Particulates Testing; Requirements and Challenges

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Many antibodies form particulates
  - Visible (and sub-visible)

Particulates are generally accepted as undesirable

Particulate formation and its consequences are generally not well understood

Visible particulates are difficult to measure subjectively
Why Of Interest?

- Guidelines and regulations
  - The formation of aggregates, sub-visible and visible particulates in the drug product is important.

- Quality

- Safety
  - Immunogenicity?
European Guidelines And Standards

- EMEA: MAB guidance 2009
- EP: MAB monograph (2031)
- EP: Parenteral monograph (0520)
- EP: Particulate Contamination: Visible Particles (2.9.20.)
- EP: Particulate Contamination: Sub-Visible Particles (2.9.19.)
Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products

- Effective 1 July 2009
- “The formation of aggregates, sub-visible and visible particulates in the drug product is important and should be investigated and closely monitored on batch release and during stability studies. In addition to the pharmacopoeial test for particulate matter, other orthogonal analytical methods………..”

- “Visible and sub-visible particulate matter in drug product should comply with the requirements set forth in the European Pharmacopoeia”.
  > Monoclonal antibodies for human use (2031)
  > Parenteral preparations (0520)
Parenteral preparations Solutions for injection, examined under suitable conditions are clear and *practically free of particles*.
- Definition of practically free?
- Subjective method of analysis (visual inspection)?

Sub-Visible particulates (2.9.19)
- Microscopy and light obscuration
- 600 and 6000 particles per container (10 micron and 25 micron)
- Capability of the methods especially for smaller particulates?
History

- 2004 first adopted with some comment from industry
- Revised version in 2009 with further comment from industry invited (in progress)

Visible particulates

- 2004: “Liquid preparations are clear or slightly opalescent, colourless or slightly yellow liquids, **without visible particles.**”
- 2009: “They (monoclonal antibodies) are **without visible particles, unless otherwise justified and authorised.**”
Firstly, particulate formation in MABs is relatively common, so this is a key consideration for the development of many products.

Issues

- Consistency between general and MAB specific EP monographs?
- Technical challenges and solutions: “Without visible particles” is an absolute statement not scientifically justifiable?
- Lack of differentiation/understanding between intrinsic and extraneous particulates?
How to measure

- **Visible**
  - Feasibility of demonstrating “Without visible particles”
  - Definition of practically free and the subjective nature of measurement?
  - How to differentiate between extraneous and intrinsic particles?
    - Intrinsic
      - Made up of associated or aggregated drug molecule
    - Extraneous
      - Process related
      - ...extraneous mobile undisolved particles other than gas bubbles *unintentionally present* in solution (EP 2.9.20. Particulate Contamination: Visible Particles).

- **Sub-Visible**
  - Suitability of current methods e.g. for small particulates?
Control of particulates

- Formulation
- Design / selection of product?
- Link between visible (intrinsic) → sub-visible → aggregates and relevance of any link?
- Mitigate visible particles by in-line filtration?
  - Acceptable for sub-visible particulates (EP 0520)
- Impact on stability
  - Significance of (low level) changes over time
Both intrinsic and extraneous particulates should be minimised

How to differentiate?

Equal importance?
- Some products contain low levels of intrinsic particles
- Particles can therefore be considered as a quality attribute of the drug product that require characterisation and testing
European Guidelines and Standards

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There is a need for clarity / harmonisation within the EP monographs in order to support the EMEA guidance.
Questions / Discussion

- Monograph requirements and the need for harmonisation
- Analytical methods – sub-visible and visible - suitability and limitations
- Relative significance of intrinsic vs. extraneous particulates
- Impact of particle formation on stability
- Control and mitigation of particulate formation