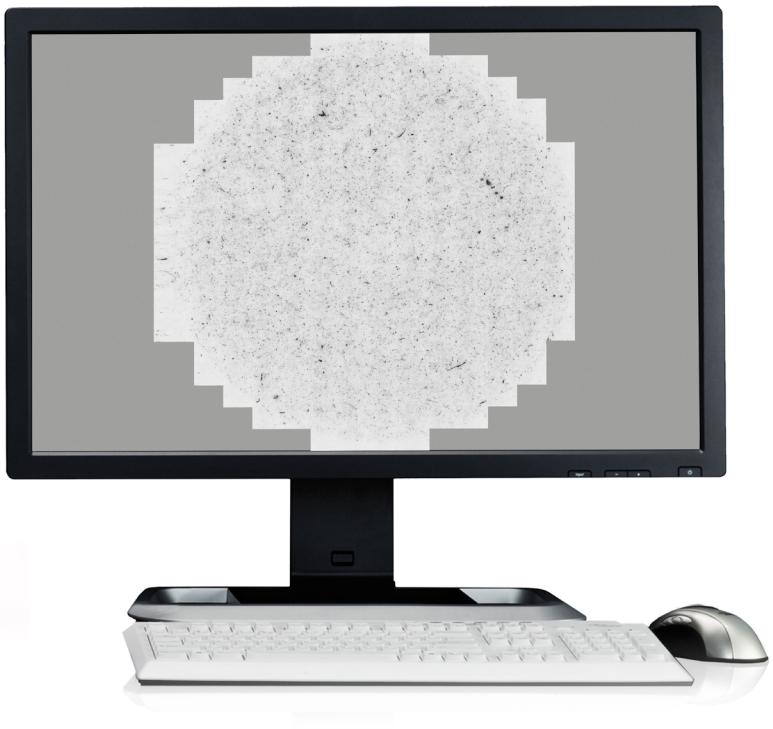
Application Note

Automated Microscopic Particle Measurement in the Pharmaceutical Industry



ZEISS

Seeing beyond

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Measuring particles in parenteral dosage forms and ophthalmics is mandatory for pharmaceutical manufacturers to ensure product quality and patient safety. Such measurements are often a precondition for the approval of a pharmaceutical product.

Parenterlas are sterile preparations intended for injection, infusion or implantation into the bodies of humans or animals. (Parenteral – Wikipedia)

Ophthalmics are medicinal substances and preparations for local or systemic treatment of ophthalmic diseases, where local application is preferable to systemic application. (Ophthalmikum – Wikipedia)

Technical equipment is needed in particular to measure smaller, non-visible particles (subvisible particles) in the size classes >10 µm and >25 µm according to USP 1788.

According to the US Pharmacopoeia (USP) and its European and Japanese equivalents, there are several test methods to choose from: Measurement using light obscuration and measurement using the membrane microscopy method. There is also the flow imaging method, which can be used to support the first two.

This article discusses the *membrane microscopy method*. This method offers significant added value through the automated acquisition and evaluation of images. On the one hand, this holistic approach makes it easier to train employees and, on the other hand, simplifies and accelerates the workflow for the user.

Non-visible particles in parenteral dosage forms

Non-visible particles in parenterals as well as in ophthalmics are defined as foreign, mobile, undissolved particles that are there unintentionally.

These particles can enter an end product through many different sources: Unsuitable (clean) room conditions, the primary packaging materials used and factors from producing the solution in bulk as well as influences from employees are possible causes of particle contamination.

Since these particles pose a great risk of irritation, tissue infarction, shock and even death of the patient, especially when present in parenteral products, the USP and the harmonized standards specify permissible limits for both large-volume (LVP) and small-volume parenterals (SVP).

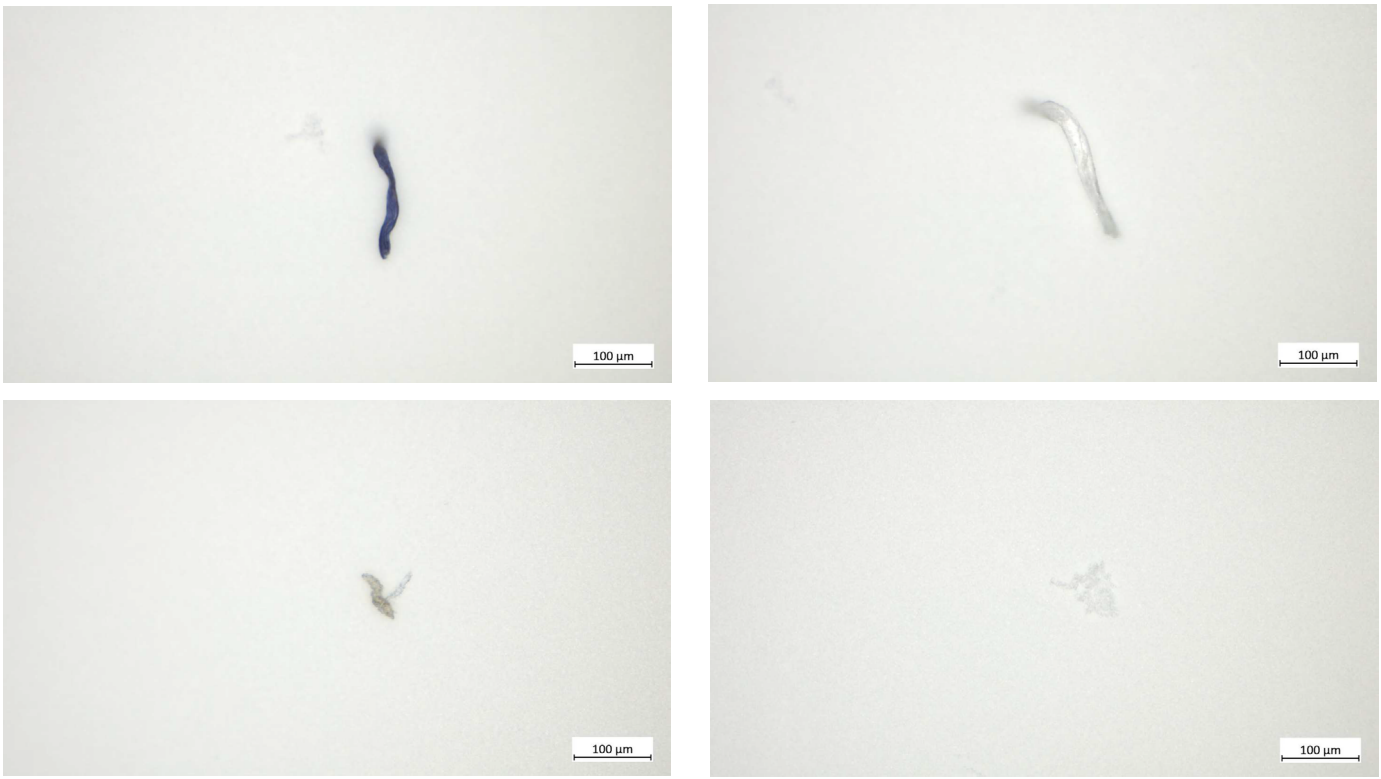

Figure 1 *Sub-visual and visual particles*

Particle measurement using an automated microscopic procedure

According to the USP, the membrane microscopy method is applicable for measuring particles. This applies in particular to emulsions, colloids or liposomal specimens.

This microscopic examination method requires the use of a light microscope and a filter holder kit with a suitable membrane filter.

The microscope is equipped with an eyepiece micrometer calibrated with an objective micrometer. It also uses a large circle with crosshairs in the field of view and reference circles with diameters of 10 µm and 25 µm. The magnification should be set to 100 ± 10. In addition to reflected light illumination, off-axis illumination should be possible.

Figure 2 *Particle filter*

When it comes to determining the particle number, additional information on sample preparation and formulas for particle determination related to a ml volume are specified in USP 1788. The USP also provides extensive details on the particle counting method by an operator, which is time-consuming and error-prone due to the large number of manual interventions when moving the filter area.

That is why the USP also outlines an automated approach.

Recommended microscope equipment

Together with its partner company Matworks from Aalen, ZEISS is offering an automated complete solution that saves time and money.

With an appropriately configured microscope, e.g. ZEISS Axio Imager with ZEISS Axiocam 506, and the particle counting algorithm programmed in the ZEN core imaging software, the relevant particles can be counted automatically and validated and the results evaluated, documented and stored.
For customers in the pharmaceutical industry, ZEISS is also providing qualification services (IQ/OQ) as well as the validatable GxP Toolkit as part of the ZEN core microscopy software, which facilitates compliance with FDA requirements (CFR 21 Part 11) for electronic records and signatures.

	Partikelanalyse Gemäß SOP	Partikel_ECD



Partikelgrößenklassen

	ECD	Klassenfläche	Partikelanzahl	Extrapolierte Anzahl	Partikel pro mL	USP 788 code1
	µm	µm²	Partikel	Partikel	Partikel/mL	
1	10	857.526,00	2	2.906,05	58,12	58
2	25	857.526,00	2	2.906,05	58,12	58
3	50	856.987,00	1	1.453,02	29,06	29
4	200,1	856.987,00	1	1.453,02	29,06	29

Parameter der größten Partikel

ID	ECD [µm]
46	431,17
17	431,10
31	416,54
36	408,08
9	405,33
22	392,01

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Figure 3 *Sample report*

References:
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