Application Note

Particle Counting in Parenteral Solutions

Parenteral Solutions

Pharmaceutical companies are manufacturers of both solid and liquid formulations. Solid formulations may be tablets, dry powers, confectionary and solid injectables; liquid formulations may be eye drops, ointments, I.V. and other parenteral solutions. Parenteral solutions are packed as large volume parenteral (LVP) solutions, small volume parenteral (SVP) solutions and dry powders requiring reconstitution as either LVP or SVP.

Large Volume Parenteral (LVP) Solutions

LVP solutions are typically bags or bottles containing larger volumes of intravenous solutions. Common uses of LVP solutions without additives include: 1) correction of electrolyte and fluid balance disturbances; 2) nutrition; 3) as a vehicle for administering other drugs. Large volume parenteral solutions are packaged in containers holding 100 ml or more. There are three types of containers: glass bottle with an air vent tube, glass bottle without an air vent tube, and plastic bags.

Small Volume Parenteral (SVP) Solutions

Small volume parenteral (SVP) solutions are usually 100 ml or less and are packaged depending on the intended use. SVPs are typically packed as ampoules, vials, small bags and prefilled syringes.

If the solution is a sterile formulation it must be free of all visible particulate material. Particulate material refers to mobile, solids unintentionally present in parenteral products. These solids may consist of individual components or mixtures of cellulose, glass, rubber cores from vials, metal and plastic fragments. Sterile suspensions may have particulate material, but these are usually the active drug or an ingredient, not contaminants.

Potential sources of particulate contamination:

1. Manufacturing environment and equipment
2. Manufacturing personnel
3. The packaging components

Counting Particles to Specifications

The devices used to administer the IV products also create potential particle contamination. Particle measurements of 50 mm or larger can be detected by visual inspection. To detect particles less than 50 mm an APSS-200 particle counter and sampler system is required. International limits apply to the number of

	Small Volume Parenterals	Large Volume Parenterals	Dry Powders
British Pharmacopoeia	None	<100/ml @ 5µm, <50/ml @10µm	None
US Pharmacopoeia	<6000 @ 10µm <600 @ 25µm per container	<25/ml @ 10µm <3/ml @ 25µm	None
European Pharmacopoeia	<6000 @ 10µm <600 @ 25µm per container	<25/ml @ 10µm <3/ml @ 25µm	<10,000 @ 10µm, <1000 @ 25µm per container

PARTICLE MEASURING SYSTEMS
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particles, which can be present in parenteral formulations (USP 24/NF19 Section <788>).

USP 24 Chapter 788 defines the allowable limits of non-infectious contaminants, i.e., those particulate materials, that may be present and, therefore, considered safe for IV administration. The standard recognizes that particles greater than 5 mm may cause prolonged venous stasis or significant injury to the veins. Specific limits are set forth for particles above 10 and 25 mm. The USP directive applies to all large-volume solutions (>100 ml) intended for single-dose infusion that are ready for use from the manufacturer.

Apparatus and Methodologies

The USP 24 Chapter <788> allows for the determination of the particulate content of LVP samples to be performed by two different methodologies, The Light Obscuration Particle Count Test and The Microscopic Particle Count Test. Not all injection formulations can be analyzed by both these methods, light obscuration is not always applicable to solutions having a different color, viscosity and clarity similar to water, and may give erroneous results. The Microscopic method is unsuitable for solutions which may contain gelatinous constituents or which will agglomerate on a filter paper. Additional evaluation may be required in these instances to support the release of a product.

The automation of particle counting predominantly is performed by an optical laser particle counter system. Two criteria are defined for the performance of an automated system.

1. The Sensor Concentration Limits – this is the concentration at which the sensor coincidence count rate is 10% at the 10 mm size limit. The APSS-200 sample system has a maximum concentration of 10,000 /ml.

2. Sensor Dynamic Range. This is the dynamic range of the instrument and must include the smallest size to be enumerated. For the USP this is 10 and 25 mm, the APSS-200 system is typically configured to sample dynamically from 2 to 125 mm, and the software can be used as alternative hardware for particles as small as 0.1 μm.

The liquid particle counter operates on the principle that the light extinguished by a particle in a liquid within a classical laser beam is a direct function of its area. Particles obscure the laser beam during transit through the laser beam. The pulses produced by electronically detecting the total laser light minus the light obscured by the particle are used to size the particle. These pulses are measured by an analog to digital converter in the sensor. The liquid is presented to the optical system through a rectangular capillary.

The capillary has a window attached to both the front and back sides which are coated to reduce reflections. A central software application controls the hardware, analyzes the data, and stores the data for future interpretation.

The variation in light caused by the passing of a particle is electronically detected by the photodetector. This signal is then amplified and converted to its digital equivalent. The value of this digital signal is converted into an equivalent particle size in a microprocessor. The different size particles are counted and stored and made available for transmission to the data display system upon request.

To ensure the APSS LiQuilaz® particle sensor, the LS-200 sampler and APSS-View control system software are acceptable and validated to perform the USP 24 <788> tests they are challenged to various tests with defined acceptance criteria. These IQ and OQ (Installation and Operational Qualification) tests challenge the following areas:

Sample Volume Accuracy

As the total number of particles is based upon a known volume of sample measured, it is critical that the sample volume is accurate. The LS-200 syringe sample is available with syringes of 1, 5, 10 and 25 ml and has sample accuracy greater than the required 5%.

Sample Flow Rate

The sample flow rate importance in based upon the speed at which a particle moves through the optical chamber, this determines the duration of the shadow, the particle presents to the photodiode. The LiQuilaz particle sensor is calibrated at two sample flow rates, 10 and 20 ml/min. The sample flow rate is timed, for a fixed volume, from when the syringe starts moving to the point at which it resets to its origination point.

Running the internal self-calibration program performs the calibration of the APSS-200 system. The program systematically requests particles of the sizes 2, 5, 10, 15, 20, 25 and 30 mm. These particles include the USP specified 10, 15 and 25 mm sizes. The algorithm built into the system micro-controller comes with an approved certificate of conformity from Particle Measuring Systems. The sizing resolution is determined by calculating the differential counts between adjacent channels, this should ideally be a 1:1.5 split and a tolerance for the 10 mm size channel is 1:±1.68 x (±10%)

Once the sizing capabilities have been established in the calibration, the counting accuracy is performed during the site PQ (Performance Qualification) procedures. A known concentration of particles is sampled by the system and the results verified as being within ±10% the total count in solution at both 10 and 15 mm.

Taking Measurements

The system is now ready to use and measure the particle count levels in the parenteral sample. The sample measurement is performed by first preparing a sample of known volume of the solution for analysis. This may be a single large volume parenteral, or an agglomeration of smaller vials into one single sample, in either case it is representative of the released product.

The LiQuilaz particle sensor and LS-200 liquid sampler are configured in the APSS-View software to match the criteria of testing required and a recipe can be defined and saved for future runs of a similar product or batch. The sample is presented to the APSS-200 system and a magnetic stirrer is used to constantly agitate the sample to ensure that any potential particulate contamination is evenly distributed and does not settle to the bottom of the sample vessel. The syringe is used to draw a known volume of sample for analysis through the LiQuilaz particle sensor. The particle count data is recorded and a number of measurements taken for the sample, data can be interpreted as either: raw counts, counts per ml, counts per container, a ratio of counts in each channel and as an average of pooled measurements for a single sample. The average of the results is then assessed for compliance to known standards.

The data is stored in a database managed by the APSS-View software and results can be printed immediately or saved for future data interpretation. To comply with the 21CFR Part 11 regulatory guidelines the data files must be, and are stored in an encrypted format to ensure that data cannot be modified. Software security features, built into the sampling system, restrict system operation and data interpretation to authorized system personnel only.

The data can then used to prove the particle matter contamination values for the product. When this data is used in conjunction with additional data from other sources proving, sterility, pyrogen-free or otherwise, stability, pH and osmotic pressure it can then be released for approval and use.

Apnote No. 40 - 09/01