**Question 2:** This is a question concerning a tunnel that is part of an isolated filling system. Is the sterilization zone required to be monitored for particulate? What frequency is the sterilization zone expected to be monitored? Is the monitoring completed prior to heating the air? Is the monitoring completed after the air temperature is at set point?

**Answer:** The hot zone is difficult to monitor due to the high temperature. ABC has had discussions with numerous companies regarding this issue and related (including cool zone monitoring). Here are some highlights about that and related issues...

Many/most filter systems, especially the high temperature filters with ceramic potting material shed significant particulate into the hot zone when operating at these high temperatures. They would never pass a Class 100 qualification challenge, much less a 99.97% HEPA filter integrity challenge. Shocking, but true once the filters are 'burned in'. Since we are dealing with such high temperatures, though, we are not relying on the HEPA filters to filter the air.

To improve performance, one client changed from a ceramic potting material to a different high temperature type filter that had much better integrity (passed 99.97%) and particulate performance. This required their reducing the hot zone temperature from approx 330C to 270-280C, but depyrogenation was still able to be qualified at the same belt speed.

The high temperature zone itself provides and maintains the required sterility in the hot zone. Therefore, at the end of the hot zone, have we somehow shed particles into the open vial? Probably. Have we shed particles that are pyrogens or viable? No, and we can prove this with validation data. ABC is not an expert on tunnels, but have seen quite a few systems and this is what we believe to be the truth. We also believe that this issue is mis-understood and glossed over at many pharm companies.

To answer your question directly, ABC has not seen the hot zone routinely monitored at high temperature. It is periodically 'qualified' via HEPA certification/re-certification, not at the operating temperature. Particulate is monitored in the entry zone (before the hot zone) and in the cool zone. The cool zone can obviously be much more easily monitored. We have seen monitoring frequencies range from continuous to 15 minute 'release' test prior to introducing vials to the isolator. Of course, Class 100 is required.

For more information, see an article by Hans Melgaard and Tom Myers entitled "Air Filtration at High Temperatures", published in the September 2002 edition of A2C2 magazine.