



STANDARD OPERATING PROCEDURE

Department: Microbiology	SOP No.:
Title: Testing of Particulate Matter in Injections and Operation and Maintenance of Liquid Particle Counter-converted	Effective Date:
Supersedes: Nil	Review Date:
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1.0 PURPOSE:

To lay down the procedure for the Testing of Particulate Matter in Injections and Operation and Maintenance of Liquid Particle Counter.

2.0 SCOPE:

This SOP is applicable for Testing of Particulate Matter in Injections and Operation and Maintenance of following Liquid particle counter present in Microbiology lab.

Instrument ID:.....

Make: Particle Measuring Systems

Model:.....

Software:.....

3.0 RESPONSIBILITY

Trained Quality Control Officer is responsible for Testing of Particulate Matter in Injections and Operation and Maintenance of Liquid Particle Counter.

4.0 PROCEDURE

4.1 General Precautions

4.1.1 Perform the test in an environment that does not contribute any significant amount of particulate matter.

4.1.2 Sample containers must be cleaned to an extent that any level of extraneous particles added has no effect on the outcome of the test.

4.1.3 Preferably, the test samples, glassware, closures, and other required equipments are prepared in an environment protected by high efficiency particulate air (HEPA) filters. Non-shedding garments and powder- free gloves are worn throughout the preparation of samples.

4.1.4 Glassware, closures and other required equipments are prepared by immersing and scrubbing in warm, non-ionic detergent solution. Rinse in flowing tap water, and then rinse again in flowing filtered purified water. Organic salts may also be used to facilitate cleaning.



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4.1.5 Flush the instrument with particle free purified water before and after testing or whenever required

4.2 Operation of Liquid Particle Counter

4.2.1 Switch on the main power switch.

4.2.2 Switch on the power button of the liquid particle counter.

4.2.3 Switch on the Liquilaz E20 from back Side.

4.2.4 The syringe will perform an auto check operation.

4.2.5 Switch on the computer.

4.2.6 Start the application by double clicking on the Icon.

4.2.7 The following window will appear



4.2.8 Enter your username and password, following window will appear.

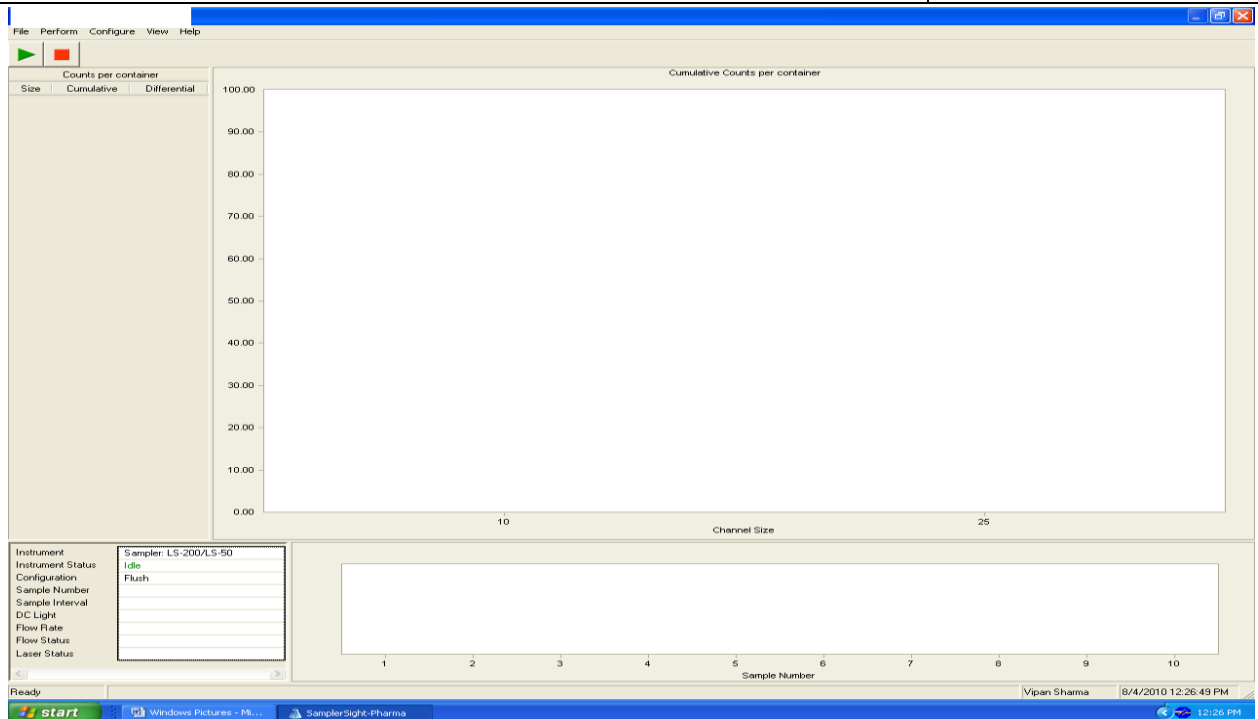


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4.2.9 File menu will provide the Log on, logoff, change password, print sample, print series and exit options.

4.2.10 Perform menu will provide the Start, stop, Halt, flush and calibration options.

4.2.11 Configure menu will provide Data, directories, instrument, sample and security options.

4.2.12 View menu will provide options for reports, tabular, time plot, activity log and calibration.

4.2.13 Help menu will provide information regarding Sampler help and About Sampler.

4.3 Sample Analysis

4.3.1 Blank Preparation and analysis



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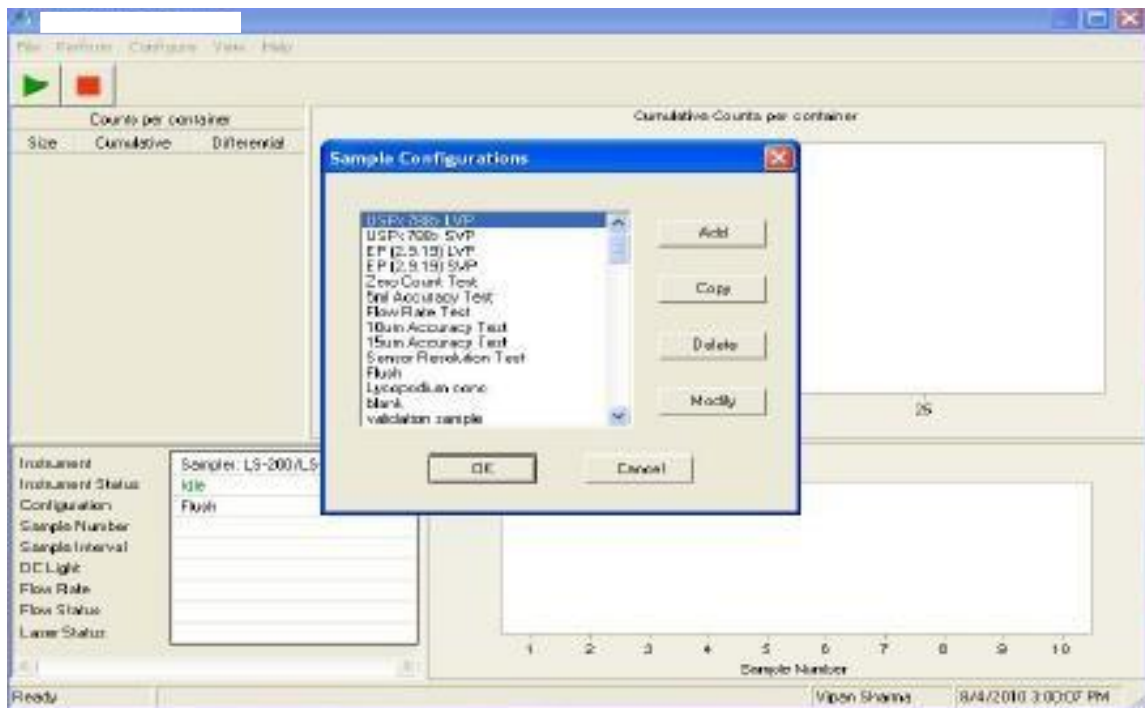
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- 4.3.1.1 Before analyzing a sample, a blank test for system suitability should be done.
- 4.3.1.2 Use glassware thoroughly cleaned with non-ionic detergent and should be free from any residue or water.
- 4.3.1.3 Take filtered purified water or Milli-Q water in not more than 500ml glass beaker or glass bottles for blank test.
- 4.3.1.4 Degas the sample by sonicating for about 30 seconds or by allowing the solution to stand undisturbed until it is free from air bubbles.
- 4.3.1.5 Analyze the sample against the white and black background for black particles, white particles, fiber particles and any other visible particle. If any type visible particles present in the preparation, then discard preparation and repeat the point no.4.3.1.2 to 4.3.1.4 until a sample free from any visible particle is obtained. For testing of sub visible particle, put the sample on the Liquid particle counter's stage. Put the sampler syringe into the sample; put a magnetic stirrer into it. Take a bottle for collection of waste and put the waste generation syringe into the waste collection bottle.
- 4.3.1.6 For analyzing the sample go to the configure menu, and subsequently go to the sample menu. Sample configuration window will appear.



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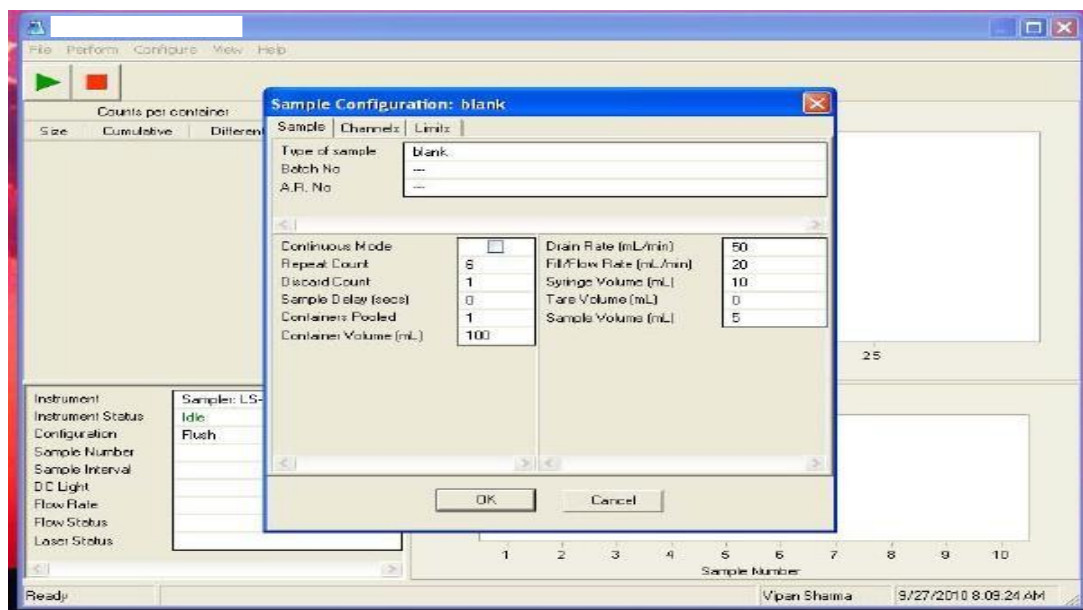


- 4.3.1.7 This window will provide the options for the addition of new sample recipe, copy option for existing recipe, delete option for existing recipe and modify option for existing recipe.
- 4.3.1.8 Either go with the existing recipe or modify the recipe by going to modify option.
- 4.3.1.9 For modification in the blank recipe, click on the blank, and then click the modify. Following window will appear.



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4.3.1.10 Modify the blank configuration as per following table:

Type of Sample – Blank			
Batch No.		--	
A.R. No.		--	
Continuous Mode	-	N/A	Drain Rate (ml/min) - 50
Repeat Count	-	6	Fill Flow Rate (ml/min.) - 20
Sample Delay/ Sec.	-	0	Syringe Volume - 10 (ml)
Container pooled	-	1	Tare Volume (ml) - 0
Container volume (ml)	-	100	Sample Volume (ml) - 5

Then click the OK button; window will automatically turn to the previous window, Click the ok button on the previous window too. Go to 'Data Configuration' select the counts as 'Cumulative' and 'Counts per container'.

4.3.1.11 Then click the perform menu, Go to the start option. Following window will appear.



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- 4.3.1.12 This window will show the configuration of last tested sample, change the configuration or go with the last configuration, as per the requirement. Before analyzing the blank/Sample, it is necessary to flush the system. So first select the flush option. After selecting the flush option, click the go button; system will automatically flush with the blank water.
- 4.3.1.13 After completion of flushing, again click perform menu, go to start option, again previous window (4.3.1.11) will appear. Select the Blank configuration, in configuration menu, verify Type of Sample, Batch No. and A.R. No. Before analyses either put a magnetic stirrer into the sample or stir the sample during analysis with slight hand agitation. Click the go icon, sampler will automatically analyze the blank sample as per the configuration.
- 4.3.1.14 After completion of test main window will appear, click on view menu on this window, go to reports and click, last tested report will open, click on printer button on the report window to print the report. Record the results in Annexure -1
- 4.3.1.15 Acceptance criteria: - Particulate matter in 5 samples of particle free water each of 5ml for 10 μm or greater size should not exceed 25 for combined 25 ml. If it exceeds the acceptance criteria then the precautions taken for the test are not sufficient. The preparatory step must be repeated until the environment, glassware and water are not suitable for the test.



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4.3.2 Test Preparation and testing

4.3.2.1 After the blank test again flush the system with blank water then proceed for the sample testing.

4.3.2.2 Put the samples on the LAF workbench provided for Liquid particle count, remove the stickers and labels by dipping into warm water. Revert the each sample vials for approx. 20 times and analyze each sample against the white and black background for black particles, white particles, fiber particles and any other visible particle. Put the results into Annexure – 1.

4.3.2.3 After completion of visual inspection clean the outer surface of container opening using a jet of particle free water and remove the closure, avoiding any contamination of the content.

4.3.2.4 **Sample Quantity and Preparation:**

- For large volume parenterals and 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 content of 10 or more units are combined in a cleaned container (beaker or glass bottle of not more than 500ml) to obtain a volume of not less than 25ml.
- Powders for parenteral use (Lyophilized products) are reconstituted with particle free water or with appropriate particle free solvent when particle free water is not suitable.
- Miscellaneous or stability samples, sample quantity may vary, however the pooled sample shall not be less than 25ml for any test.

4.3.2.5 Degas the sample by sonicating for about 30 seconds or by allowing the solution to stand undisturbed until it is free from air bubbles.

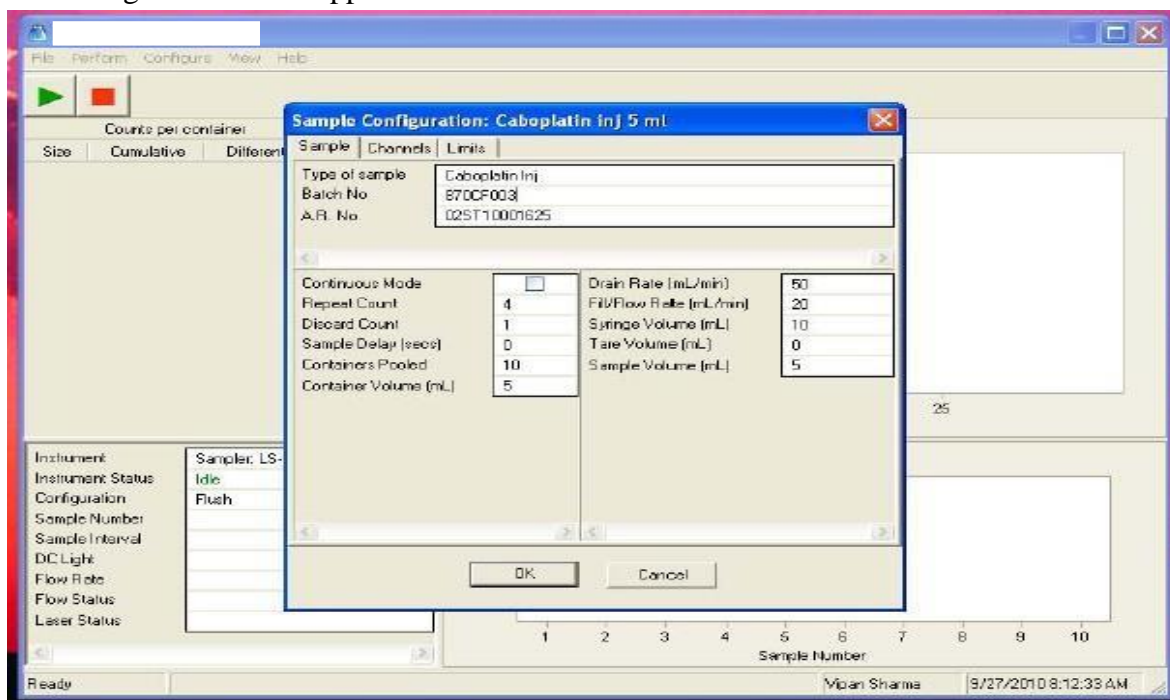
4.3.2.6 Go the sample configuration menu as per 4.3.1.6 to 4.3.1.8



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4.3.2.7 For modification in the test recipe, click on the sample name then click the modify option. Following window will appear.



4.3.2.8 Modify the test recipe as per following table

Type of Sample – (Type the name of the sample)	
Batch No. – (Enter Batch No of the sample)	
A.R. No. – (Enter the AR No of the sample)	
Continuous Mode	- N/A
Drain Rate (ml/min)	- 50
Repeat Count	- 4
Fill Flow Rate (ml/min.)	- 20
Sample Delay/ Sec.	- 0
Syringe Volume (ml)	- 10
Container pooled	- (As per requirement)
Tare Volume (ml)	- 0
Container volume (ml) -Vol. of one container	Sample Volume (ml) - 5



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4.3.2.9 Then click the OK button, window will automatically return to the previous window, Click the OK button on this window too. Go to 'Data Configuration' and select the counts as 'Cumulative' and 'Counts per container' or 'Counts per millileter' as required (For Small Volume Parenterals, select 'Counts per Container' and for large volume parenterals select 'Counts per Milliliter'). .

4.3.2.10 Proceed for analysis as per 4.3.1.11 to 4.3.1.12

4.3.2.11 After completion of flushing, again click perform menu, go to start option, again previous window (4.3.1.11) will appear. Select the test sample configuration, in configuration menu, verify the Product Name, Batch No. and AR No. (if any).

4.3.2.12 Before analyses either put a magnetic stirrer into the sample or stir the sample during analysis with slight hand agitation. Click the GO button, sampler will automatically analyze the test sample as per the configuration.

4.3.2.13 After completion of test main window will appear, click on view menu on this window, go to reports and click, last tested report will open, click on printer button on the report window to print the report. Record the results in Annexure -1

4.3.2.14 Acceptance Criteria:

Large Volume Parenterals	Small Volume Parenterals
≥ 10 µm – 25 particles per ml	≥ 10µm – Less than 6000 particles per container
≥ 25 µm – 3 particles per ml	≥ 25µm – Less than 600 particles per container

4.4 Maintenance of Liquid Particle Counter

4.4.1 Cleaning of the capillary tube



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Cleaning of capillary shall be performed when DC light reading reaches 7.0. Cleaning shall be performed with capillary cleaning kit.

- 4.4.1.1 Use the LiQuilaz power entry module to turn the power off.
- 4.4.1.2 Disconnect the sample input and output tubes at the LiQuilaz.
- 4.4.1.3 Fill one syringe from the capillary cleaning kit with filtered water or if required glassware cleaning solution.
- 4.4.1.4 Connect the filled syringe to the LiQuilaz sample input connection.
- 4.4.1.5 Press the other syringe's plunger all the way into the syringe cylinder.
- 4.4.1.6 Connect the (empty) syringe to the LiQuilaz sample out put connection.
- 4.4.1.7 Press the plunger of the filled syringe to force the cleaning solution through the LiQuilaz and into the other syringe
- 4.4.1.8 Repeat above step about 12 times or few minutes.
- 4.4.1.9 Flush the cleaning solution from the LiQuilaz with purified water.
- 4.4.1.10 Setup the LiQuilaz tubing and run the LiQuilaz while checking the DC light level.
- 4.4.1.11 If the DC light level is still not achieved 7.0 repeat the cleaning process. If after further cleaning if the DC light does not read greater than 7.0, contact the service engineer
- 4.4.2 Cleaning the syringe with the detergent / bleach process
 - 4.4.2.1 Start the sample, shut the LS-200 off when the syringe is in mid way. Remove the syringe.
 - 4.4.2.2 Fill the syringe with the weak detergent or 10% bleach solution.



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4.4.2.3 Allow the solution to remain in the syringe for 30 minutes.

4.4.2.4 Flush the syringe minimum of 10 times with distilled or deionised water

4.4.3 Cleaning the syringe with the Acid / Base procedure

4.4.3.1 Start the sample; shut the LS-200 off when the syringe is in mid way. Remove the syringe.

4.4.3.2 Fill the syringe with 0.1 N NaOH or 0.1 N HCL

4.4.3.3 Allow the solution to sit in the syringe for 10 minutes

4.4.3.4 Flush the syringe minimum of 10 times with distilled or purified water.

4.5 **Sample Volume, Flow Rate and Counting Accuracy Test (Internal Calibration)**

4.5.1 Sample Volume Test: The purpose of this test is to verify that the volume sampled is accurate and reproducible.

4.5.1.1 In the software go to 'Configure – Sample' and select "5.0 ml Accuracy test" with sample parameters of "Repeat Count – 1, Discard Count – 0, Sample Delay (secs) – 0, Containers Pooled – 1, Container Volume (ml) – 100, Drain Rate (ml/min) – 20, Fill/Flow Rate (ml/min) – 20, Syringe Volume (ml) – 10, Tare Volume (ml) – 0 and Sample Volume (ml) – 5".

4.5.1.2 Weigh a clean empty beaker on the analytical balance. Record the weight of the beaker as T (Tare).

4.5.1.3 Fill the beaker with filter water (approximately 60 ml). Weigh the filled beaker and record the weight of the beaker with water as G (Gross).

4.5.1.4 Take the beaker to the liquid particle counter and analyze the sample with "5.0 Accuracy test" configuration.



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- 4.5.1.5 Wait until the end of the sample, remove the beaker and weigh. Record the weight as G1 (Gross1).
- 4.5.1.6 Repeat the above two steps (4.5.1.4 and 4.5.1.5) for 4 more samples. Record the weight of the beaker after every sample as G2 (Gross2), G3 (Gross3), G4 (Gross4) and G5 (Gross5).
- 4.5.1.7 Calculate the NET weights for each sample and record the results in Annexure - II.
- 4.5.1.8 Acceptance Criteria: The sampled volume should be $5g \pm 0.25g$.
- 4.5.1.9 In case of any non-conformance repeat the test for a second time and if a result does not conform in the second time, then contact the service engineer.
- 4.5.2 Sample Flow Rate Test: The purpose of the test is to verify that the sample flow rate is accurate and reproducible.
- 4.5.2.1 In the software go to 'Configure – Sample' and select "Flow Rate Test" with sample parameters of "Repeat Count – 5, Discard Count –1, Sample Delay (secs) – 0, Containers Pooled – 1, Container Volume (ml) – 100, Drain Rate (ml/min) –50, Fill/Flow Rate (ml/min) – 20, Syringe Volume (ml) – 10, Tare Volume (ml) – 0 and Sample Volume (ml) –10".
- 4.5.2.2 Fill a beaker with approximately 100 ml water. Keep a Stopwatch ready for timing the sample.
- 4.5.2.3 Analyze the sample with "Flow Rate Test" configuration.
- 4.5.2.4 Start the stopwatch when the syringe initiates. Stop the stopwatch when the syringe has reached the bottom of its travel.
- 4.5.2.5 Repeat above step for all the 4 sample runs and record the time taken for each sample in Annexure - II.
- 4.5.2.6 Acceptance Criteria: Time for 10 ml sample at 20 ml/min should be 30 seconds \pm 2 seconds.



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- 4.5.2.7 In case of any non-conformance repeat the test for a second time and if a result does not conform in the second time, then contact the service engineer.
- 4.5.3 Accuracy Verification – Particle Size 15 µm: The purpose of this test is to verify that the particle counting accuracy of the system using known number of particles in the range >15 µm.
- 4.5.3.1 In the software go to ‘Configure – Sample’ and select “15µm Accuracy Test” with sample parameters of “Repeat Count – 4, Discard Count –1, Sample Delay (secs) – 0, Containers Pooled – 1, Container Volume (ml) – 25, Drain Rate (ml/min) –50, Fill/Flow Rate (ml/min) – 20, Syringe Volume (ml) – 10, Tare Volume (ml) – 0 and Sample Volume (ml) –5”. Enable the 2, 5, 10, 15 and 25 channel sizes.
- 4.5.3.2 Run a blank sample or zero count test with blank provided and referring the document provided with standard.
- 4.5.3.3 Open the particle count standard bottles and analyze with “15µm Accuracy Test” configuration. Refer the certificate and other documents provided with the standard.
- 4.5.3.4 Record results of particle count accuracy test and calculate the Ratio of counts at 10µm to the counts at 15µm. Record the results in Annexure – II.
- 4.5.3.5 Acceptance Criteria: The counts at 10µm and Ratio of counts at 10µm to the counts at 15µm should conform Certificate of Particle Count Reference Standard used.
- 4.5.3.6 After completion of analysis with particle count standard, run ‘Flush’ configuration with filtered water to flush the system. After this run a blank sample or zero count test.
- 4.5.3.7 Verify that the blank sample results conform to blank sample acceptance criteria (4.3.1.15). If results are not satisfactory then repeat the above step till acceptable results are obtained.
- 4.5.4 Frequency: The above three tests shall be performed once in a six month.
- 4.6 Calibration: Sensor Resolution Test**



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4.6.1 This shall be performed by authorized agency once in a year.

4.7 Enter all test, cleaning and calibration details in instrument usage logbook.

5.0 ABBREVIATIONS AND DEFINITIONS

SOP	Standard Operating Procedure
QCM	Quality Control Microbiology
Rev.	Revision
No.	Number
QCC	Quality Control chemical
%	Percent
N	Normality
NaOH	Sodium hydroxide
HCl	Hydrochloric acid
HEPA	High efficiency particulate air filter
µm	Micrometer

Particulate Matter in Injections: Particulate matter in injections and parenteral infusions consists of mobile un-dissolved particles, other than gas bubbles, un-intentionally present in the solutions. For the determination of particulate matter, two methods: Light Obscuration Particle Count Test and Microscopic Particle Count Test are used. The method adopted in this SOP is Light Obscuration Particle Count Test.

6.0 REFERENCE DOCUMENTS

USP <788> Particulate Matter in Injections
Ph. Eur. Method 2.9.19: Particulate Contamination
Operators Manual: LIQUID SAMPLER 200
Operators Manual:
Validation Manual:
SOP: Instrument usage Log Book



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8.0 REVISION LOG

Revision Number	Effective Date	Reason for Revision
00		New Documents

7.0 ANNEXURE/ATTACHMENTS

Annexure I: Form I – Test Data Sheet for Particulate Matter Analysis

Annexure II: Form II – Test Data Sheet for Sample Volume, Flow Rate and Counting Accuracy Test (Internal Calibration)