than those in the other two pharmacopoeias; therefore, the criteria are not interchangeable at that volume.

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 may 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 in accordance with 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, the monographs of the Ph. Eur. have mandatory applicability. 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, Particulate

Contamination: Sub-visible Particles: 20919, 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.

5. References Used for the Q4B Evaluation

5.1 The PDG Stage 5B sign-off document: Japanese Pharmacopoeial Forum, Volume 13, Number 3 (August 2004)

5.2 The pharmacopoeial references for Particulate Matter for this annex are:

5.2.1 European Pharmacopoeia (Ph. Eur.): 5th Edition (official on January 2005) Particulate Contamination: Sub-visible Particles (reference 01/2005: 20919)

5.2.2 Japanese Pharmacopoeia (JP): 6.07 Insoluble Particulate Matter Test for Injections as it appears in the JP Fifteenth Edition (March 31, 2006, The Ministry of Health, Labour and Welfare Ministerial Notification No. 285). The method was changed in September 2007 to correct a sentence in the introduction as underlined in the text that is appended.

5.2.3 United States Pharmacopeia (USP): <788> Particulate Matter in Injections, Revision Bulletin, April 4, 2007

< Corrected >

6.07 Insoluble Particulate Matter Test for Injections

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

The insoluble particulate matter test for injections or infusions is the method to test for insoluble particulates, to confirm that they are not present in excess of specified levels in the solutions. For the determination of particulate contamination 2 procedures, Method 1 (Light Obscuration Particle Count Test) and Method 2 (Microscopic Particle Count Test), are specified hereinafter. When examining injections and parenteral infusions for sub visible particles Method 1 is preferably applied. However, it may be necessary to test some preparations by Method 1 followed by Method 2 to reach a conclusion on conformance to the requirements.

Not all parenteral preparations can be examined for subvisible particles by one or both of these methods. When Method 1 is not applicable, e.g. in case of preparations having reduced clarity or increased viscosity, the test should be carried out according to Method 2. Emulsions, colloids, and liposomal preparations are examples. Similarly, products that produce air or gas bubbles when drawn into the sensor may also require microscopic particle count testing. If the viscosity of the preparation to be tested is sufficiently high so as to preclude its examination by either test method, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary, to allow the analysis to be performed.

The results obtained in examining a discrete unit or group of units for particulate contamination cannot be extrapolated with certainty to other units that remain untested. Thus, statistically sound sampling plans must be developed if valid inferences are to be drawn from observed data to characterise the level of particulate contamination in a large group of units.

Method 1. Light Obscuration Particle Count Test

Use a suitable apparatus based on the principle of light blockage which allows an automatic determination of the size of particles and the number of particles according to size. ◆It is necessary to perform calibration, as well as to demonstrate the sample volume accuracy, sample flow rate, particle size response curve, sensor resolution, and counting accuracy, at least once a year.◆

◆Calibration

Particles to be used for calibration should be subject to particle size sensitivity measurement, using spherical polystyrene particles having at least 5, 10 and 25 μm in diameter (PSL particles) in mono-dispersed suspension. The PSL particles should have either a domestic or international traceability in terms of length, with a level of uncertainty at not greater than 3%. The particles to be used for calibration should be dispersed in *particle-free water*.

Manual method

The particle size response of the system to be applied should be determined using at least 3 channels for threshold-voltage setting, according to the half counting method of window moving type. The threshold-voltage window should be ±20% of the measuring particle size. After measuring the sensitivity of response for the designated particle size, the size response curve is prepared by the method indicated by the manufacturer from particle-response measuring point, and threshold-voltage of 5, 10 and 25 μm of the apparatus is obtained.

Electronic method

In the use of multichannel peak height analyzer, the particle size response is measured by half-count method of moving window system same as the manual method, and the particle size response curve is prepared by the method designated by the instrument manufacturer, then, the threshold-voltage of 5, 10 and 25 μm of the apparatus is obtained. In this case, the instrument manufacturer or the user should validate the obtainability of the same result as that of the manual method.

Automated method

The particle size response curve of the apparatus may be obtained by using the software developed by the user or supplied by the instrument manufacturer, whereas, the manufacturer or the user should validate the obtainability of the same result as that of the manual method.

Sample volume accuracy

Sample volume accuracy should fall within 5% of the measuring value in case measuring the decrease of test solution by the mass method after measuring the test solution of 10 mL.

Sample flow rate

The flow rate of the sample indicated into the sensor should be calculated from the observed sample volume and time, and should be conformed within the range of the manufacturer's specification for sensor used.

Sensor

There is a possibility of changes of particle size resolution and counting rate of particle-detecting sensor in each sensor by assembling accuracy and parts accuracy even in the same type sensor. The threshold accuracy also needs to be confirmed. Testing should accordingly be performed for each of particle size resolution, accuracy in counting and in threshold setting, using Particle Count Reference Standard Suspension (PSL spheres having mean diameter of approximately 10 μm, of a concentration at 1000 particles/mL ±10%, not more than 5% of CV value).

During measurement, stirring should be made for assuring the uniformity in sample concentration.

Sensor resolution (Particle size resolution of apparatus)

Measurement should be made by either one of the following methods.

1. Manual method to obtain the spread of histogram prepared from the counting value of the apparatus.
2. Electronic method to obtain the spread of histogram of the classification of system-responding signal by using the multichannel peak height analyzer.
3. Automated method to obtain the spread of histogram of responsive signal of the test-particle by using the software prepared by the manufacturer or the user.

The difference between the threshold of particle size counting 16 and 84% of the total counts and the test-particle size should be within 10%, whereas, electronic method and automated method should be both validated for obtaining the

same result as that of the manual method.

Particle counting accuracy

Data obtained by counting particles of 5 μm and greater should be 763 to 1155 particles per 1 mL.

Threshold accuracy

Particle size calculated from a threshold corresponding to 50% counts for particles of 5 μm and greater should fall within ±5% of the mean diameter of the test particles.

Reagents

Particle-free water: The purified water containing not more than 5 particles of 10 μm or greater size, and not more than 2 particles of 25 μm or greater size in 10 mL of the insoluble particle number measured by the light obscuration particle counter.

General precautions

The test is carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Very carefully wash the glassware and filtration equipment used, except for the membrane filters, with a warm detergent solution and rinse with abundant amounts of water to remove all traces of detergent. Immediately before use, rinse the equipment from top to bottom, outside and then inside, with *particle-free water*.

Take care not to introduce air bubbles into the preparation to be examined, especially when fractions of the preparation are being transferred to the container in which the determination is to be carried out.

In order to check that the environment is suitable for the test, that the glassware is properly cleaned and that the water to be used is particle-free, the following test is carried out: determine the particulate contamination of 5 samples of *particle-free water*, each of 5 mL, according to the method described below. If the number of particles of 10 μm or greater size exceeds 25 for the combined 25 mL, the precautions taken for the test are not sufficient. The preparatory steps must be repeated until the environment, glassware and water are suitable for the test.

Method

Mix the contents of the sample by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of *particle-free water* and remove the closure, avoiding any contamination of the contents. Eliminate gas bubbles by appropriate measures such as allowing to stand for 2 min or sonicating.

For large-volume parenterals or for small-volume parenterals having a volume of 25 mL or more, single units are tested. For small-volume parenterals less than 25 mL in volume, the contents of 10 or more units are combined in a cleaned container to obtain a volume of not less than 25 mL; where justified and authorised, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 mL with *particle-free water* or with an appropriate solvent without contamination of particles when *particle-free water* is not suitable.

Powders for parenteral use are reconstituted with *particle-free water* or with an appropriate solvent without contamination of particles when *particle-free water* is not suitable.

The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals

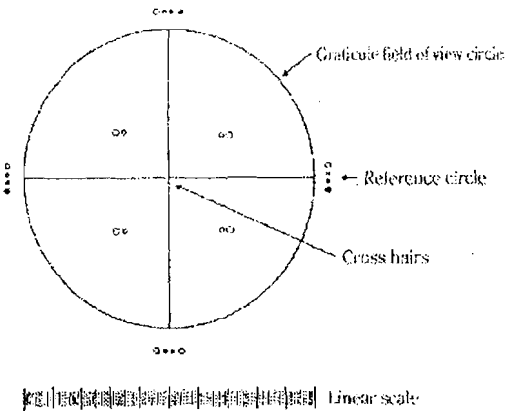

Fig. 6.07-1 Circular diameter graticule

or for small-volume parenterals having a volume of 25 mL or more, fewer than 10 units may be tested, based on an appropriate sampling plan.

Remove 4 portions, each of not less than 5 mL, and count the number of particles equal to or greater than 10 μm and 25 μm. Disregard the result obtained for the first portion, and calculate the mean number of particles for the preparation to be examined.

Evaluation

If the average number of particles exceeds the limits, test the preparation by Method 2 (Microscopic Particle Count Test).

Test 1.A—Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of equal to or more than 100 mL

The preparation complies with the test if the average number of particles present in the units tested does not exceed 25 per milliliter equal to or greater than 10 μm and does not exceed 3 per milliliter equal to or greater than 25 μm.

Test 1.B—Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL.

The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 μm and does not exceed 600 per container equal to or greater than 25 μm.

Method 2. Microscopic Particle Count Test

Use a suitable binocular microscope, filter assembly for retaining particulate contamination and membrane filter for examination.

The microscope is equipped with an ocular micrometer calibrated with an objective micrometer, a mechanical stage capable of holding and traversing the entire filtration area of the membrane filter, two suitable illuminators to provide episcopic illumination in addition to oblique illumination, and is adjusted to 100±10 magnifications. The ocular micrometer is a circular diameter graticule (see Fig. 6.07-1) and consists of a large circle divided by crosshairs into quadrants, transparent and black reference circles 10 μm and 25 μm in diameter at 100 magnifications, and a linear scale graduated in 10 μm increments. It is calibrated using a stage micrometer that is certified by either a domestic or interna-

tional standard institution. A relative error of the linear scale of the graticule within ±2 per cent is acceptable. The large circle is designated the graticule field of view (GFOV).

Two illuminators are required. One is an episcopic bright-field illuminator internal to the microscope, the other is an external, focussable auxiliary illuminator adjustable to give reflected oblique illumination at an angle of 10° to 20°.

The filter assembly for retaining particulate contamination consists of a filter holder made of glass or other suitable material, and is equipped with a vacuum source and a suitable membrane filter.

The membrane filter is of suitable size, black or dark gray in color, non-gridded or gridded, and 1.0 μm or finer in nominal pore size.

General precautions

The test is carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Very carefully wash the glassware and filter assembly used, except for the membrane filter, with a warm detergent solution and rinse with abundant amounts of water to remove all traces of detergent. Immediately before use, rinse both sides of the membrane filter and the equipment from top to bottom, outside and then inside, with *particle-free water*.

In order to check that the environment is suitable for the test, that the glassware and the membrane filter are properly cleaned and that the water to be used is particle-free, the following test is carried out: determine the particulate contamination of a 50 mL volume of *particle-free water* according to the method described below. If more than 20 particles 10 μm or larger in size or if more than 5 particles 25 μm or larger in size are present within the filtration area, the precautions taken for the test are not sufficient. The preparatory steps must be repeated until the environment, glassware, membrane filter and water are suitable for the test.

Method

Mix the contents of the samples by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of *particle-free water* and remove the closure, avoiding any contamination of the contents.

For large-volume parenterals, single units are tested. For small-volume parenterals less than 25 mL in volume, the contents of 10 or more units is combined in a cleaned container; where justified and authorised, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 mL with *particle-free water* or with an appropriate solvent without contamination of particles when *particle-free water* is not suitable. Small-volume parenterals having a volume of 25 mL or more may be tested individually.

Powders for parenteral use are constituted with *particle-free water* or with an appropriate solvent without contamination of particles when *particle-free water* is not suitable.

The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals or for small-volume parenterals having a volume of 25 mL or more, fewer than 10 units may be tested, based on an appropriate sampling plan.

Wet the inside of the filter holder fitted with the membrane filter with several milliliter of *particle-free water*. Transfer to the filtration funnel the total volume of a solution pool or of a single unit, and apply vacuum. If needed add stepwise a portion of the solution until the entire volume is filtered. After the last addition of solution, begin rinsing the inner walls of the filter holder by using a jet of *particle-free water*. Maintain the vacuum until the surface of the membrane filter is free from liquid. Place the filter in a petri dish and allow the filter to air-dry with the cover slightly ajar. After the filter has been dried, place the petri dish on the stage of the microscope, scan the entire membrane filter under the reflected light from the illuminating device, and count the number of particles that are equal to or greater than 10 μm and the number of particles that are equal to or greater than 25 μm. Alternatively, partial filter count and determination of the total filter count by calculation is allowed. Calculate the mean number of particles for the preparation to be examined.

The particle sizing process with the use of the circular diameter graticule is carried out by transforming mentally the image of each particle into a circle and then comparing it to the 10 μm and 25 μm graticule reference circles. Thereby the particles are not moved from their initial locations within the graticule field of view and are not superimposed on the reference circles for comparison. The inner diameter of the transparent graticule reference circles is used to size white and transparent particles, while dark particles are sized by using the outer diameter of the black opaque graticule reference circles.

In performing the microscopic particle count test (Method 2) do not attempt to size or enumerate amorphous, semi-liquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane filter. These materials show little or no surface relief and present a gelatinous or film-like appearance. In such cases the interpretation of enumeration may be aided by testing a sample of the solution by Method 1.

Evaluation

Test 2.A—Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of equal to or more than 100 mL

The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per milliliter equal to or greater than 10 μm and does not exceed 2 per milliliter equal to or greater than 25 μm.

Test 2.B—Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL

The preparation complies with the test if the average number of particles present in the units tested does not exceed 3000 per container equal to or greater than 10 μm and does not exceed 300 per container equal to or greater than 25 μm.