Towards improvements in metrological traceability for medical devices R&D and regulatory considerations

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Background of evolving regulatory requirements

New biocompatibility guidance ISO10993-22; regulatory framework for nano-object characterisation is still evolving

Instrumentation for nanoparticle characterisation also still evolving, particularly for nanoparticles of < 30nm size

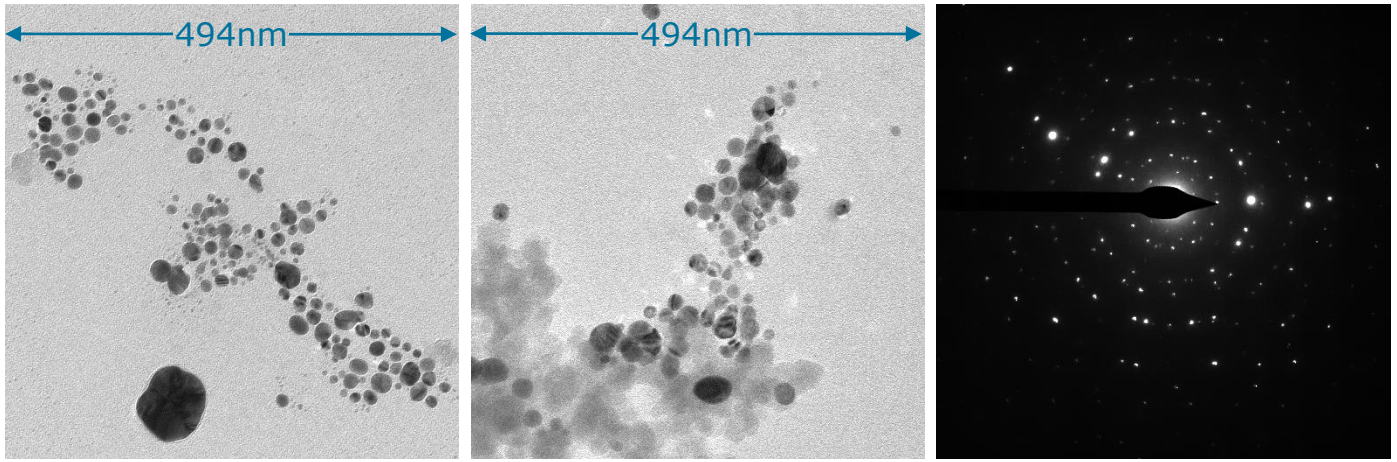
Analytical challenges include accurate dimensional analyses, accurate particle counts, appropriate sample presentation regimes:

- Huge specific surface areas, appropriate representation of adsorbing/desorbing molecular entities may be important
- Aggregates/agglomerates? appropriate representation of ionic/colloidal forces at play

Traceability and Certified Reference Materials (CRM's) is therefore of great value in de-risking Medical Device Product registrations, both inorganic and organic/biological CRM's are ideally needed (Medical Device characterisation involves both materials and biological tissues, fate in tissue)

Characterisation techniques

FEGSEM, TEM (direct visualization, limited numbers of particles observed/analysed)



Chemical speciation via electron beam diffraction, STEM ED-X, EELS, 3D Nano-SIMS, sp-ICP-MS, etc.

Brownian motion Particle Tracking Analysis (PTA, *en-masse*, size distribution & counts/ml)

Analytical Differential Centrifugation Sedimentation (DCS, *en-masse*, size distribution & counts/ml)

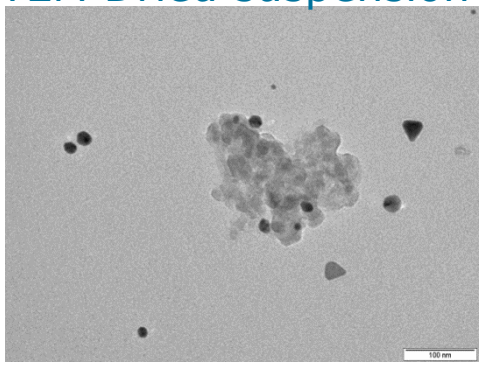
Hydrodynamic Chromatography (*en-masse*, HDC, estimates sizes)

Asymmetric Flow Field Flow Fractionation (*en-masse*, AF4 estimates sizes and counts, no ionic quant., potentially lower recoveries, but lower sizes detected than sp-ICP-MS)

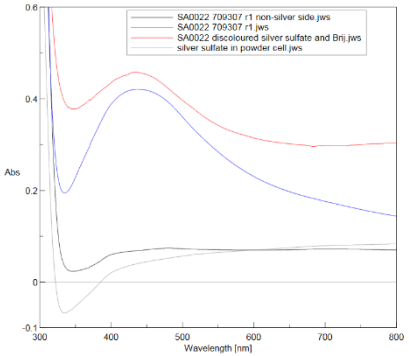
Single Particle Inductively Coupled Plasma Mass Spectrometry; Fate in tissue? sp-ICP-MS, useful for tissue digests, (*en-masse*, but single particle data resolved for size distribution, counts/ml & chemistry and ionic quantification)

Characterisation techniques

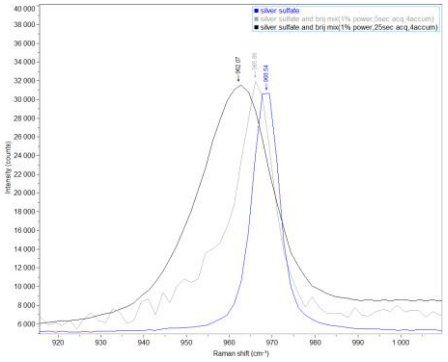
TEM Dried suspension



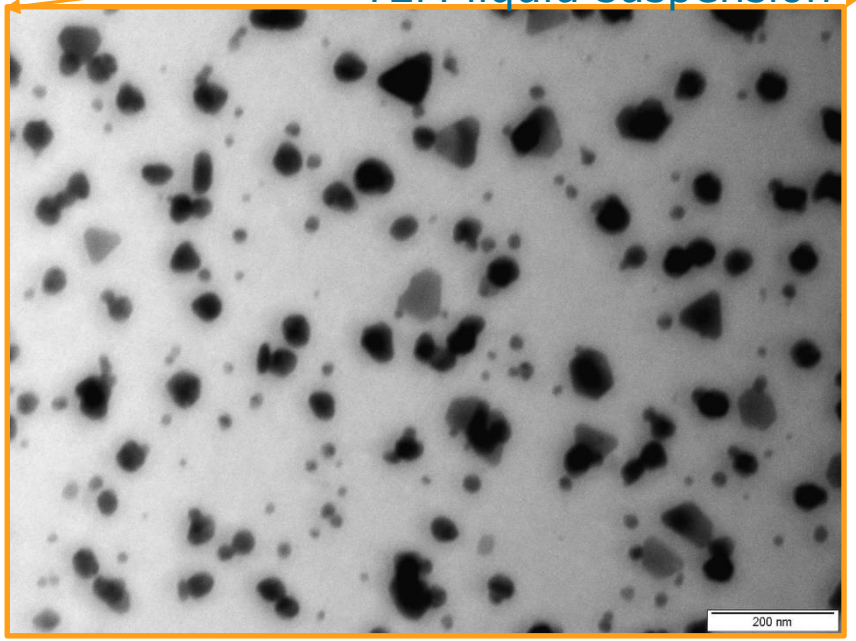
UV-Vis

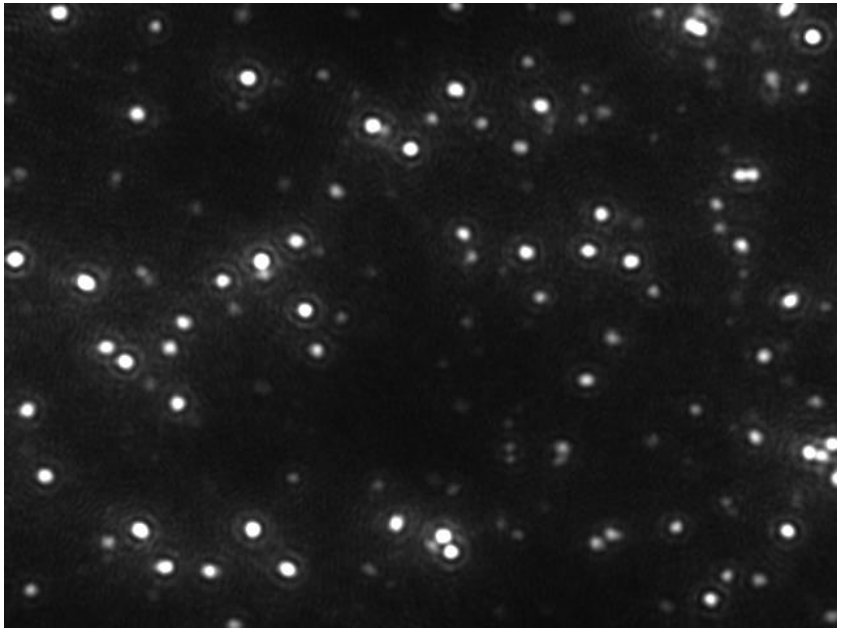


Raman



TEM liquid suspension





Trying to ensure robust data at the nanoscale

Participation in nanoparticle characterisation study; national and international, multi-laboratory, including UK-NMS labs and other national standards labs:

Studies using standardised particles to evaluate method-specific reproducibility (e.g. EURAMET)

Studies underpinning specific products (e.g. A4I scheme)

Invaluable for:

- Benchmarking methodologies
- Benchmarking our own laboratory
- Shared learning and dissemination of expertise/practice across standards institutions, academia and industry
- De-risking product development

Analytical/characterisation challenges

Definition

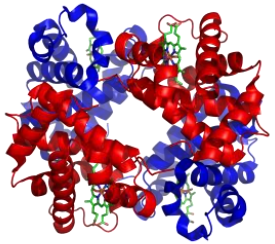
Multiple definitions exist, but ISO/TR 10993 part 22 adopts definition of nanomaterial given in ISO/TS 800041: 2010, 'a material is considered a nanomaterial when it has a size at the nanoscale including external and internal dimensions, i.e. when it has a size or is composed of structures with a size of approximately between 1 nm and 100 nm'

The Size of Things – 1 nm is very small

Nanomaterials are one hundred to ten thousand times smaller than human cells.

They are similar in size to large biological molecules such as enzymes and receptors.

For example, haemoglobin molecule ca. 5 nm diameter.



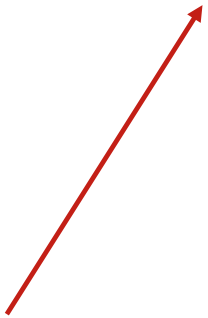
Nanomaterials smaller than 50 nanometres can easily enter most cells, while those smaller than 20 nanometres can move out of blood vessels as they circulate through the body.

Example of analytical challenge - TEM

Epoxy resin embedded tissue specimen – TEM micrographs of adjacent areas

How much distortion?

How does it affect apparent dimensions of organelles?



Note electron beam induced distortion of these tissue sections

Example of analytically challenge - TEM

Smallest nanoparticles (<20 nm) similar in size to biomolecules such as proteins and proteins complexed with ligands such as metals

Heavier metal-protein complex may appear electron-dense – nanoparticles or complexes?

Complexes may also be beam-sensitive

Such questions compounded by spatial resolution limits of composition analyse such as X-ray microanalysis

Regulatory situation for Medical Devices

Currently, many Notified Bodies (i.e. FDA, EMA, MHRA) require full biocompatibility test data compliant with ISO 10993, part 22 to support new product registrations if:

- new device product incorporates or produces releasable nano objects (1-100 nm)
- and where >50% v/v of the material may be released as nanoparticles/rods/plates from any surface of the device in contact with the body
- Where device may be in contact with broken skin or internally, full requirement for both in-vitro and pre-clinical in-vivo studies; latter involves analyses of tissue samples with significant complexity and sample presentation challenges
- Just obtaining analytical data from nanomaterials in tissue represents significant challenge
- Obtaining a degree of traceability within such datasets is the next goal
- Full traceability to SI with a biologically appropriate reference material would be valuable
- A biological Certified Reference Material (CRM) is therefore desirable to help underpin future product registrations

Conclusions & Acknowledgements

Conclusions:

- Aimed to provide 'whistle-stop' appreciation of establishing metrological traceability for nanomaterials in medical devices; for pharma and bio-pharma the regulatory hurdles are likely more stringent and challenges therefore more difficult
- Nanomaterial testing for biocompatibility benefits from use of multiple complementary analytical methods just as a baseline approach even without traceability
- CRM with similar electron beam sensitivity to biological tissue would add further useful 'tool' with regard to biocompatibility studies
- Collaborative projects bring excellent added value in terms of shared/best practice
- Encouragement to industry to leverage national measurement institutions
- Improved metrological quality and traceability invaluable for underpinning regulatory evidence provided for product development

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