

### Particle Reduction

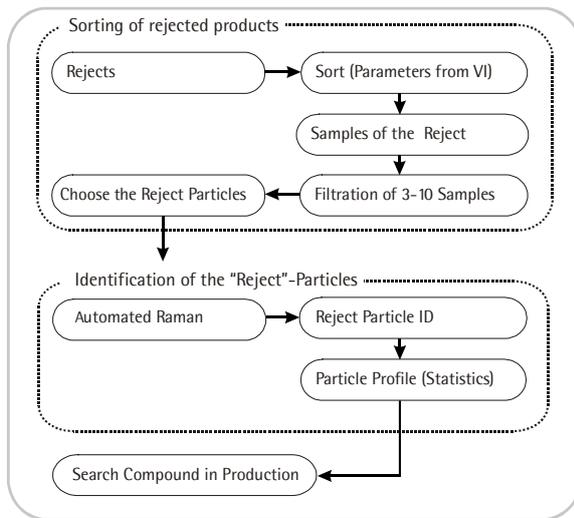
Root cause search is necessary when a known process does not conform to its specification. If the reason is a high load of unwanted particles or visual particle contamination, it is necessary to search and eliminate the source of contamination.

First, the particles that are responsible for the out of specification (OOS) situation have to be identified and labelled as Reject Particles. After Reject Particles are isolated on APSys-membranes® automated Raman spectroscopy is performed. After obtaining spectra from the Reject Particles, a sample of the suspected material can be taken during production to verify the conclusion.

### Identification of the Reject Particles

Typically, different types of particles are categorized through visual inspection. In most cases "fibers" or "black particles" are recognized. The result of this selection is used for the further determination of particles.

After this procedure the samples are filtered on the membrane and investigated as described in [1].



The automated database search usually gives reliable results. The finding is ranked and the automated system only gives a result if the spectrum fits better than 85% to the stored spectrum. The integrated database consists of more than 600 spectra of real life samples of pharmaceutical production and is customized for each customer with no more than 100 product specific spectra. Identification results of 500 parenterals show that 95% of particles (material classes) were correctly identified.

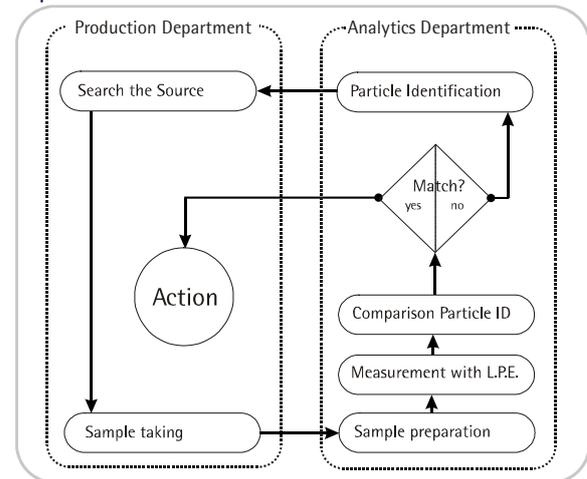
The search for the specific particle source in the production can then be started directly and purposefully. For example, identification of polyethylene (PE) with a consistency of 86% leads to a search for different

sources of PE. If the exact match e.g. high-density polyethylene (HDPE) of a specific cap is found, the consistency rises up to 98%.

Less accurate spectra itself points at the class of the material. If, for example, an Ester Raman band show up, some more trial samples have to be collected and measured. The APSys Identifier® and standard procedure software make it easy for any user to compare samples with the spectra of the Reject Particles. rap.ID supports its customers by offering external database searches. Customers use this service simply by sending a spectrum via Email to obtain the result within minutes.

### Allocation of the materials to the process

Performing statistical measurements can lead to major contamination identification [1]. The following figure shows a scheme that describes the iterative approach and the intensive cooperation between the production and analytical/quality assurance departments.



After material identification has been performed with automated Raman spectroscopy it is very important to track down the assumed source of the contamination in the production process and to obtain its spectrum for final result verification. After successful allocation, the new spectra from the material sample will be added to the database with a mouse click. Additional data will be the best basis for future supervision.

### Benefits

Contamination source identification and allocation during the production process save time and money. The reject rate is lowered significantly and the danger of batch loss is minimized.

[1]rap.ID Application Note: Identification of Foreign Particles in Small Volume Parenterals.