Tech Talk

Do Particulates Matter…?

9 recalls in USA already this year suggest they do!

The visual appearance of sterile drug products is obviously a key quality attribute for any formulated product, yet the pharma industry still struggles to define, control and set in place effective monitors. Freedom from particulates has been a compendial requirement for three decades so why is it that there are typically two to five US recalls per month that cite a lack of assurance of visual quality causing a perception of significant patient risk? Why is the industry struggling to prevent foreign body contamination in parenteral formulations and why is the market clearly still experiencing drug shortages due to recalls of this nature?

When faced with either single or multiple customer complaints (always linked to field alerts in the USA), or when identifying concerns while batches are still in the factory, what questions are you faced with?

- The most crucial concern will be associated with the effect on patient safety: Does the event create a risk to the patients?
- Does the event represent a case of adulteration or breach of registered specifications?
- Does the event appear to be a significant quality defect?
- Does the event undermine corporate branding or diminish customer confidence?

In the case of patient safety, despite some historical references to animal testing proving negligible human risk, foreign body contamination is still noted by regulators as an unacceptable quality defect, largely because registered specifications, compendia and end users demand this to be the case. After all, who would readily inject or infuse a product into an injured or ill person knowing that it contained visible foreign body contamination?

In all cases, firms utilize their medical practitioners and QA teams to help write a medical risk assessment that will take into account:

- Biological activity and toxicity of the particle and any relevant leachables
- Route of administration and aspects of absorption, distribution, metabolism and excretion of the particle
- Size, shape and origin of the particle
- Potential of the particle to harbor microorganisms
- For biotech products, any risk of immunogenicity or aggregation

A key risk occurs when particles at the edge of visual detection (~20 microns) enter the injection site because they can then be distributed readily to pulmonary capillaries. Larger particles are easier to detect on administration, tend to remain close to the injection site and, though painful, are unlikely to be fatal. Other key effects can include phlebitis, inflammation, granuloma formation, occlusions, fibrosis, thrombi, microemboli

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and immunogenic/antigenic reactions. It is also important to remember a tragic event in the USA in 1994, when two patients died from pulmonary emboli from calcium precipitates in an IV total nutrient mixture. In the UK in 1988, polypropylene shards from a syringe caused a small bowel infarction that led to the patient's death. Granulomas found in Puntis' post mortem study in 1992 of 41 TPN-fed patients were linked directly to cotton fibers and glass fragments. These cases are individually very disturbing, yet represent only a small fraction of deaths tied to particulates.

Obviously, it is vital that your quality system can:

- Prevent particles appearing in formulations
- Detect the key sources of risk throughout the process
- Remove them by visual or automated inspection

So where are these defects coming from?

According to Dempsey and Webber's article Hazards of Particle Injection (Pharmaceutical Journal, July 1983), the most common source of particles is from the rubber stopper with coring (during needle penetration), closely followed by glass particles, fibers, hair and crystal formation.

In terms of prevention and detection/removal of particle contamination, NSF Health Sciences recommends a five point plan:

- SIPOC style risk assessments conducted throughout the production process by the area owners, but facilitated by a VI expert
- Relentless observation of best practices during sampling, gowning, processing and inspection; ensuring your team is based on the shop floor ensuring short interval control and monitoring of adverse conditions
- Extension of your quality system to your suppliers; cutting the risk of particulates at the source
- Robust processes for selection, education, supervision and periodic monitoring of any staff involved in manual inspection (production and QC inspection)
- Employment of validated automated visual inspection equipment; subject to detailed short interval checks and calibrations

In conclusion:

- The overall patient safety risk for macroscopic, biologically inert particles is relatively low though this depends on the health of the patient and the route of administration
- The presence of foreign bodies should be seen as an indicator of process capability and can signal a process out of control
- Zero defects is an aspirational target and can be used to drive continuous improvement, but is not a workable acceptable criterion
- Large molecule bioproducts need special considerations as do large volume parenteral formulations

If you recognize any of these concerns in your operation, please contact NSF as we have significant technical expertise in helping to diagnose the issues, assessing the impact and mitigating the risks. Our research shows that sterile manufacturers still struggle to contain this issue and we are active in supporting their efforts to protect their customers and in turn their future business.

Figure 1. SIPOC – understanding processes