Specialist Pharmacy Service

Management of Particulate Contamination of Aseptically Prepared Products

NHS Pharmaceutical Quality Assurance Committee Guidance Note

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Version 1

The first stop for professional medicines advice

Executive Summary

Where there are extraneous particles within an injection preparation the default position should always be to reject the product and to record and manage the incident through the Pharmaceutical Quality System. Any other outcome must only follow a robust quality risk management exercise and must not become routine.

Background

The question is often asked as to whether an injectable medicine prepared in an aseptic unit can be safely released and administered if it contains a particle or particles bearing in mind most administration sets do contain a particle filter. The situation has been further complicated in recent years due to several monoclonal antibody products allowing small proteinaceous particles in the final product in their SmPCs (some examples are given in the table below). This document sets out to define the considerations when deciding as to the disposition of injectable products in which particles have been seen.

Legal Position

Within the UK, products supplied as medicines must comply with the British Pharmacopoeia (BP) this applies to both licensed and unlicensed medicines and hence would include aseptically prepared injectable products made under a MS Specials Licence or under Section 10 exemption. Products must comply with the individual product monograph where one exists, they must also comply with relevant general monographs such as in this case Parenteral Preparations and Unlicensed Medicines.

The BP definition of particulate contamination states that this consists of *mobile undissolved substances, other than gas bubbles, unintentionally present in liquid preparations*[1]. The Parenteral products monograph states *Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles*[2]. Suspensions or emulsions are, of course, outwith this stipulation.

There are two key points of interpretation here, 'practically free from particles' should be interpreted to mean that any injection in which an extraneous particle is seen when viewed using the standard method (or other equivalent method) does not comply with the monograph. The reason the word "practically" is included is to account for the fact that not every particle will be spotted when viewing injections. Secondly is the term "unintentionally" which does then exclude preparations where particles would be expected to be present, but also where they may be present such as the proteinaceous particles expected to be seen in some monoclonal antibody or other protein-based medicines if this is stated in the SmPC.

Product Viewing Advice

The BP contains the method for viewing of injectable medicnes[1] which should be followed for all clear solutions, the equipment required is described within the BP and consists of a well-lit white and black split screen. Gently swirl or invert the container, ensuring that air bubbles are not introduced, and observe without magnification in front of the white panel, repeat in front of the black panel.

The following is a guide to the time periods required to adequately view certain volumes of infusions, it is noted that all operatives are different and younger eyes are much faster to adjust also some containers are more transparent than others, hence this is only a guide. Inspection must be 100% of units made.

Volumes less than 50mL	5-10 secs
Volumes 50mL to 250mL	10-20 secs
Volumes greater than 500mL	30-60 secs

For emulsions or suspensions the viewing screen offers little benefit and other methods of particle viewing need to be employed.

Standard Release Criteria

It is strongly advised that a release specification is built into all product worksheets. Where the solution should be clear and particle free this should be stated. If this specification is not met then an unplanned deviation needs to be raised and the situation investigated and managed through the Pharmaceutical Quality System (PQS) on a case by case basis. It is important that you clearly record factors considered as part of the final decision to release or not and any subsequent actions taken.

Where the SmPC allows for a degree of particulate contamination to be present for example small white or translucent proteinaceous particles, then this should be included in the release specification.
Example products which allow some particulates in their SmPC[3]

Daratumumab (Darzalex) concentrate for solution for infusion	The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.	SmPC revision 11th June 2020
Infliximab (Remicade)	The solution is colourless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. Do not use if opaque particles, discolouration, or other foreign particles are present.	SmPC revision 19 September 2019

Ipilimumab (Yervoy)	Clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.	SmPC revision 09 July 2020
Nivolumab (Opdivo)	The concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.	SmPC revision 23 April 2020
Panitumumab (Vectibix)	The solution should be colourless and may contain visible translucent-to-white, amorphous, proteinaceous particulates (which will be removed by in-line filtration).	SmPC revision September 2019
Azacitidine (Accord)	The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates.	SMPC revision 13 February 2020

A compliant product can be released as normal, although any permitted particulate matter present should be recorded in the release statement. Anything outside of the description should be raised and investigated through the PQS. Management through the PQS is required whatever the final product disposition (i.e. even when the product is discarded).

Risk Issues

The following risk issues (this may not be an exclusive list) need to be considered when investigating and deciding whether to release a product with extraneous particulate contamination

1) Can the nature of the particle(s) be determined and if so what are the implications?
   a. Bung core particles would indicate that bung integrity has been lost, increasing microbiological contamination risk but it is also most certainly unintentionally present and therefore it would be difficult to warrant release
   b. Shards of plastic from IV bags, these may have been present within the bag or may be from scraping the additive port with the needle, certainly unintentionally present and therefore it would be difficult to warrant release without further risk mitigation.
   c. Proteinaceous particles in protein-based pharmaceuticals where this is not mentioned within the SmPC and hence release specification. Proteinaceous strands can act as a focus for further aggregation and hence there is risk of further loss of drug in the filters particularly if the product will be stored ahead of use. The situation should be raised with the MA holder for the product and further advice sought from them.

d. Drug precipitations - clearly a precipitated drug cannot be issued and generally once a precipitation process has started it will only become more severe. Precipitation may also be a sign of drug instability and hence may be indicative of an error in preparation or a drug defect.
e. If the root cause of the particle source cannot be determined then a full risk analysis cannot be performed and release of the product cannot be considered.

2) What is the level of extraneous particulate contamination? although a single particle will make an injection non-compliant, multiple particles and larger particles are likely to be indicative of a more serious problem.

3) The properties of the medicinal product also need to be considered. For example, some drugs (Fluorouracil, Etoposide, Docetaxel and Paclitaxel to name a few) are particularly prone to precipitation and any extraneous particles within these can potentially act as a focus for further precipitation. The risk of precipitation during administration is a further consideration as this will likely impact on the dose that the patient receives.

Biopharmaceuticals such as monoclonal antibodies are also prone to aggregation and this can be increased where extraneous particles including silicone oil droplets are present.

4) Can the product be remade, for example is there sufficient stock to remake the dose? if there is not then this needs to be reflected in the risk assessment although should not lead to risk taking if other factors suggest not to release.

5) Is the product going to be stored ahead of use and does this increase the risk of precipitation?

6) Can the product safely be reprocessed to remove the particle, for example by transferring to another container? It is highly unlikely that a product in a syringe could be safely transferred back into the grade A zone and hence this is not likely to be an option. If a product in a bag is to be transferred this should be to the same container type and it must be ensured that the level of aseptic manipulation required is within that validated for the unit and operator.

7) Will the product be infused via an administration set with a (minimum) 15-micron filter which should remove the visible particles? If not, such as for bolus injections, the product should not be released. If it is then will the loss of drug in the filter be significant.

8) Are there any specific patient risk factors (e.g. neonates)?

Reduction Strategies / Potential Preventative Actions

The following points may be considered in management of the risks to particulate contamination

- Use of needle free bags
- Choice of device to make additions and withdrawals from vial – for example: spikes, needles, vents, butterfly devices
- Starting material choice – important to trend issues to starting material manufacturers
- Operator training and technique.
- Lighting in work zones and sufficient time to work in a controlled and careful manner
- Use of change control including post change reviews to help with trend analysis

Conclusions

Unless the presence of particulates is specifically mentioned and accepted within the SmPC then any incident of particulate contamination needs to be managed through the PQS, it is not acceptable for the acceptance of extraneous particle contamination in injectable medicines to become routine. A risk based decision should be taken, and recorded, on an individual basis and must consider all risk factors as set out above. There may be exceptional circumstances where a product with particulate contamination is released for patient use based on the clinical urgency and non-availability of stock to remake the product, alongside a risk mitigation plan including discussions with the clinical team responsible for the patient.

Where the source of particles cannot be elucidated this should be raised as a defect with the MIA holder for the licensed product used to prepare it.

References

1. BP 2020 Appendix XIII B. Particulate Contamination: Visible Particles (Ph. Eur. method 2.9.20)
2. BP2020 Parenteral Preparations (Ph. Eur. monograph 0520)
3. SmPCs accessed on-line 30th July 2020

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Appendix 1: Decision Flow Chart