Designation: E3230 – 20

Standard Practice for Extraction of Particulate Matter from the Surfaces of Single-Use Components and Assemblies Designed for Use in Biopharmaceutical Manufacturing[1]

This standard is issued under the fixed designation E3230; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice describes the requirements for development, qualification, and routine application of a procedure for the effective liquid extraction of particulate matter from the surfaces of single-use components and assemblies designed for use in biopharmaceutical manufacturing processes. The extraction generates a suspension of particulate matter in liquid which makes the particulate matter readily available for analytical characterization.

1.2 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.3 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.4 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E3060 Guide for Subvisible Particle Measurement in Biopharmaceutical Manufacturing Using Dynamic (Flow) Imaging Microscopy

2.2 *USP Documents:*[3]

USP <788> Particulate Matter in Injections, 2012

USP <790> Visible Particulates in Injections, 2017

USP <1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions, 2012

USP <1790> Visual Inspection of Injections, 2018

2.3 *ISO Documents:*[4]

ISO 16232:2018 Road Vehicles – Cleanliness of Components and Systems

2.4 *Other Documents:*

BPSA Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Process Equipment, 2014[5]

JP 6.07 Insoluble Particulate Matter Test for Injections[6]

Ph. Eur. 2.9.19 Particulate Contamination: Sub-Visible Particles[7]

VDA 19 Part 1 Inspection of Technical Cleanliness, March 2012[8]

3. Terminology

3.1 *Definitions:*

3.1.1 *agitation, n*—an extraction method by which a test article partially filled with test liquid is moved to create liquid motion relative to the internal surfaces of the test article.

3.1.2 *bioprocess container, n*—a container (bag, bottle, tank, etc.) used primarily for liquid, frozen liquid, or powder storage during various stages of biopharmaceutical manufacturing processing.

3.1.3 *background particle count, n*—average or range, or both, of particle counts obtained upon executing the extraction procedure without the test article present.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[4] Available from International Organization for Standardization (ISO), ISO Central Secretariat, BIBC II, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, http://www.iso.org.

[5] Available from BioProcess Systems Alliance, 1400 Crystal Drive, Suite 630 Arlington, VA 22202, https://bpsalliance.org.

[6] Available from Japanese Pharmacopoeia.

[7] Available from European Pharmacopoeia.

[8] Available from Verband der Automobilindustrie, https://www.vda.de/en.html.

3.1.4 *background test, n*—application of the same extraction conditions required for the extraction procedure, but without the test article present.

3.1.5 *collection equipment, n*—any device (conical flask, beaker, tray, funnel, etc.) suited to the collection of all the extraction liquid obtained from the test article.

3.1.6 *external rinsing, n*—an extraction method based upon flow of test liquid on the outside surfaces a test article.

3.1.7 *extraction, n*—operation required to transfer particulate matter present on a surface into a test liquid, thus collecting the particulate matter for subsequent analysis.

3.1.8 *extraction apparatus, n*—all equipment applied in delivering clean test liquid to a test article, and all collection equipment applied in collecting the extraction liquid obtained from a test article

3.1.9 *extraction curve, n*—trend of the extraction effectiveness index (EIn) as a function of the number of extraction steps (n).

3.1.10 *extraction conditions, n*—parameters under which an extraction procedure is carried out (for example, test liquid volume and flow rate, time, temperature, etc.).

3.1.11 *extraction effectiveness index (EIn for extraction step n), n*—the ratio of the particle count (Pn) extracted in an extraction step n, divided by the particle count total (PTn), which is the sum of Pn up to and including step n.

3.1.12 *extraction liquid, n*—test liquid loaded with particulate matter extracted from the test article.

3.1.13 *extraction method, n*—technique (agitation or rinsing) applied to detach particulate matter from the test article.

3.1.14 *extraction procedure, n*—complete sequence of actions under controlled extraction conditions applying one or more extraction methods to the test article.

3.1.15 *extraction step (n), n*—one application of the extraction procedure which creates one batch of extraction liquid.

3.1.16 *extraction volume, n*—volume of test liquid used to extract particulate matter from a test article.

3.1.17 *extraction time factor, n*—for a method based upon rinsing, the time factor is the total volume of test liquid applied for a method based upon agitation, the time factor is the total agitation time applied.

3.1.18 *final rinsing, n*—application of test liquid to remove any residual particulate matter from the surfaces of the collection equipment.

3.1.19 *internal rinsing, n*—an extraction method based upon flow of test liquid on the internal surfaces of a test article.

3.1.20 *particulate matter; particle, n—particulate matter and particle are equivalent terms (USP <1790>)*, a portion, piece or fragment of potentially loose mobile and non-soluble matter present on the surfaces of a single-use component or assembly, which may contact or end up in the process fluid or drug product during biopharmaceutical processing.

3.1.21 *particle count (Pn), n*—number of particles in a defined particle size range (determined by a particle measurement method) found in the extraction liquid obtained from the extraction step n.

3.1.22 *particle count total (PTn), n*—total particle count obtained for all extraction steps up to and including extraction step n.

3.1.23 *particle count specification, n*—maximum particle count allowed in a single-use component or assembly.

3.1.24 *particle load, n*—(*1*) particulate matter load; (*2*) totality of all particles present on the surfaces of a test article.

3.1.25 *particle measurement, n*—implementation of a particle measurement method to obtain a particle count.

3.1.26 *particle measurement method, n*—a qualified method for counting and sizing particles for a defined particle size range.

3.1.27 *particle size, n*—chosen measure of the size of a particle (for example, Feret diameter, equivalent circular diameter, fiber length, etc.).

3.1.28 *qualification criterion, n*—criterion required for qualification of an extraction procedure (EIn $\leq$ 0.10 for any of the extraction steps n, where n = 6).

3.1.29 *qualification test, n*—process by which a chosen extraction method is verified to meet the criteria for effective extraction of particulate matter.

3.1.30 *reference particles, n*—standardized test particles of known type, size and concentration.

3.1.31 *routine test, n*—a test performed regularly on samples of components/assemblies from a manufacturing process involving a qualified particle extraction procedure combined with a qualified particle measurement method.

3.1.32 *single-use assembly, n*—parts assembled together to produce a stand-alone single-use system.

3.1.32.1 *Discussion*—An assembly is comprised of multiple single-use components.

3.1.33 *single-use component, n*—parts assembled together to produce single-use assemblies.

3.1.33.1 *Discussion*—The most common components are bioprocess containers, tubing, connectors, clamps, valves, sensors and filters.

3.1.34 *single-use system (SUS), n*—stand-alone process equipment used in biopharmaceutical manufacturing.

3.1.34.1 *Discussion*—A system is comprised of multiple single-use assemblies.

3.1.34.2 *Discussion*—Often composed of plastic components which are used once and then disposed or recycled.

3.1.35 *soaking time period, n*—a time period over which the surfaces of the test article are wetted by the test liquid, but no energy input (agitation or rinsing) is applied.

3.1.36 *test article, n*—a single component or assembly from which particulate matter is extracted.

3.1.37 *test liquid, n*—liquid used to extract particulate matter from a test article.

3.1.37.1 *Discussion*—This liquid is terminally filtered to ensure it has minimal background particle count.

3.1.38 *test liquid delivery system, n*—equipment to deliver a controlled flow of filtered test liquid (equipment to pressurize the test liquid, a filtration system, tubing, adapters, nozzle, etc.).

4. Significance and Use

4.1 Conventional stainless-steel process equipment for biopharmaceutical manufacturing require cleaning and sterilization prior to implementation. Single-use systems (SUS), standalone equipment typically composed of plastic components and assemblies, are usually assembled in cleanrooms and are usually not cleaned or rinsed prior to implementation (with the exception of filters, which are often rinsed prior to use). SUS cleanliness with respect to particulate matter depends upon the quality of the SUS manufacturing process, and also upon the care and handling of the SUS upon implementation by the end-user.

4.2 In the process of manufacturing single-use components or assemblies, particulate matter may adhere to the interior (fluid contacting) or exterior surfaces of SUS (BPSA). Visual inspection of SUS components and assemblies for particulate matter is often limited by translucent or opaque materials which inhibit visualization, especially of interior fluid-contacting surfaces. Also in some cases, the large size of single-use assemblies significantly reduces the effectiveness of visual inspections. A more complete assessment of particulate matter load requires a method to extract particulate matter from the surfaces of single-use components or assemblies using a test liquid, which makes the particles readily available for analytical characterization using counting, sizing and chemical/physical identification methods.

4.3 Pharmaceutical manufacturers use a wide variety of configurations and sizes of single-use components and assemblies, such as bioreactors, bioprocess containers, tubing, connectors, clamps, valves, sensors and filters. Extraction of particulate matter may be relatively easy from small components with readily accessible surfaces, however, extraction of particulate matter from large and complex assemblies with less readily accessible interior surfaces may require significantly more effort.

4.4 The wide variety of single-use components and assemblies inhibits specification of a narrowly defined extraction procedure with a universally prescribed volume of test liquid and energy input (rinsing/agitation) conditions. The approach described in this practice allows for flexibility and innovative approaches to maximize particle extraction which are specifically tailored to the component or assembly of interest.

4.5 In most cases, relatively small amounts of particulate matter are non-uniformly dispersed over large surface areas, and the particulate matter also is often inhomogeneous in chemical composition and morphology. Standardized single-use components and assemblies with controlled amounts of known standardized particulate matter which simulate real systems are challenging to prepare. Thus in the development of a particle extraction procedure, a practical and expedient methodology is required to assess whether the chosen extraction procedure is effective and extracts as many particles as practically possible

4.6 A well-established standardized methodology for demonstrating effective extraction of particles from the surfaces of automotive components provides guidance (ISO 16232:2018, VDA 19 Part 1). The standard practice described here for the extraction of particulate matter from the surfaces of single-use components and assemblies is closely based upon the principles described in the ISO 16232:2018 standard for automotive components. This "multiple extractions" approach to qualification of an extraction procedure significantly increases the probability that particulate matter adhering to surfaces is removed upon extraction, and that the extraction procedure so qualified is effective. The qualification criterion described in this practice is essentially the same as the "declining criterion" described in ISO 16232:2018. In essence, this criterion requires that during qualification the chosen extraction procedure must achieve an effectiveness of greater than 90% particle removal on a relative basis.

4.7 Note that this practice does not specify the particle measurement method required to count and size the particles. The qualification of the extraction procedure described in this practice will be compatible with particle measurement methods typically used for both so-called "visible" (≥ 100 micron) or "sub-visible" (10 to 100 micron) particle size ranges (USP <788>, USP <1788>, USP <790>), which includes methods such as light obscuration, membrane microscopy or dynamic flow imaging (Guide E3060). In order for this practice to be effective, the chosen particle measurement method shall have been qualified for reliable determination of the particle count (number of particles in the particle size range of interest).

4.8 The overall goal of a chosen extraction procedure for particulate matter on the surfaces of single-use components and assemblies is to maximize the probability that particles are extracted in an effective, practical, consistent and controlled way.

5. Requirements for Effective Extraction of Particulate Matter

5.1 *General Principles:*

5.1.1 In order to determine the particle load of single-use components and assemblies, the first procedure required is an extraction procedure, whereby the particulate matter is removed from the surfaces of components/assemblies (test article) by means of a liquid extraction method, which is essentially a surface cleaning process. A test liquid is applied to the surfaces of a test article using rinsing or agitation extraction methods, or both, and the extraction liquid (test liquid containing the extracted particles) is collected for further analysis using a particle measurement method. The chosen particle measurement method (not specified in this practice) shall have been qualified for determination of the particle count in the particle size range of interest.

5.1.2 Since reference test articles with a known amount of standardized particulate matter are not readily available to allow absolute quantitative determination of extraction effectiveness, development of an extraction procedure with a high degree of effectiveness (measured on a relative basis) requires the following steps:

5.1.3 *Qualification Test:*

5.1.3.1 The appropriate extraction procedure for effective extraction of particles from the surfaces of a component or assembly is determined by performing the qualification test.

The qualification approach and qualification criteria stated in this document ensure that as many as possible of the particles adhering to the surfaces of the test article are removed upon extraction. Once a specific test article has undergone a qualification test, it cannot be retested. The requirements, parameters, and results of the chosen extraction procedure shall be documented.

5.1.4 *Routine Test:*

5.1.4.1 Depending upon requirements, the routine test will consist of one or more extractions routinely performed on a sampling of components or assemblies, typically for process monitoring and control, or component/assembly product release based upon particle count specifications, or both.

5.1.5 *Background Test:*

5.1.5.1 During qualification and routine testing, a background test is required. In the background test, the extraction procedure for the test article of interest is applied, but without the test article present. The result of the background test is the background particle count, a measure of the amount of particulate matter introduced from sources other than the test article, such as the extraction apparatus and the surrounding environment.

5.2 *Selection of the Extraction Method:*

5.2.1 Particulate matter is extracted from the surfaces of a component or assembly in a surface cleaning process, whereby the surfaces are flushed with a test liquid. The ease with which particulate matter is removed from surfaces by liquid extraction depends upon the strength of adhesion between particle and surface, and the ability to deliver test liquid with the required force to flush the desired surfaces of the test article. The extraction method is determined by the features of the test article, such as size, shape, and the accessibility of the surfaces. The purpose of selecting an extraction method, determining extraction conditions, and qualifying the procedure, is to optimize the removal of particulate matter from the test article. The main parameters which influence the extraction result are the wetting and suspension properties of the test liquid, temperature, energy input (shear forces imparted by the test liquid upon rinsing or agitating with the test liquid, or both) and the amount of time the surfaces of the test article are exposed to the test liquid (ISO 16232:2018, VDA 19 Part 1). For this practice, the extraction procedure shall have rinsing or agitation steps, or both.

5.3 *Disassembly of Single-Use Assemblies:*

5.3.1 Extraction of large or complex assemblies, or both, may require careful disassembly (for example, cutting of tubing lines) in order to allow practical handling, or to allow access to flow-restricted interior regions of the assembly. Care should be taken to minimize the generation of particulate matter during disassembly (for example, cut tubing lines using a sharp knife).

5.4 *Environmental Conditions:*

5.4.1 In the implementation of this practice, care must be taken to minimize particulate matter originating from foreign sources other than the surfaces of the single-use components or assemblies of interest. Potential foreign sources include the test liquid, the delivery system for the test liquid, the collection equipment used to receive the extraction liquid, particles shed by the test operator (for example, clothing fibers), and particles present in the general environment. It is recommended to terminally filter the test liquid prior to use through a non fiber shedding filter having a nominal pore size smaller than the smallest particle size to be counted by the chosen particle measurement method. Carefully clean the extraction apparatus, properly gown the test operator, and perform all procedures in a clean environment.

5.4.2 The cleanliness of the environment under which the extraction procedure occurs must be adequate to meet the required background particle count. In most cases in order to meet the required background particle count, a controlled laboratory environment will be required: a laminar-flow cabinet, proper operator gowning (garments and gloves), and decontaminated tools and sample handling equipment. The suitability of the environment is confirmed by meeting the required background particle count.

5.5 *Test Liquid:*

5.5.1 Particulate matter adheres to the fluid-contacting surfaces via a variety of forces, and the role of the test liquid is to overcome these forces and remove (wash off) particulate matter from the surfaces. The test liquid chosen combined along with the extraction conditions shall meet the requirements for effective extraction as described in the qualification test. The test liquid chosen shall not chemically attack or etch the surfaces of the test components. If agitation is applied, the test liquid shall be non-foaming since foam may not completely drain from the component and could potentially trap particles. Care shall be taken that the test liquid is also compatible with the chosen particle measurement method. In most cases, purified water or water plus salt(s) (for example, buffers) meet the criteria noted above.

5.6 *Extraction Apparatus:*

5.6.1 The extraction apparatus generally consists of the following items:

5.6.1.1 A system adequate to prepare clean test liquid with low particle count which meets the required background particle count.

5.6.1.2 A system to deliver the test liquid to the test article. This system provides test liquid at flow rates adequate to rinse particulate matter from test article surfaces, and also to rinse surfaces of collection equipment (funnels, collection containers, etc.) applied in the extraction procedure.

5.6.1.3 If needed, adapters to connect the test liquid delivery system directly to components or assemblies, or plugs, or both, to close component or assembly openings.

5.6.1.4 If needed, equipment to impart controlled agitation (at specified amplitude and frequency).

5.6.1.5 Collection equipment to receive the extraction liquid obtained after extraction of the test article (for example, flasks, beakers, trays, funnels, etc.).

6. Qualification Test

6.1 *General Principles:*

6.1.1 In order to properly assess the particle load of a single-use component or assembly, the chosen extraction procedure shall be determined to be effective. Effective means

that it shall be proved that the chosen extraction procedure extracts the maximum amount of detachable particulate matter from the test article surfaces of interest.

6.1.2 Absolute determination of the particle load of a single-use component or assembly is challenging, since creation of standard test articles with a defined load of standardized reference particles is difficult. In many cases, creation of a test article with a standardized load of particles is impractical, considering the broad range of materials and geometries of single-use components and assemblies, the possible range of particulate matter types and concentrations, and potential variations in adhesion strength between particles and material surfaces. Consequently, this practice describes a multiple extractions approach for the qualification of an effective extraction procedure, which avoids the need for reference particles.

6.1.3 Qualification tests are carried out to define an effective extraction procedure for routine testing. The qualification test determines the extraction curve, the trend of the extraction effectiveness index (EIn) as a function of the number of extraction steps (n) applied. Each extraction step (n) is a repeat of the same extraction procedure (same conditions and method). After each extraction step, the particle count (Pn) in the extraction liquid is determined, and the EIn for each step n calculated by dividing the particle count from step n (Pn) by PTn, which is the particle count total for all extraction steps executed up to and including the extraction step n. Thus, EIn = Pn/PTn and should generally decrease as n increases, since after each extraction step, the test article should be cleaner and release less particles (Pn decreases), and the cumulative total of particles extracted over n extraction steps (PTn) should increase (Fig. 1). In this practice, an extraction procedure is considered properly qualified if within one of 6 repeated extraction steps of the same test article (n = 6), less than 10% of the cumulative particle count (up to and including the considered extraction step) are extracted in the extraction step under consideration. Specifically, the qualification criterion for an effective extraction procedure is EIn ≤ 0.10 for any of the extraction steps n, where n = 6.

6.1.4 The qualification test procedure comprises the following steps:

6.1.4.1 Determination and procuring the number of test articles required for qualification.

6.1.4.2 Cleaning the extraction apparatus.

6.1.4.3 Executing a background test to determine background particle count.

6.1.4.4 Determination if background particle count requirements are satisfied.

6.1.4.5 Preparation of the test article.

6.1.4.6 Extraction of the test article.

6.1.4.7 Final rinsing of the collection equipment (optional).

6.1.4.8 Determination of the particle count in the extraction liquid.

6.1.4.9 Determination of the extraction effectiveness index (EIn).

6.1.4.10 Repeat the above steps up to 5 more times until the qualification criterion is met.

6.1.5 If the background particle counts meet requirements, and the qualification criterion for effective extraction is met, the extraction procedure is qualified, and the extraction procedure (extraction conditions and methods, along with background particle count) shall be documented in detail.

6.1.6 A qualification test procedure shall never be repeated on a test article which has already been put through the qualification test. The qualification test shall be carried out for a component/assembly or a representative member of a closely related family of components/assemblies. If significant modifications to the manufacturing process, geometry or materials of construction of a component/assembly occur, the qualification test shall be repeated.

6.2 *Procedure: Qualification Test:*

6.2.1 Select the number of test articles needed to meet chosen statistical sampling requirements.

6.2.2 Verify the ability to deliver a consistent and known amount of test liquid.

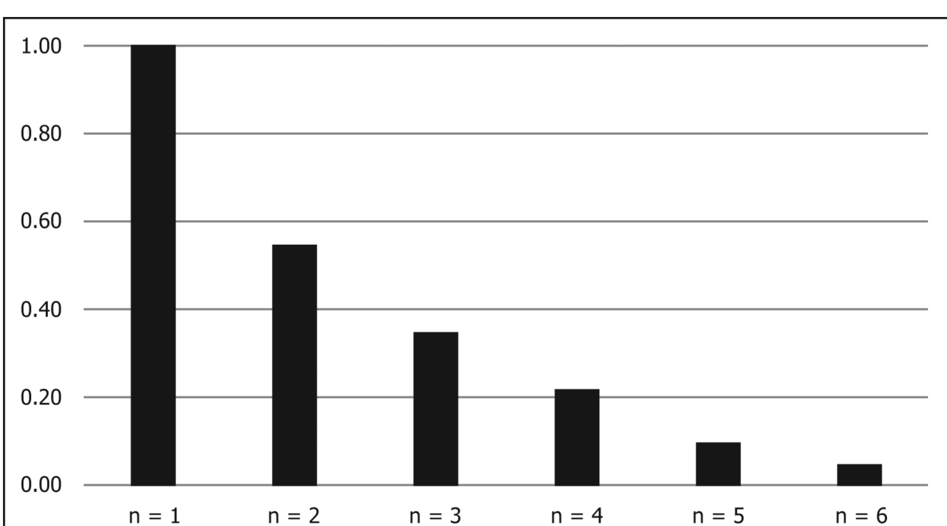

FIG. 1 General Trend of an Extraction Curve (EIn versus n)

6.2.3 *Background Test:*

6.2.3.1 Perform a background test after cleaning the extraction apparatus. The background particle count found shall meet the background particle count requirement. If the background particle count does not meet the requirement, additional cleaning of the extraction apparatus or improvements in the environmental conditions may be required. In the qualification test, background particle count is not subtracted from the particle count obtained in each extraction step.

6.2.4 *Preparation of Test Article:*

6.2.4.1 Remove plugs or closed connectors from any ports of the test article if necessary. Note that removal of plugs or connectors may generate particulate matter. If needed, apply suitable adaptors to directly connect the test liquid delivery system to ports on the test article.

6.2.5 *Extraction of the Test Article:*

6.2.5.1 For extraction procedures using rinsing, rinse the test article with the chosen volume of test liquid at the chosen liquid flow rate, and collect the extraction liquid (containing the particles) into the collection equipment, ensuring that as little as possible extraction liquid remains on the surfaces of the test article, and as much as possible of the extraction liquid is recovered.

6.2.5.2 For extraction procedures using agitation, fill the test article with a chosen volume of test liquid, plug or clamp any open ports closed, and agitate the test article with controlled frequency and amplitude over a defined time period. If desired, a soaking time period, where the surfaces of the test article are wetted with test liquid but not agitated, may also be applied. Remove the plug or clamp from the chosen outlet port, and empty the extraction liquid (containing the particles) from the test article into the collection equipment, ensuring that as much of the extraction liquid as possible drains out of the test article.

6.2.6 *Optional*—After collection of the extraction liquid, do a final rinsing of the collection equipment (beakers, funnels, etc.) with additional test liquid to ensure full recovery of any particles potentially retained on the surfaces of the collection equipment.

6.2.7 *Optional*—A reference particle recovery test (using standard reference particles added at known concentration to the test liquid) may be applied to confirm recovery of the test liquid (Appendix X3).

6.2.8 Apply the chosen particle measurement method to the extraction liquid obtained, and determine the particle count. This value is denoted as Pn.

6.2.9 Repeat the extraction procedure (single extraction step n) 5 more times (n = 6) on the same component, applying the same extraction method(s) under the same extraction conditions.

6.2.10 *Determination of the Extraction Effectiveness Index:*

6.2.10.1 For each repeated extraction procedure (single extraction step n), calculate the particle count total PTn, which is the cumulative number of particles extracted in all prior steps up to and including the step under consideration. PTn is the sum total of Pn for all extraction steps n executed:

$$PTn = \sum_{i=1}^{n} Pi \quad (1)$$

Divide Pn by PTn for the step n under consideration to determine the extraction effectiveness index (EIn) for the extraction step n under consideration. If:

$$EIn = \frac{Pn}{PTn} \leq 0.10 \quad (2)$$

for any of the n = 6 extraction steps, the chosen extraction procedure meets the qualification criterion of this practice.

6.2.11 *Optional*—Perform a background test after the 6th extraction step. The background particle count shall meet requirements.

6.2.12 Repeat the qualification test on as many test articles as needed to meet chosen statistical sampling requirements.

6.2.13 The qualified extraction procedure (methods and conditions), the qualified particle measurement method, along with reproducibility, acceptance criteria and background particle count shall be documented in a qualification report.

6.2.14 *If the Qualification Criterion is Not Achieved:*

6.2.14.1 If the qualification criterion is not achieved after 6 extraction steps, the extraction conditions (volume of test liquid, time, temperature, energy input) shall be modified, or a different extraction method chosen (rinsing, agitation, or a combination of both), and the qualification test shall be repeated with a new test article.

6.2.14.2 A range of shapes of the extraction curve (EIn versus n) are possible, and Annex A1 possible interpretations of the trends, and provides information to guide improvements to the effectiveness of the extraction procedure in order to help achieve the qualification criterion.

7. Routine Test

7.1 *General:*

7.1.1 A routine test is a test performed regularly on samples of components/assemblies from a manufacturing process and requires a qualified particle extraction procedure combined with a qualified particle measurement method.

7.1.2 The routine test is based upon chosen requirements for manufacturing process monitoring, control and continuous improvement, along with any component/assembly specific release criteria based upon particle count specifications.

7.2 *Routine Testing:*

7.2.1 Once the extraction procedure is qualified using the qualification criterion described above, the routine test shall consist of one or more applications of the qualified extraction procedure (one or more of the qualified extraction steps).

7.2.2 Prior to a series of routine tests, a background test is performed with the chosen frequency required to monitor and maintain the background particle count.

7.2.3 For the chosen routine test procedure, the qualified particle measurement method, along with reproducibility, acceptance criteria and the background particle count shall be documented in a qualification report.

8. Background Test

8.1 *General:*

8.1.1 The background test measures any contributions of the (*1*) overall test environment, (*2*) operators and handling procedures, and (*3*) test liquid and extraction apparatus, to the