WG2 - DELIVERABLE D2.2

ROADMAP AND CONSENSUS PROTOCOLS FOR CONTROLLING OF SELECTED NEW/EXISTING CHEMICAL ENTITIES AND/OR NANOMATERIALS

Action working group	WG2
Deliverable Nature	Report
Deliverable Identifier	D2.2
Dissemination level	Public
Contractual date of Delivery	20-10-2020
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TABLE OF CONTENTS

1. Prerequisites and challenges for controlling nano-enabled medical products in cancer medicine

Nanopharmaceuticals are medical products enabled nanotechnology that offer improved efficacy and safety profiles for diagnostic and therapeutic use. However, prior to any successful clinical translation, clear regulatory route and reliable standardizes test methods should be available for use. Nanomaterials that are used in medicine are characterized by great heterogeneity and batch-to-batch variability during production, while there is huge lack of standardized methods, relevant reference materials and test guidelines for evaluation of their quality, efficacy and safety (QES). These challenges led to significant increase in regulatory-oriented activities in nanoscience across Europe and worldwide. Thus, the Global Summit on Regulatory Science workshops in 2015 and 2016 (GSRS15 and GSRS16), fostered timely identification of the main regulatory priorities for nanomedicine [1-9]. Recommendations gained by interaction between regulatory bodies, research institutions and industry are listed in Table 1 [10].

Table 1. Recommendations on regulatory needs for controlling nano-enabled medical products in cancer medicine.

Parameter	Challenges	Main recommendations
Critical Quality Attributes (CQA)	Availability and suitability of relevant methods for identification and assessment of CQA (e.g. size distribution, biomolecular corona formation, nano-bio interactions…)	Improvement of methods targeting main properties recognized as CQAs (size/size distribution, physical and chemical stability, zeta potential, encapsulation efficiency, chemical structure, drug/carrier association/drug release, impurities/endotoxin contamination) in close collaboration with other nanotechnology sectors; Prioritization strategies for selection and development of methods according to suitability for NMs, regulatory application, robustness, sensitivity, cost etc.; Implementation of Quality-by-design and Safety by-design approaches
Critical Material Attributes (CMA) and Critical Process Parameters (CPP)	The absence of prior risk assessment, production scale-up, process analytical technology and control strategy	

Table 1.(continued)

Parameter	Challenges	Main recommendations
Standardization	Lack of characterized, widely available reference materials (RMs) in the context of nanomedicine; stability required for RMs;	Development of a generic liposome RMs as liposomal formulations represent the single largest class of nanopharmaceuticals; development of RMs with (certified) reference values for one or more critical quality attributes (size, size distribution, morphology, composition, etc.) that are stable in physiological media; development of RMs with quantifiable surface-active species (e.g., ligands, coating, active pharmaceutical ingredient).
	Adoption of monographs for complex and heterogeneous substances; adoption of OECD Test Guidelines for NMs; comparability of results obtained by different groups; applicability of standardized methods to a wide range of NMs	Selection of an appropriate regulatory framework for nanomedicines considering guidance documentation from at least three different areas (i.e., medical devices, low-molecular weight drugs and biopharmaceuticals); implementation of a decision-tree model
Regulatory framework	Implementation of Quality-by-Design and Safety-by-Design concepts in the nanomedicine	Early dialogue with regulatory agencies; Knowledge and experience sharing

2. Strategies for controlling nanopharmaceuticals in cancer medicine

Early establishment of strategies for ensuring the best QES attributes of nanopharmaceuticals via Quality-by-Design (QbD) and Safe-by-Design (SbD) approaches ensure reduce time-to-market for innovative formulations, reduce manufacturing and disposal costs, reduce energy consumption and finally fulfill regulatory requirements at the later stages [1,11]. Such strategy should be based on implementation of system which ensures quality and safety by verification, qualification and standardization of premises, equipment and processes. The best approach is Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) that both represent an integrated part of pharmaceutical Quality Management (QM).

Main components of GLP and GMP systems are:

1) Good Documentation Practices (GDP) that collectively and individually ensure attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate documentation (paper or electronic)
2) Control Strategy including input material attributes (e.g. drug substance, excipients, container closure), equipment operating conditions, in-process controls, finished product specifications, controls for each unit operations, methods and frequency of monitoring and control of Quality Target Product Profile (QTPP), Critical Quality Attribute (CQA) and (CPP).
3) Application of quality by design and quality risk management linked to an appropriate pharmaceutical quality system by (a) SOP generation at early stages both for analytical methods (characterization) and manufacturing, (b) early establishment of QC and IPC; (c) training of the personnel already at the lab scale, (d) performing regular validation programe.

However, for successful implementation of GLP/GMP in nanomedicine, there is urgent need for the following concepts:

- Personalized and modular characterization pathways depending on the type of nanopharmaceutical composition, matrix and technology readiness level that should be provided as a fast, modular and personalized characterization pathway for each material.

- Changing the characterization habits of developers, innovators and producers by installing widely available, affordable, and standardized facilities.
- New techniques to keep pace with innovation.

GLP/GMP-compliant development is indispensable for the bioactive substances intended to reach market. In the case of nanopharmaceuticals, submitting IND files to regulators can be even more challenging due to the complexity of active substances [1-9]. Respecting that, physicochemical characterization of novel entities and nanomaterials produced becomes of vital importance. It should also be noted that documenting of testing results in the case of nanomaterials should be conducted very carefully even at the level of a research lab, with the special attention given to the reproducibility of results and testing conditions [12].

To understand differences in the organization of a workflow in research labs, GMP-compliant testing/production facilities and GLP-compliant production facilities, we compare relevant topics in the Table 2.

Considering the whole technological process of the nanopharmaceuticals development – from the bench to the bedside – we point out the following issue: the limiting step in the development of nanopharmaceuticals is likely the transfer of promising substances or formulations from research labs to testing and producing facilities (i.e., industry) [10-12]. As it can be deduced from the table, this issue partially arises from the gap in the organization of the workflow. Naturally, activities of research labs, GMP-compliant testing/production facilities and GLP-compliant production facilities are different, so are requirements applied. Nevertheless, adopting proper data gathering and documenting protocols can help researchers to reach GLP/GMP-compliant development of nanopharmaceuticals easier and sooner.

We still lack a clear strategy to select GLP/GMP-compliable and non-compliable nanoconstructions at the research lab stage. Given that a considerable part of nanopharmaceuticals is produced and commercialized by start-ups spun off research labs, establishing criteria of transferability of potent new formulations from labs to the industry can help researchers/innovators save resources choosing right nanoconstructions to be commercialized. In particular, some types of nanoparticles can hardly be approved for use in humans because of their instability or producing potentially toxic metabolites. In this case, investing in developing nanopharmaceuticals on their base is highly risky, even despite scientific soundness of results obtained.

Table 2. Relevant topics for GLP/GMP compliant facilities.

Topic	GLP	GMP	Research labs
Study Director	Person taking full responsibility and control of the study.	No specific Study Director assigned.	PI of a project or/and the director of the Lab
Quality Assurance/Control Unit	Independent Quality Assurance Unit is engaged in inspecting critical points/stages of a study as well as checking facilities for the compliance with GLPs.	Quality Control Unit approves all aspects of product production and testing	PI or a designated person
Testing Facility Management	Supervises overall production and staff. Takes administrative decisions.	Properly trained supervisors.	PI
Type of Testing Conducted	Assessment of product characteristics for external use (including regulators)	Assessment of whether or not a product meets manufacturing requirements.	Assessment of whether or not a product meets research needs
Facility	Facilities are to be designed to fit the work conducted. Areas of different use are separated.	Facilities are to be designed to fit the work conducted. Areas of different use are separated.	Facilities are to be designed to fit the work conducted. Areas of different use are separated.
Equipment	Testing equipment must be appropriate and calibrated. The accuracy, sensitivity, and reproducibility of methods used should be verified and properly documented.	Testing equipment must be appropriate and calibrated. The accuracy, sensitivity, and reproducibility of methods used should be verified and properly documented.	Testing equipment must be appropriate and calibrated. The accuracy, sensitivity, and reproducibility of methods used should be verified.
Standard Operating Procedure (SOP)	Drafted by any qualified personnel, approved by Testing Facility Management. Each study requires a specific protocol indicating objectives and methods of the study. The protocols should be approved by both the Study Sponsor and Study Director.	Drafted by any qualified personnel, approved by Quality Control Unit. Study-specific protocols are not required. Standard written procedures are followed.	Drafted by any qualified personnel, approved by the PI Study-specific protocols are not required. Standard written procedures are followed.
Master Schedule	An index of all studies is maintained by the Quality Assurance Unit.	Master Schedule is not necessary.	Master Schedule is not necessary.
Records and Reports	Records should contain signature or initials of persons conducting all manipulations as well as dates. Records are kept in an archive.	Records should contain signature or initials of persons conducting all manipulations as well as those of a supervisor/controller. Records are kept in an archive.	Made in a personal paper or electronic lab notebook; may contain signatures (person conducting manipulations, supervisor/controller); owned by the institution and kept in the laboratory.

Special attention should be given to the reproducibility of the data and to the high-performance testing, i.e., robotized equipment implementing SOPs and documenting results automatically. A possible solution is to facilitate the access of research labs to the certified GMP-compliant testing facilities and GLP-compliant production facilities in the private sector, by means of governmental/industrial grants or targeted subsidies.

Finally, it seems very important to provide relevant feedback from GMP-compliant testing facilities to research labs to improve characteristics of future products [1-12].

3. Interaction within regulatory frameworks

Proper and timely QES evaluation strategy for controlling the nanopharmaceuticals should involve active participation and collaboration of regulatory and scientific bodies. Although, the regulatory framework in EU and elsewhere is constantly adjusting to new realities and incorporating the best scientific standards in anticipation of the regulatory needs, nanobiotechnology-based medicines and medical devices are currently regulated in the same manner and using the same protocols as 'conventional' diagnostics and therapeutics. However, the QES of nanopharmaceuticals includes numerous specific challenges associated with the complexity of their formulations, which calls for urgent action by the scientific community.

Currently, nanopharmaceuticals are regulated on a case-by-case basis within the Pharmaceutical Legislative Framework for Medicinal Products for Human Use. However, nanobiotechnology-based products, pose significant challenges for the regulators due to several reasons, one being the lack of harmonized, validated specific protocols to characterize the active nanopharmaceuticals and nanoproducts at physicochemical, biological and physiological levels. Despite numerous efforts in the last decade, consensus on procedures, assays and protocols to be employed during pre-clinical development and characterization of nanomedicines and biomaterials is still lacking. Robust methodology is essential to ensure reliable, cost-effective risk/ benefit analysis and long-term safety/risk management. Global regulatory trends are yet to be defined. A science-based regulatory strategy is critically needed to provide clarity and legal certainty to all stakeholders: manufacturers, policymakers, healthcare providers, and patients. The main goal of nanomedical community should

be to facilitate and accelerate development and application of nanobiotechnology-based medicines and medical devices by significant advancement of regulatory science and practice.

A reliable science-based regulatory framework for nanomedicine and biomaterials should be created as a high-impact testing platform for more tailored risk assessment and decision making framework for nanopharmaceuticals. This should include development of an alternative testing strategy consisting of a spectrum of tools covering physico-chemical characterisation, environmental risk assessment models, in silico-, high-throughput- (HTP), and in vitro-models.

Such platform would drive a paradigm shift within the regulatory path of nanopharmaceuticals towards a harmonised, integrated and intelligent approach taking into account QbD and SbD tools and considering mode-of-action specific testing to allow successfully facing current and upcoming challenges of regulatory approval and industrial implementation of novel nanopharmaceuticals. Ideally, such platform integrates aspects of the Safe Innovation Approach (SIA), the 3R's strategy (Replacement, Reduction and Refinement of Animal Testing), and Adverse Outcome Pathway (AOP) concept into a truly innovative, applicable testing platform where needs of all relevant stakeholder groups are fully met for the benefit of patients and society.

Effective interactions with all relevant stakeholders on a national and international scale will intensify communication with and among the national agencies to facilitate the harmonization of regulatory and industrial standards at EU and global level.

Chemistry, Manufacturing, and Controls (CMC) information is required for the Investigational New Drugs (IND) or Investigational Medicinal Product Dossier (IMPD) applications at the FDA or EMA, respectively, to ensure proper identity, strength or potency, quality, and purity of the drug substance and drug product.

Manufacturing procedures that require complex and/or laborious synthesis methods generally have limited clinical translation potential, as it can be quite problematic to perform the scale-up of the pharmaceutical manufacturing operations [13]. Pharmaceutical manufacturing development is centered on quality and cost. In the case of nanomedicine manufacturing exists additional challenges due to: (i) poor quality control; (ii) scalability complexities; (iii) incomplete purification from contaminants (by-products and starting materials); (iv) high material and/or manufacturing costs; (v) low production yield; (vi) insufficient batch-to-batch reproducibility, consistency and storage stability of the final product; (vii) lack of infrastructure and/or in-house expertise; (viii) chemical instability or denaturation of the encapsulated compound during the manufacturing process; and (ix) shortage of industry investment [14].

An essential requirement for clinical translation is to have access to a preparation method that allows the production of large scalable quantities manufactured at a high level of quality and batch-to-batch reproducibility to set specifications [14]. In the case of liposomes, a relative simple nanomedicine, it was possible to develop and to establish suitable methods for the industrial scale-up production without the need for numerous manufacturing steps or the use of organic solvents [15]. However, the challenges come up when the nano-carrier system is more complex, the addition of surface modification with coatings, inclusion of multiple targeting components, or by encapsulating more than one therapeutic agent, inevitably creates problems for large-scale GMP-manufacturing, increases the cost of production, and makes the quality assurance and quality control evaluation of such products more challenging since it becomes a complex multiple steps production process [16]. In addition, nanomedicines need to be stable after the manufacturing process, during long-term storage, and during-upon clinical administration.

The type of information filling in the IND or IMPD documents will depend on the phase of the investigation, the extent of the human study, the duration of the investigation, the nature and source of the drug substance, and the drug product dosage form. Regulatory agencies have highlighted the need for assessing the stability, uniformity (dispersibility), morphology, charge, purity, drug encapsulation efficiency, endotoxin testing, and agglomeration behavior as highly relevant before entering into clinical trials. The characterization and validation of more complex nanoparticules can be particularly challenging due to the additional number of parameters to address such as multiple drug encapsulation efficiency, coating efficiency, and density of conjugated ligand, in general proteins or monoclonal antibodies [17]. Additional information such as the assessment of the solubilized fraction before and during the testing of metals and metal oxides seems to be more relevant at a later stage of the product development [18].

Currently, only very few standard test methods specifically addressing the application of nanotechnology in the health sector are available. In order to seek for consensus on standardisation needs, a series of workshops were organized under the umbrella of the Global Summit on Regulatory Science (GSRS16, 2016) [19]. In addition, to facilitate the regulation of nanoproducts, the FDA formed a Nanotechnology Task Force, which issued an FDA Task Force report back in 2007 [20]. In the USA, the Nanotechnology Characterization Laboratory of the National Cancer Institute (NCI-NCL) (https://nanolab.cancer.gov) has provided a thorough characterization of the quality and safety of nanomedicines already for more than 10 years, supporting product developers and contributing to the smooth translation of such products to the market. At the same time, the

NCI-NCL offers the experience and knowledge related to the assessment of nanomedicines to the regulatory agency. Since 2015, the European Nanomedicine Characterisation Laboratory (EU-NCL) (www.euncl.eu) offers a similar service for the European product developers and it can be anticipated that also European regulatory agencies and standardization bodies will benefit from the knowledge and experiences of this platforms [21]. Moreover, several initiatives have already proposed initial lists of physicochemical and/or toxicological parameters relevant for the characterisation of nanomaterials used in the health sector. The European Commission's SCENIHR has released a guidance document on the "Determination of Potential Health Effects of Nanomaterials Used in Medical Devices" (SCENIHR, 2015) [22]. Also, to provide guidance to developers in the preparation of marketing authorization applications, the EMA released some reflection papers regarding nanomedicines with surface coating, intravenous liposomal, block copolymer micelle, and iron-based nano-colloidal nanomedicines [23]. The principles outlined in these documents address general issues regarding the complexity of the nanosystems and provide basic information for the pharmaceutical development, non-clinical and early clinical studies of block-copolymer micelle, "liposome-like," and nanoparticle iron medicinal products drug products created to affect pharmacokinetic, stability and distribution of incorporated or conjugated active substances in vivo. Important factors related to the exact nature of the particle characteristics, that can influence the kinetic parameters and consequently the toxicity, such as the physicochemical nature of the coating, the respective uniformity and stability, the bio-distribution of the product and its intracellular fate are specifically detailed [24].

Another caveat for a harmonised regulation of nanomedicines is the current lack of a consistent terminology and categorization of nanomedicines that complicates the communication between regulatory agencies [25].

One of the important factors contributing to the slow pace in the clinical translation of nanomedicines is the structural and physicochemical complexity of the formulation itself. Regulatory agencies around the world continue to struggle in their efforts to develop, significant regulatory definitions and balance them with policies that are already in place. However, guidance is critically needed to provide clarity and legal certainty to manufacturers, policy-makers and pharmaceuticals companies. Nevertheless, industry and stakeholders fully understand that generalized and broad guidelines, assays or tests may not be possible for all nanoproducts.

References

[1] Ehmann F, Sakai-Kato K, Duncan R, Hernán Pérez de la Ossa D, Pita R, Vidal JM, Kohli A, Tothfalusi L, Sanh A, Tinton S, Robert JL, Silva Lima B, Amati MP. 2013. Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines. Nanomedicine (Lond). 8(5), 849-856.

[2] http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf;

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004008.pdf

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf

[5] http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[6] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AC%3A2016%3A173%3AFULL

[7] http://www.nanoreg.eu/images/20150530_SbD_Working_Draft_EU_US_and_ProSafe.pdf

[8] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC96418/eurl%20ecvam%20toxicokinetics%20strategy.pdf

[9] http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

[10] Halamoda-Kenzaoui, B., Baconnier, S., Bastogne, T., Bazile, D., Boisseau, P., Borchard, G.,...Bremer-Hoffmann, S. (2019). Bridging communitiesin the field of nanomedicine.Regulatory Toxicology and Pharmacology 106, 187–196.

[11] Oomen AG, Steinhäuser KG, Bleeker EAJ, van Broekhuizen F, Sips A, Dekkers S, Wijnhoven SWP, Sayre PG. 2018. Risk Assessment Frameworks for Nanomaterials: Scope, Link to Regulations, Applicability, and Outline for Future Directions in View of Needed Increase in Efficiency. NanoImpact 9,1–13.

[12] Pita R, Ehmann F, Papaluca M. 2016. Nanomedicines in the EU—Regulatory Overview. AAPS J 18, 1576–1582.

[13] Teli, M. K., Mutalik, S., and Rajanikant, G. K. (2010). Nanotechnology and nanomedicine: going small means aiming big. Curr. Pharm.Des. 16, 1882–1892. doi: 10.2174/138161210791208992.

[14] Hua S, de Matos M., Metselaar J, Storm G. (2018). Current Trends and Challenges in the Clinical Translation of Nanoparticulate Nanomedicines: Pathways for Translational Development and Commercialization Frontiers in Pharmacology. 9.

[15] Kraft, J. C., Freeling, J. P., Wang, Z., and Ho, R. J. (2014). Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. J. Pharm. Sci. 103, 29–52. doi: 10.1002/jps.23773.

[16] Tinkle, S., McNeil, S. E., Muhlebach, S., Bawa, R., Borchard, G., Barenholz, Y. C., et al. (2014). Nanomedicines: addressing the scientific and regulatory gap. Ann. N. Y. Acad. Sci. 1313, 35–56. doi: 10.1111/nyas. 12403

[17] Emily M, Ioanna N, Scott B, Beat F.(2018) Reflections on FDA Draft Guidance for Products Containing Nanomaterials: Is the Abbreviated New Drug Application (ANDA) a Suitable Pathway for Nanomedicines? AAPS J. Aug 20;20(5):92.

[18] Bremer-Hoffmann S, Halamoda-Kenzaoui B, S Borgos S (2018). Identification of regulatory needs for nanomedicines Journal of Interdisciplinary Nanomedicine. 14 March.

[19] https://www.fda.gov/media/99865/download

[20] http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf

[21] Bremer-Hoffmann S, Halamoda-Kenzaoui B, S Borgos S (2018). Identification of regulatory needs for nanomedicines Journal of Interdisciplinary Nanomedicine. 14 March.

[22] https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_045.pdf

[23] www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105048.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/01/WC500159411.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/08/WC500147874.pdf; www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf

[24] Soares S, Sousa J, Pais A, Vitorino C. Nanomedicine: Principles, Properties, and Regulatory Issues (2018). Frontiers in Chemistry. 6, 360.

[25] Quiros Pesudo L, Balahur A, Gottardo S, Rasmussen K, Wagner G, Joanny G, Bremer S. (2018). Mapping Nanomedicine Terminology in the Regulatory Landscape. https://op.europa.eu/web/eu-law-and-publications/publication-detail/-/publication/1f1f68de-9ea3-11e8-a408-01aa75ed71a1/language-en