Particulate Matter Contamination of Pharmaceutical Products

Tepnel Pharma Services

Pharmaceutical products are produced in vast number but are restricted to a specified number of administration routes. In this article we will look at one of the key characteristics of one such administration route, which is critical towards the safe use of products in patients.

Parenteral administration refers to any routes of administration that do not involve drug absorption via the GI tract, including the IV, intramuscular (IM), subcutaneous (SC or SQ), and transdermal routes.[1]

Amongst a number of important quality control parameters, is the presence of sub-visible particles in parenteral products that can have a major impact on patients.

Particulate matter contamination of pharmaceutical products can cause significant harm to patients. According to the NCBI, "Clinicians have had concerns about particulate matter contamination of injectable drug products since the development of the earliest intravenous therapeutics."[2]

Particulate matter contamination is an unavoidable consequence of pharmaceutical manufacturing of parenteral products. Significant numbers of single dose or repeat dose units are manufactured every year and as a critical part of Good Manufacturing Practices (cGMP) it is vital that these contaminants are both understood and controlled throughout the manufacturing process.

The myriad of potential side effects of injected particulate matter on patients are large and varied but stringent regulations exist to ensure that manufacturers ***"continue to minimize the risk of particle-induced sequelae, especially in high-risk patients, without trading unnecessary manufacturing burden for minimal safety gains".***[2]

Particulate contamination can come from a number of different sources;

- the solution itself
- any added ingredients
- the production process
- environmental factors (the manufacturing environment, equipment & personnel)
- the product packaging
- out of the control of cGMP, the preparation of the product for administration

If we consider where the introduction of these potential contaminations originate, they can be segregated into two possible classes of source:

- Extrinsic from environmental contamination, manufacturing equipment, primary packaging e.g. stainless steel, hair, fibres, glass, rubber etc.
- Intrinsic from the formulation, excipients, API, Proteins etc.

It is the responsibility of all manufacturers to identify and mitigate by QbD or other in-process controls, potential contamination sources and as a consequence test for the efficacy of their mitigation strategy.

Whilst the control of processes remains the preserve of the manufacturer, the guidance on what is and isn't acceptable post-production is clearly defined.

Both the European Pharmacopoeia and the United States Pharmacopoeia, have prescriptive methods for the examination of market authorised products and investigational medicinal products (IMP's) to ensure that patient safety is at the forefront of therapeutic use.

Sub-Visible Particle Measurement to the Ph Eur[3] 2.9.19 and USP[4] <788> by Light Obscuration sets the standard for parenteral solutions by either injection or infusion. By definition of the pharmacopeias, any manufactured parenteral product requires to be ***"both clear and practically free from particles when examined under suitable conditions of visibility".***[3,4]

The USP & Ph Eur set the limits for the acceptable quantity of particulate matter in solutions for injection or infusion according to the size of the container as follows:

Limits for Solutions for Infusion or Injection[3]

Container Size	Limits
>100 mls	≤ 25 particles per ml 10 µm and <3 particles per ml ≥ 25 µm
<100 mls	<6000 particles per container ≥ 10 µm and <600 particles per container ≥ 25 µm

In 2011 the monoclonal antibody monograph was revised in the Ph. Eur from "without visible particles" to "without visible particles unless otherwise authorised or justified".[5] This was due to the nature of therapeutic proteins such as monoclonal antibodies having electrostatic attractions and therefore the ability to form aggregates which can range in size from nanometres (oligomers) to microns (sub-visible and visible particles).

These limits are unquestionably set for patient safety with the aforementioned possibility of an adverse reaction being a major concern of the regulators.

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4. United States Pharmacopeia (USP): <788> Particulate Matter in Injections.
5. PDA J Pharm Sci Technol. 2016 July;70 392-408.