FINAL PUBLISHABLE REPORT

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1 Overview

This project has worked to increase the adoption of novel nanoparticle-based products and to disseminate the findings of EMPIR project 14IND12 InNanoPart (Metrology for Innovative Nanoparticles). This has been achieved by drafting of an ISO technical report on methods to measure nanoparticle number concentration, which has subsequently been converted to an ISO technical specification. This will enable the nano-technology industry instrument manufacturers, regulators, NMIs and academia to evaluate and use the most appropriate method to measure nanoparticle number concentration.

2 Need

Innovative nanoparticles have the potential to significantly improve our lives. The advantages they bring in drug delivery, highly sensitive disease diagnostics, advanced electronics and opto-electronics, efficient photovoltaics, selective catalysis and many other applications have been unequivocally demonstrated. For example, metal oxide nanomaterials can act as sun blockers in sunscreen formulations to protect human skin and reduce the risk of skin cancer. The major challenge for industry is to translate these improvements into reliable, useful and safe products. A recurring and common issue for nanoparticles is the irreproducibility of their synthesis, which is typically sensitive to small variations in reaction conditions. It is possible to mitigate these sensitivities by advanced process control, but only if measurement methods are available to identify the variability in the synthesised nanoparticles. Therefore, there is a need for improved knowledge of nanoparticle concentration, so that scientists in relevant industries can optimise formulations, evaluate and minimise batch-to-batch viability, boost productivity, reduce hazardous nanomaterial waste and comply with regulations including EU definition of nanomaterials (2011/696/EU) and chemicals regulation REACH (Regulation (EC) No 1907/2006). There are also no documentary standards nor certified reference materials currently available.

Consequently, the need for standardisation in nanoparticle characterisation was marked as an area of high priority by ISO/TC 229 ‘Nanotechnologies’. The chair of ISO/TC 229 and primary supporter of this project, Dr Denis Koltsov asked that the underlying metrology developed in the EMPIR project 14IND12 InNanoPart be adapted and published as an ISO Technical Report in order to meet ongoing industry and legislative needs. The project has addressed these needs by collating the best practice and guidance for nanoparticle number concentration measurement that was developed within 14IND12 InNanoPart and by making them available to end-users as an ISO Technical report, that will be published as an ISO document beyond the end of the project lifetime. In addition, the ISO document will also provide clear guidance on the evaluation of measurement uncertainty providing laboratories with the required tools so end-users can have increased confidence in their data.

3 Objectives

The overall aim of the project was to increase the adoption of novel nanoparticle-based products by maximising the impact of 14IND12 InNanoPart through the following objectives:

1. To ensure that good practice measurement guidance for nanoparticle number concentration is formalised through the publication of an ISO Technical Report in ISO/TC 229 “Nanotechnologies” on methods to measure nanoparticle number concentration.

2. To increase awareness of the ISO Technical Report among the wider stakeholder and end-user community, and to disseminate the findings of 14IND12 to a wide audience via a range of activities.

4 Results

The overall objective of the SIP was to increase the adoption of novel nanoparticle-based products by maximising the impact of a previous EMPIR project JRP 14IND12 Innanopart. Specifically, the SIP achieved this via the following objectives:

Objective 1. To ensure that good practice measurement guidance for nanoparticle number concentration is formalised through the publication of an ISO Technical Report in ISO/TC 229 “Nanotechnologies” on methods to measure nanoparticle number concentration.
This objective was the main aim of the project which was led by NPL with input into specific sections from LGC with the aim of maximizing the impact of 14IND12 InNanoPart where much of the technical metrology was developed and tested. An outline of the technical report on methods to measure nanoparticle number

concentration was written by the consortium and agreed by ISO/TC 229. A more complete draft was written based on outputs from JRP 14IND12 and other inputs with LGC writing the spICP-MS and PTA sections and NPL leading the writing of the other sections. The draft was circulated to the experts and improved by them and the consortium over a number of cycles. This included ISO TC24/SC4 experts and experts from the wider stakeholder community. The ISO Form 4 (new work item ballot proposal form) was completed along with an ISO/TC 229 metrology checklist. These two documents along with the complete draft were all sent to the ISO TC/229 JWG2 Secretary on 30 June 2020 for as a proposal for a new work item. The ballot for this was held 8 July to 30 September 2020 and approved with 27 countries voting positively, 0 no votes and 10 abstentions. Furthermore, 10 countries nominated experts, with 5 countries submitting comments along with the EU JRC (Joint Research Centre) experts, all together there were 35 pages of comments to address. The document was then edited and improved by the consortium based on the comments from the new work item ballot and further discussion held at the ISO TC229 meeting in November 2020. Here, with expert input the meeting resolved five key issues. Following the meeting and resolution of the issues, the document was updated by the consortium and circulated to the experts on 6 January asking for comments by February 2021. This circulation included a completed comments matrix from the new work item ballot. Comments were received from the experts and an updated version of the draft document was circulated to ISO TC229 JWG2 experts on 26 April 2021. This was prior to the May ISO TC229 meeting where the document was discussed, and input received. Following the meeting, the document was again updated and circulated to ISO experts on 28 May 2021. A teleconference with ISO TC229 experts was held on 17th June. At that teleconference, permission was sought and granted from the ISO TC229 JWG2 committee to send the document out for draft technical report ballot.
The draft ISO technical report was sent to the ISO TC229 programme manager on 5 July 2021 for final ballot. The ballot was launched by ISO TC229 on 9 July 2021 and will close 15 September 2021. The ballot documents were also circulated to ISO TC24 experts who were invited to submit comments. The document was approved for publication with 25 Countries voted positively and 1 voting negatively. There were approximately 45 pages of comments. The document was firstly updated by the consortium based on these comments. The document and comments were then discussed in detail at the November 2021 ISO TC229 meeting and at a follow-on meeting between the consortium and US experts to resolve issues on one section of the document. The document was then finalized and sent to ISO for technical report publication on 27 January 2022. Unexpectedly, ISO CS (Central Secretariat) rejected the document as a technical report and advised that the document should be published as an ISO technical specification. The consortium had a number of detailed discussions with ISO CS and the ISO TC229 chair and committee manager to find the best course of action given the limited time of the project. It was decided to accept the strong advice of ISO CS to convert the document to an ISO technical specification. This will involve very little if any changes to the actual document itself but will required lengthy additional ballots in ISO TC229 which will take place beyond the lifetime of this project. However, the resultant technical specification is a normative document so of greater importance than a technical report. It will maximize the benefits of the EMPIR project JRP 14IND12 Innanopart and allow users to evaluate and compare methods to measure nanoparticle number concentration.

The key output is the draft ISO document on guidance on measurement of nanoparticle number concentration, which will be published by ISO in due course as a higher-level technical specification as opposed to a technical report. This objective has been partially completed due to the ISO Committees decision to produce the Technical Specification that will take time outside of the project's duration for publication.

Objective 2. To increase awareness of the ISO Technical Report among the wider stakeholder and end-user community, and to disseminate the findings of JRP 14IND12 to a wide audience via a range of activities.
The project was presented at the annual ISO TC229 meetings in November 2019, May 2020, November 2020, May 2021 and November 2021. These meetings were attended by NMIs, instrument manufacturers, industry representatives and the chief stakeholder and LGC and NPL. Feedback from the attendees on the project was also obtained during this meeting as well as at ISO ballot where formal comments from ISO experts were received.

Members of the project consortium presented the results of 14IND12 to the CCQM-P194 (Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology) (CCQM), IAWG (Working Group on Inorganic Analysis). The project has also been presented to CEN TC352 (European nanotechnologies). There were detailed discussing with both the committee and individual experts from ISO TC24/SC4 (particle characterisation). This included contributions to the technical writing and commenting on the draft document.

A trade article entitled “An invitation to participate in standardisation of particle measurements for Pharmaceuticals” was written highlighting the standard and the need for standards in nanoparticle number concentration. This article was published in OnDrugDelivery. The trade article was publicised using social media. A web article “New standard on nanoparticle number concentration to be published” summarising the standard was also written and published on the NPL website. Social media including Linkedin and Twitter was used to promote this web article. The LinkedIn posts gained at least 2000 views. NPL and LGC collaborated on this objective. The objective has been completed.

5 Impact

8 oral presentations have been given at National, European and International conferences (including AVS66 International Symposium and Exhibition, Global summit on regulatory science 2019 - Nanotechnology and nanoplastics and 1st Oyster Open Day, Nano-Korea 2020 and 4th Symposium in Science and Engineering of Materials). These presentations also related the results to various aspects of the 14IND12 research findings. In addition, a presentation on standardisation of the measurement of number concentration of nanoparticles was given at an ASTM International E56 Committee meeting, and an invited talk titled “Complementary Measurements of Colloidal Nanoparticles and their Coatings by In-situ and Vacuum-based Methods” was given at the Faculty of Medical Science in UCL. The project partners have been actively engaging with ISO/TC 229 Nanotechnologies as well as ISO/TC24 SC4 particle characterisation experts. In addition, two peer-reviewed publications have been written, along with a trade article and a web article which summarises the standard. These were publicised using social media.

The project has expanded the nanometrology developed in 14IND12 InNanoPart by producing a soon to be published ISO document under the auspices of ISO/TC 229 (the primary supporter) in liaison with ISO/TC 24/SC4. This will provide guidance for reliable and reproducible measurements of nanoparticle number concentration for which no standard currently exists and is vital to support the commercialisation of innovative nanoparticle-based products and their exploitation in relevant industry sectors such as pharmaceutical, medical, cosmetic, electronics and catalysis. Through these advances, nanomaterial suppliers and users will be able to demonstrate product safety with greater confidence and minimise batch-to-batch variability.

Engagement with ISO/TC 229 and ISO/TC 24/SC-4 helped ensure the maximum impact and drive progression towards standardisation. These industry-focused committees include members from industry, instrument manufacturers, NGOs, regulators, NMIs and academia who are keen for the ISO Technical Report to be developed and are global leaders in nanotechnologies and particle measurement standardisation. To further increase impact, the project team have been in discussion with experts and users from the wider stakeholder community throughout the development. The change of ISO output to a technical specification, which is a normative document, is a significant step and will strongly increase the impact and usage of the document. It will allow countries and regions to adopt the document as national and regional standards that would not be possible as a technical report.

The wide dissemination of the ISO Technical Specification and engagement with end-users on best measurement practice will provide laboratories with the required tools to increase confidence in their data, assess process repeatability, ensure effective product development, manufacture, quality control and risk assessment procedures. This will ultimately boost the sustainable advancement of nanotechnology businesses across various industries and provide society with better performing products. The Technical specification will enable industrial users to demonstrate compliance with EU regulations linked to the definition of nanomaterials ((2011/696/EU) and allow the European Chemical Agency (ECHA) to evaluate more accurately the properties of new nanomaterials submitted for authorisation under the REACH legislation (Regulation (EC) 1907/2006).

Providing a validated international standard for these measurements will ultimately lead to a ‘gold standard’ ensuring performance and safety of nanoparticle-based products globally, which will lead to enhanced world-wide trade in nanomaterials and increased European competitiveness. In terms of the wider social impact this will positively impact on quality of life as nanoparticle-based medical and pharmaceutical products are increasingly made available commercially, providing consumers with enhanced products and increased confidence in their safety. There is significant public concern over the potential environmental impact of nanoparticles including their dispersal in air, sea and rivers and their potential toxic effects. The measurement of number concentration of nanoparticles is a major determinant here, hence this ISO technical specification will provide the methods to determine this.

6 List of publications

1. Susana Cuello-Nunez, Isabel Abad-Alvaro, Dorota Bartczak, M. Estela del Castillo Busto, David Alexander Ramsay, Francesco Pellegrino and Heidi Goenaga-Infante, *The accurate determination of number concentration of inorganic nanoparticles using spICP-MS with the dynamic mass flow approach*, J. Anal. At. Spectrom., 2020,**35**, 1832-1839, https://doi.org/10.1039/C9JA00415G
2. Caterina Minelli, Magdalena Wywijas, Dorota Bartczak,Susana Cuello-Nuñez, Heidi Goenaga Infante, et al, .*Versailles project on advanced materials and standards (VAMAS) interlaboratory study on measuring the number concentration of colloidal gold nanoparticles*, Nanoscale, 2022,**14**, 4690-4704, https://doi.org/10.1039/D1NR07775A

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