EU-US Nanomedicine Collaboratory

Background

The Joint Research Centre (JRC) and US National Institute of Standards and Technology (NIST) convened a joint workshop on "Characterization methods and standards for nanoparticles in medical products". Experts from a number of key EU and US organizations, including FDA, NCI-NCL, University of Michigan, CEA, EMPA, Astra Zeneca, University of Geneve, NPL, BAM, met at JRC in Ispra, Italy, on December 3-4, 2018. The principal output of this meeting was a consensus agreement to form a "collaboratory" of experts to address critical needs for validated methods and standardized measurements within the emerging field of nanomedicine. This "pre-standardization" effort is science driven and intended to advance the field while also addressing regulatory needs.

The objectives of this collaborative action are:

- To coordinate and harmonize measurements in the field of nanomedicine relevant to critical quality attributes (CQAs).

- To evaluate and refine existing methods or develop new methods focused on Nano-Enabled Medical Products (NEMPs) and attributes considered high priority by regulators (CQAs).

- To conduct inter-laboratory comparisons to validate those methods.

- To then define best practices for selected measurements, as a basis for subsequent consensus standardisation by international standards development organizations.

Selection of NEMPs and of critical attributes:

By consensus, liposomes were selected as the initial testing based on their prominence and regulatory importance, and will serve as the proof-of-principle for the Collaboratory. Intravenous iron-carbohydrate complexes for treatment of anemia were selected as a second priority material. Three criteria were used to select the CQAs: i) is it a 'critical' attribute, for which the link to the safety or efficiency of the drug product is clear; ii) is the attribute required as basic information by one or more regulatory agencies and iii) do protocols or guidance documents exist for the measurement of the attribute (feasibility). Accordingly, six attributes were selected as the core set for the initial work plan: (i) Size and morphology (ii) Free/bound drug (iii) Chemical composition (iv) Drug release in complex media (v) surface charge and (vi) Transition temperature.

Ongoing pilot studies:

There are presently two pilot studies underway as part of the Collaboratory.

PILOT STUDY #1: Size and Morphology by Multi-Detector Asymmetrical-Flow Field Flow Fractionation (MD-AF4). This study, conducted between JRC, NIST and CEA/EUNCL, is focused on translation of an existing ISO Technical Specification (ISO/TS 21362) and EUNCL protocol to establish a validated best practice based on MD-AF4 applied to doxorubicin-liposomes. The method will be evaluated across instrument platforms, formulations (commercial and generic products) and participating laboratories. Comparison will be with measurements obtained by orthogonal techniques. The results will be published jointly, while the methodology will be developed into a new consensus test method via ASTM International Committee E56 (Nanotechnology).

PILOT STUDY #2: **Quantitative Lipid Composition by Liquid Chromatography Separation in Conjunction with Mass Flow-Sensitive Detection**. This collaborative study, conducted among scientists at CEA, JRC, NPL, FDA, SINTEF, EMPA and NIST, is focused on measuring the analytical robustness and comparability of three different FDA-optimized chromatographic approaches for quantifying the major lipid components within doxorubicin-based liposomes. The three methods will be evaluated across instrument detection (i.e. charged aerosol, evaporative light scattering and tandem mass spectrometry) platforms, formulations (commercial and generic products) and participating laboratories. The data and results generated from this study will be published jointly, while the methodology will be developed into a new consensus Standard Test Method via ASTM International Committee E56 (Nanotechnology).

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