WG4 - DELIVERABLE D4.2

Formulation of guidelines and documents concerning regulatory aspects of nanomedicines

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4.2.2. Need of a unified set of global regulations in nanomedicines.

- **Analysis of the current FDA and EMA guidance for industry related to nanomedicines or medical devices in the cancer field**

To date, all the regulatory agencies recommend a case-by-case analysis, introducing specific trial modifications for each and using the same regulatory process as applied for conventional drugs.

Table. Main regulatory agencies and their regulatory progress in nanomedicines.

	Food and Drug Agency (FDA) United States of America	European Medicines Agency (EMA) European Union	Ministry of Health, Labour and Welfare, MHLW, Japan
Biopharmaceutical application with innovative technologies with NPs	The Investigational New Drug (IND) application and New Drug Application (NDA). Reformulated Drug Products: Abbreviated New Drug Application (ANDA).	Investigational Medicinal Product Dossier (IMPD).	Investigational New Drug (IND) application or New Drug Application (NDA) under the format: Common Technical Document (CTD).
Nanomedicines Characterization Laboratory	US-NCL	EU-NCL	Research Center for Functional Materials
Main Guidelines for nanomedicines	Guidance for Industry on Drug Products, Including Biological Products that Contain Nanomaterials–Guidance for Industry. Liposome Drug Products Guidance for Industry. CDER and CBER Guidance.	Reflection Paper on: Nanotechnology-Based Medicinal Products for Human Use. Liposomal products. Surface coatings. Iron-based nano-colloidal products.	Guideline for the Development of Liposome Drug Products. Reflection paper on the development of block copolymer micelle medicinal products (MHLW/EMA). Reflection paper on silencing ribonucleic acid (siRNA).

In the European Union, the development of nanomedicines is regulated by the European Medicines Agency (EMA). The EMA applies the General Medicinal Product legislation to nanomedicines, with a legal reference regarding nanomaterials published in 2011 (Recommendation 2011/696/EU) by the European Commission (EC) [1], which sets the first suitable definition of "nanomaterial" within the EU for legislative and policy use; however, this recommendation is not legally binding nor imposed across the EU.

The EMA provides guidance documents for the development of nanomedicines, which can be found on their website. Some of these guidance documents include:

1. Guideline on the quality, non-clinical and clinical aspects of medicinal products containing nanomaterials (2018): This guideline provides guidance on the quality, non-clinical, and clinical aspects of medicinal products containing nanomaterials, including nanomedicines.
2. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (2018): This reflection paper provides guidance on the data requirements for intravenous liposomal products, which are a type of nanomedicine.
3. Guideline on the pharmaceutical development of medicines for paediatric use (2020): This guideline provides guidance on the pharmaceutical development of medicines for paediatric use, including nanomedicines.

Several regulatory bodies of the EU are involved in the regulation of nanomedicines. The European Medicines Union (EMU) has initiated specific preliminary guidelines to standardize nanomedicine preparation standards; however, official regulatory guidelines remain unpublished [2,3]. Task forces and consortiums, including the Nanomedicines Expert Group, the Nanomedicine Characterization

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:en:PDF

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-nanomedicines

3 Halamoda-Kenzaoui B, Holzwarth U, Roebben G, Bogni A, Bremer-Hoffmann S. Mapping of the available standards against the regulatory needs for nanomedicines. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2019 Jan;11(1):e1531.

Laboratory (NCL) and the Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices (REFINE) project [4], have launched different initiatives to establish definitions and guidelines for the regulation of nanomedicines and provide constantly updated knowledge on preclinical characterization methods [5,6,7]. The European Chemical Agency (ECHA) addresses the safety of chemicals (including nanomaterials) under the regulation of the European Chemical Legislation (REACH EC 1907/2006) [8]. The EU currently regulates nanomedicines using risk/benefit-analysis principles.

In the United Kingdom, the development of nanomedicines is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA provides guidance documents for the development of nanomedicines, which can be found on their website. Some of these guidance documents include:

1. Guidance on the regulation of medicines for children in the UK (2020): This guidance provides information on the regulation of medicines for children in the UK, including nanomedicines.
2. Guidance on the clinical trials of nanomedicines (2017): This guidance provides information on the clinical trials of nanomedicines, including the regulatory requirements for conducting clinical trials.
3. Guidance on the quality, non-clinical and clinical aspects of nanomedicines (2016): This guidance provides information on the quality, non-clinical, and clinical aspects of nanomedicines, including the regulatory requirements for the development and approval of nanomedicines.

The approval of nanomedicines by the MHRA is managed on a case-by-case basis, with researchers encouraged to communicate with the MHRA for support throughout the development process.

The development of nanomedicines in the United States is regulated by the Food and Drug Administration (FDA). The FDA has released several guidance documents to assist drug developers in navigating the regulatory landscape for these products. Here are some of the key guidance documents issued by the FDA:

1. Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology [9]. This guidance provides a framework for determining whether a product involves the application of nanotechnology, and thus whether it may be subject to regulatory oversight by the FDA.
2. Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials [10]. This guidance provides recommendations for the characterization, quality, and nonclinical testing of drug products that contain nanomaterials.
3. Guidance for Industry: Safety Testing of Drug Metabolites [11] .This guidance outlines considerations for the safety testing of metabolites of drug products that contain nanomaterials.

[4] http:// refine-nanomed.eu/
[5] Rauscher H, Roebben G, Amenta V, Boix Sanfeliu A, Calzolai L, Emons H, et al. Towards a review of the EC Recommendation for a definition of the term “nanomaterial”; Part 1: Compilation of information concerning the experience with the definition. 2014.
[6] Rauscher H, Roebben G, Amenta V, Sanfeliu AB, Calzolai L, Emons H, et al. Towards a review of the EC Recommendation for a definition of the term “nanomaterial” Part 2. Luxemb Publ Off Eur Union. Luxemburg; 2014.
[7] Rauscher H, Roebben G, Rauscher H, Roebben G, Sanfeliu AB, Emons H, et al. Towards a review of the EC Recommendation for a definition of the term “nanomaterial” Part 3. Luxemburg; 2015.
[8] https://echa.europa.eu/pt/regulations/nanomaterials
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-including-biological-products-contain-nanomaterials-guidance-industry
[11] https://www.fda.gov/media/72279/download

4. Guidance for Industry: Immunogenicity-Related Considerations for Low Molecular Weight Heparin [12]. This guidance provides recommendations for evaluating the potential immunogenicity of drug products that contain nanomaterials.
5. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling [13]. This guidance provides recommendations for the design and analysis of pharmacokinetic studies in patients with impaired renal function, which may be relevant for drug products that contain nanomaterials.

The current regulatory landscape for nanomedicines is characterized by fragmented guidelines and regulations, which vary across different regions and countries. For instance, the US Food and Drug Administration (FDA) has issued several guidance documents related to the development of nanomedicines, such as the "Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" and the "Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials." Similarly, the European Medicines Agency (EMA) has published a reflection paper on the regulatory guidance for nanomedicines. These documents provide valuable guidance for the development and evaluation of nanomedicines; however, they are not binding and may lead to different interpretations and implementation.

Regulatory guidance for the development of drug products that contain nanomaterials can vary by country and region. Here are some resources for regulatory guidance in Asia:

1. Japan: The Pharmaceuticals and Medical Devices Agency (PMDA) provides guidance for the quality, safety, and efficacy of pharmaceuticals containing nanomaterials in Japan. PMDA has also issued specific guidelines for nanotechnology-based medical products, including drug products. Including specific guidelines for the regulation of liposome-based drug products in 2016. As in the USA and EU, the Pharmaceutical Affairs Law framework in Japan legislates nanomedicines on a case-by-case basis in close collaboration with the EMA.
2. South Korea: The Ministry of Food and Drug Safety (MFDS) provides guidelines for the safety and efficacy evaluation of nanomaterial-containing pharmaceuticals. The guidelines outline the requirements for the characterization, quality control, and non-clinical and clinical safety assessment of drug products containing nanomaterials.
3. China: The China National Medical Products Administration (NMPA) has issued guidance on the development and evaluation of drug products containing nanomaterials. The guidance provides requirements for quality, safety, and efficacy evaluation, as well as for labeling and post-market surveillance.
4. India: The Central Drugs Standard Control Organization (CDSCO) has released draft guidance on the safety, efficacy, and quality assessment of nanotechnology-based drug products. The guidance outlines the requirements for characterization, stability, safety, and efficacy evaluation of nanomaterials in drug products. In 2019, the Indian government published the first guidelines for nanomedicine regulation, covering the development of new drugs and their comparison with existing entities.

The main challenges for harmonized global regulations of nanomedicines among the main agencies include the complex nature of nanomaterials, the lack of standardized methods for their characterization, and the rapid pace of technological innovation. Nanomaterials exhibit unique physical and chemical properties that can influence their biological behaviour and toxicity. Therefore, the development of standardized methods for their characterization and evaluation is

[12] https://www.fda.gov/files/drugs/published/Immunogenicity-Related-Considerations-for-Low-Molecular-Weight-Heparin-Guidance-for-Industry.pdf

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and

essential to ensure the reproducibility and comparability of the results. Additionally, the rapid pace of technological innovation in nanomedicine requires flexible and adaptive regulatory frameworks that can keep pace with these changes.

In conclusion, a unified set of global regulations for nanomedicines is necessary to facilitate their clinical translation and to ensure their safety and efficacy. Early dialogue with regulatory agencies, knowledge and experience sharing, and the development of standardized methods for the characterization and evaluation of nanomaterials are essential to overcome the challenges associated with the harmonization of global regulations for nanomedicines.

A harmonised terminology and established definitions are essential for a mutual understanding among different communities of stakeholders including scientific experts and regulators. The definition and classification of nanotechnology-based products represent additional challenges—while related products can be classified as medicines or medical devices, a lack of consensus exists across the globe. For this reason, the regulatory framework for a given nanomedicine will change according to the country, thereby hindering approval and regulation. Currently a formal definition of nanomedicines does not exist. For example, in the case of the EMA a working definition for nanomedicines has established based on the following three considerations [14]: (1) purposely designed systems for clinical applications; (2) at least one component at nano-scale size that should not exceed 1000 nm; and (3) resulting in definable specific properties and characteristics.

In April 2022, the Food and Drug Administration (FDA) announced the availability of a final guidance for industry entitled "Drug Products, Including Biological Products, That Contain Nanomaterials[15]". This guidance finalized the draft guidance issued on December 18, 2017, developed to provide industry with the FDA's recommendations for the development of human drug products, including those that are biological products, in which a nanomaterial is present in the finished dosage form. This FDA document covers the manufacturing and evaluation of drug products (i.e., finished dosage forms) intended for human use. It does not cover manufacturing of drug components, such as active ingredients and excipients (i.e., inactive ingredients). The recommendations concern the characterization, control, testing and qualification of nanomaterial components in the drug product. This guidance also includes recommendations for applicants and sponsors of investigational, pre-market, and post-market submissions for these products. This guidance focuses on considerations relevant to FDA's regulation of these drug products under the Federal Food, Drug, & Cosmetic Act (FD&C Act) and Public Health Service Act (PHS Act). These recommendations set forth in International Council for Harmonization (ICH) guidances adopted by FDA, the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) addressing nonclinical safety of drug products and their components containing nanomaterials.

The FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms [16]. As described in FDA's nanotechnology considerations guidance (issued in June 2014), at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, the term "nanomaterial" will refer to materials falling within either point 1 or 2 below:

(1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm).

[14] Pita, R., Ehmann, F., & Papaluca, M. (2016). Nanomedicines in the EU—Regulatory Overview. The AAPS Journal, 18(6), 1576–1582. https://doi.org/10.1208/s12248-016-9967-1

[15] "Drug products, including biological products, that contain nanomaterials guidance for industry". U.S. Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). April 2022. FDA-2017-D-0759. https://www.fda.gov/media/157812/download.

[16] See FDA's guidance for industry Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (June 2014). For the most recent version of a guidance, check the FDA guidance web page at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

(2) whether a material or end-product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm). Because materials or end products can also exhibit related properties or phenomena attributable to a dimension(s) outside the nanoscale range of 1 nm to 100 nm that are relevant to evaluations of safety, effectiveness, performance, quality, public health impact, or regulatory status of products.

Close collaborations between the FDA and the US government departments and agencies through the National Nanotechnology Initiative (NNI) aims for early dialogue during product development. The NNI focuses on preparing guidance documents for the characterization and quantification of nanomaterials based on six areas: measurement infrastructure, human exposure assessment, human health, environment, risk assessment and management, and informatics and modeling. The Nanotechnology Characterization Laboratory of the National Cancer Institute (NCL-NCI) also contributes to nanomedicine regulation [17].

The absence of changes in nanomedicine regulation guidelines has raised concerns and evoked criticisms of the FDA; however, the establishment of general industry guidelines related to liposomal-drug products represents an important step towards the construction of regulatory frameworks for nanomaterials [18] and could prompt the establishment of draft guidance for other types of nanomedicines. Therefore, nanomedicines prepared using existing approved components move rapidly through regulatory procedures as no additional pharmacotoxicology studies would be needed to address the safety of the individual parts to those required for the nanomedicine new chemical entity (NCE).

The FDA regulates nanotechnology-based products on a case-by-case basis [19]. As in the UK, the FDA encourages drug developers to consult these guidance documents and engage with the FDA early in the development process to ensure compliance with safety information, regulatory issues, and marketing.

International pharmaceutical regulation is the responsibility of the International Pharmaceutical Regulators Program (IPRP) [20] under the scope of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Their main objective is to establish harmonized regulatory frameworks for nanomedicines—namely, what information needs to be reported to regulators—by maintaining close collaborations with all international regulatory agencies. The lack of specific guidelines for the adequate characterization of nanomedicines at the physicochemical and physiological levels may have contributed to the failures of certain nanomedicines at late clinical stages [21]. Reflection articles currently provide limited guidelines on the pharmaceutical development of specific nanomedicines; however, defining the parameters that must be considered to adequately evaluate nanomedicine quality control and safety and associating those parameters to a regulatory definition by differentiating active pharmaceutical ingredients (APIs), excipients, and drug products from a physico-chemical point of view remain important tasks. The Nanomedicines Working Group of the IPRP comprises a working group that includes America, Asia, Europe, and Oceania and covers emerging issues related to nanomedicines and nanomaterials in drug products. This Working Group has been created as a platform to further facilitate an exchange of information and regulatory cooperation of the pharmaceutical regulatory bodies in different regions. Harmonization of regulatory practice in nanomedicine refers to the process of

[17] https://www.cancer.gov/nano/research/ncl
[18] https://www.fda.gov/media/70837/download
[19] https://www.fda.gov/science-research/science-and-research-special-topics/nanotechnology-programs-fda
[20] https://www.iprp.global/home
[21] Sainz V, Conniot J, Matos AI, Peres C, Zupancic E, Moura L, Silva LC, Florindo HF, Gaspar RS. Regulatory aspects on nanomedicines. Biochem Biophys Res Commun. 2015 Dec 18;468(3):504-10.

aligning the regulatory requirements and guidelines for the development, approval, and commercialization of nanomedicine products across different countries or regions. This can be achieved through the adoption of international standards, guidelines, and best practices that are recognized and accepted globally.

In 2018, a survey among the members of the Nanomedicines Working Group of the IPRP was conducted to address the regulatory experience with liposomal products [22]. The results of this survey showed that several liposomal products were approved under the different current regulatory frameworks suggesting that no specific regulation was needed for this class of products. The most critical issues related to the regulation of liposomal products included:

- Approaches for regulation of generic liposomal drugs.
- It will be needed to develop a common definition of liposomes that would be acceptable for all regulators.
- Correlation of *in vitro* and *in vivo* data
- Limitations of analytical methodology; in particular, the comparability of data obtained with different measurement methods.
- Identification of quality attributes that are critical during the manufacturing process. In this sense, the option of sharing the submission data among the regulators could be of benefit in the identification of critical quality attributes.
- Selection of reference standards

Nanotechnology-enabled health products have no particular legislative or regulatory framework and follow the current regulation of medicinal products or medical devices. Nanomedicines have been in the forefront of pharmaceutical research in the last decades, creating new challenges for research community, industry, and regulators. However, despite these efforts, significant challenges remain in achieving global harmonization of regulatory practices in nanomedicine, including differences in regulatory frameworks, variations in the interpretation of data requirements, and the lack of consensus on the definition and classification of nanomaterials.

Tremendous advances in the biomaterials and nanotechnology fields have prompted their use as promising tools to overcome important drawbacks associated to the non-specific effects of conventional therapeutic approaches. However, the characteristics of nanotechnology-based products create some challenges when it comes to regulatory approval processes which are already recognized by regulatory authorities through the provision of initial reflection papers and guidance documents. Nevertheless, more efforts are needed to take up translational and regulatory science into academic research and educational programmes in order to support the development of regulatory structures that can be adaptive to the increasingly complex innovative health products. Moreover, current research activities focus on the development of multifunctional drug delivery systems that release their therapeutic cargo to the diseased tissue and act through external stimuli such as magnetic fields, ultrasound, pH, temperature or light. Such hybrid structures combining physical stimuli with pharmacologically active substances pose additional challenges in their regulation, since they can exhibit more than one mechanism of action. Depending on their main mode of action they must follow primarily the regulatory framework of medicinal products or medical devices, the components of the product may belong to several categories including biopharmaceuticals, advanced therapy medicinal products and medical devices, which requires the navigation between several directives and frameworks [23].

[22] http://development.iprp.backend.dev6.penceo.com/sites/default/files/2018-09/IPRF_NWG_LiposomalResults_HC_Survey_Summary_Final.pdf
[23] Halamoda Kenzaoui, B., Box, H., Van Elk, M., Gaitan, S., Geertsma, R., Gainza Lafuente, E., Owen, A., Del Pozo, A., Roesslein, M. and Bremer, S., Anticipation of regulatory needs for nanotechnology-enabled health products, EUR 29919 EN, Publications Office of the European Union, Luxembourg, 2019, ISBN 978-92-76-12553-2.

The wide range of application of nanomedicines demands a profound knowledge and characterization of these complex products. Their properties need to be extensively understood to avoid unpredicted effects on patients, such as potential immune reactivity. Research policy and alliances have been bringing together scientists, regulators, industry, and, more frequently in recent years, patient representatives and patient advocacy institutions.

To successfully enhance the development of new technologies, improved strategies for research-based corporate organizations, more integrated research tools dealing with appropriate translational requirements aiming at clinical development, and proactive regulatory policies are essential in the future. On the other hand, excessive regulation is not required, which can affect the advancement of products in the marketplace, increasing costs to achieve regulatory approval and/or consuming a significant portion of the life of a patent.

The regulation of nanomedicine is a complex issue due to the interdisciplinary nature of the field, the rapid pace of technological advancements, and the potential risks associated with the use of nanomaterials in medical applications. Regulatory Science aspects driving a faster and safer development of nanomedicines will be a central issue for the next years. However, excessive regulation is not required, since it can affect the advancement of products in the marketplace, increasing costs to achieve regulatory approval and/or consuming a significant portion of the life of a patent.

The recommendation on the early dialogue with the regulators is shared by the majority of regulatory agencies world-wide. A parallel EMA-FDA scientific advice can be requested by product developers, especially in case of products being developed for indications lacking sufficient development guidelines.

It is important to note that regulations and guidelines for the development of drug products containing nanomaterials are constantly evolving, and companies should consult with regulatory agencies for the most up-to-date information. To address these issues, early dialogues with regulatory agencies are necessary to ensure a common understanding of the regulatory requirements for nanomedicines. The early engagement with regulatory agencies can help to identify potential issues and to develop a more efficient regulatory pathway for nanomedicines. Moreover, knowledge and experience sharing among regulatory agencies can facilitate the development of harmonized global regulations.

4.2.3. Economics

- **Real overall cost-effectiveness on nanomedicines compared to current therapies**
- **Landscape of currently government's fundings, investments' funds and venture capitals dedicated to nanomedicine and nanotechnologies applied in medicine**

Real overall cost-effectiveness on nanomedicines compared to current therapies

Nanomedicine, which involves the use of nanotechnology in medicine, has the potential to revolutionize healthcare by enabling more targeted and effective treatments with fewer side effects. They have gained significant attention in recent years due to their potential to revolutionize the field of medicine by providing targeted and personalized treatment options. However, the cost-effectiveness of nanomedicines compared to current therapies is a complex issue that requires careful analysis. The cost-effectiveness of this novel therapeutic approach depends on various factors, including the specific application, the type of therapy being replaced, and the overall healthcare system.

On the one hand, nanomedicines can offer several advantages over traditional therapies. For example, they can improve drug delivery by targeting specific cells or tissues, reducing the amount of medication needed and minimizing side effects. This targeted delivery can also reduce the overall dose required, potentially lowering the cost of treatment. Additionally, nanomedicines can be engineered to have improved pharmacokinetic and pharmacodynamic properties, which can further enhance their therapeutic potential. They can also enable new types of therapies, such as gene therapy or immune modulation, that were previously not possible. In some cases, nanomedicines can even reduce the overall healthcare costs by reducing hospitalization time, lowering the need for repeat treatments, or preventing disease progression.

However, the development and production of nanomedicines can be expensive and time-consuming. The cost of nanomaterials, equipment, and regulatory compliance can be high, and the production process may require specialized expertise. The regulatory requirements for nanomedicines can also be more stringent, leading to higher development costs. Additionally, the long-term safety and efficacy of nanomedicines are still being studied, which can add to the overall cost of development. In addition, the clinical trials required to demonstrate the safety and efficacy of nanomedicines can be lengthy and costly.

When considering the cost-effectiveness of nanomedicines, it is important to take into account the specific disease being treated, the current standard of care, and the potential benefits and risks of the nanomedicine. In some cases, the improved efficacy and reduced side effects of nanomedicines may outweigh the higher cost, making them a more cost-effective option. In other cases, the cost of nanomedicines may be prohibitive, especially in low-income countries where access to healthcare is limited.

In conclusion, while the cost-effectiveness of nanomedicines compared to current therapies is complex issue that requires careful evaluation on a case-by-case basis. The cost-effectiveness of nanomedicines is likely to vary depending on the specific application and the healthcare system in question. While nanomedicines have the potential to revolutionize the field of medicine, their cost and long-term safety and efficacy must be carefully considered to ensure that they provide value for patients and healthcare systems. However, as more research is conducted and more nanomedicines are developed, it is likely that their cost-effectiveness will improve, and they will play an increasingly important role in healthcare.

Landscape of currently investments' funds and venture capitals dedicated to nanomedicine and nanotechnologies applied in medicine

Drug delivery is the most profitable application of nanotechnology in medicine, and even generally, over the next two decades. Emerging methods for drug delivery, increased use of nanomedicine across various applications, increased government backing and funding, the surge in demand for

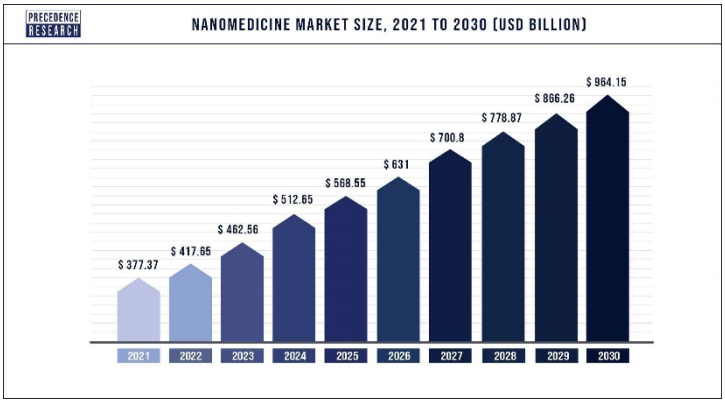
therapies with fewer side effects, and cost effectiveness of therapies are driving the worldwide nanomedicine market. On the other hand, the nanomedicine market's growth is limited by the lengthy licensing process and the hazards involved with nanomedicine.

Cancer research illustrates many of the medical potentials of nanotechnologies in the longer term. It is hoped that nanoscale devices and processes will help to develop:

- Imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest stages,
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation,
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer,
- Agents that can monitor predictive molecular changes and prevent precancerous cells from becoming malignant,
- Novel methods to manage the symptoms of cancer that adversely impact quality of life,
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance.

Regarding investments in nanomedicine and nanotechnologies applied in medicine, there has been significant interest from both private and public sources. According to a report by Allied Market Research, the global nanomedicine market was valued at $111.91 billion in 2020 and is expected to reach $261.06 billion by 2030, growing at a compound annual growth rate (CAGR) of 9.4% from 2021 to 2030.

Figure. The global nanomedicine market size was estimated at US$ 377.37 billion in 2021 and it is expected to hit over US$ 964.15 billion by 2030 (Adapted from Precedence Research Report 2022-2030[24]).



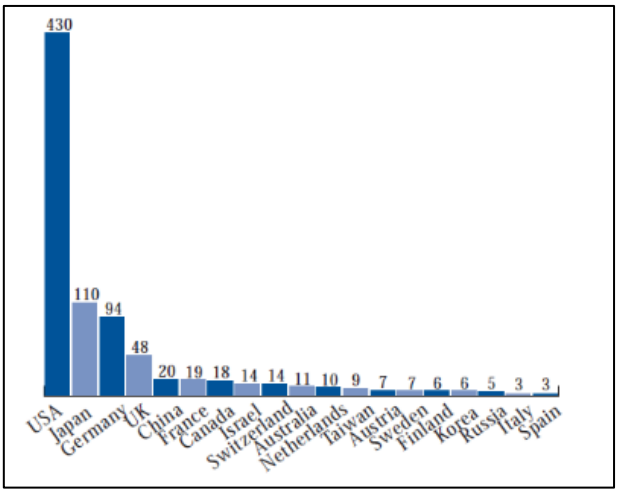
The roles of the different financial players in the nanotech sector are no different from those elsewhere [25]:

- large organizations, with the resources to investigate longer-term technologies, seek applications to improve margins, lower costs or increase market share,
- start-ups, seeking to apply technologies to capture market share or disrupt existing markets,
- economic blocs compete for supremacy, mindful of the economic benefits that strength in many of the applications of nanotechnology will bring,
- public agencies attempt to capture the maximum number of links in the value chain.

[24] https://www.precedenceresearch.com/nanomedicine-market
[25] Risks and rewards of nanotechnology, from OECD and Allianz. June 2005. https://www.oecd.org/science/nanosafety/44108334.pdf.

As the Figure below shows, most nanotech companies are in the US, mainly because of the more developed venture capital market (over half the venture capital investors in nanotechnology are from the US). Statistics for universities and research institutes also shows a strong, but less marked, US bias.

Figure. Word-wide location of nanotech companies (Adapted from the Report Risks and rewards of nanotechnology, 2005 [26]).



A survey by the VDI (the Society of German Engineers) have showed that one of the major barriers for innovation by small- and medium-sized enterprises in Germany in the area of nanotechnology is a lack of capital [27]. To develop new products and processes and to penetrate new markets, sizeable investments are needed, especially in the seed phase. There are many venture capital firms and investment funds that focus on nanomedicine and related technologies. Some examples include Nanostart AG, Lux Capital, and NEA, which have all invested in nanomedicine companies. Venture capital firms in nanotechnology will have a key role in transferring technology knowledge from the research centers to the industry and the markets.

In addition, many major pharmaceutical companies, such as Pfizer, Novartis, and Merck, have invested in nanomedicine research and development. Pharmaceutical companies are least likely to have an explicit nanotechnology strategy; they also invest the lowest level of people and funding compared with other sectors. Asian companies across industries show the highest levels of staffing, funding, and executive sponsorship for nanotech.

An OECD survey published in 2004 indicates that in many countries the R&D nanomedicines programs vary considerably in size and scope [28]. In many countries, programs are aimed at developing world-class R&D capability in nanotechnology, recognizing its importance in a number of industrial fields and in addressing a number of social needs. Japan, for example, has a range of programs aimed at basic research and nano-materials. Canada has established the National Institute of Nanotechnology as an integrated research institute with 150 researchers from various disciplines and a business incubation facility. Denmark has established three new research centers, two of which focus on interdisciplinary approaches to nanoscience, and one of which will address nano systems engineering. In 2003, the United States passed the 21st Century Nanotechnology Research and Development Act, authorizing $3.7 billion in federal subsidies for three years beginning in 2005. This is for projects supported by the National Nanotechnology Initiative (NNI), a federal R&D

[26] Risks and rewards of nanotechnology, from OECD and Allianz. June 2005. https://www.oecd.org/science/nanosafety/44108334.pdf.
[27] Risks and rewards of nanotechnology, from OECD and Allianz. June 2005. https://www.oecd.org/science/nanosafety/44108334.pdf
[28] OECD: 2004 Results of OECD mini-survey on nanotechnology R&D programmes DSTI/STI/TIP(2004)9

program established in 2001. Government funding for the NNI itself was projected to be $886 million for 2005, roughly 3% of overall US government R&D expenditure [29]. Actually, there are several government-funded nanotechnology programs focused on oncology research in USA. Some of these include:

1. National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer: This program is part of the U.S. National Institutes of Health (NIH) and focuses on the development and application of nanotechnology to improve cancer diagnosis, treatment, and prevention.
2. Cancer Nanotechnology Program (CNTP): This program is funded by the National Cancer Institute in the US and focuses on the development of nanotechnology-based tools and therapies for cancer diagnosis, treatment, and prevention.
3. Cancer Prevention and Research Institute of Texas (CPRIT): This state-funded organization provides funding for cancer research in Texas, including nanotechnology-based approaches for cancer prevention and treatment.

The EU's Sixth Research Framework Program (FP6) has also included nanotechnologies and nano-sciences, knowledge-based multifunctional materials and new production processes and devices among its priorities, with total Community support of around 1 billion over 2002-2006. The program's main objectives were the development of a successful European nanotechnology industry, and the application of nanotechnologies in existing industrial sectors. Additional nanotechnology research is supported by other parts of FP6. The follow-up, FP7, calls for almost 5 billion to be spent on nanotechnology over 2007-2013 [30]. Afterwards, the European Union Horizon 2020 Program, which funds a range of research projects related to nanotechnology and oncology, including the development of nanomedicines and nanodiagnostics for cancer. In UK, we can find the National Cancer Research Institute (NCRI) Nanotechnology Initiative, which aims to support the development of nanotechnology-based approaches for cancer diagnosis and treatment.

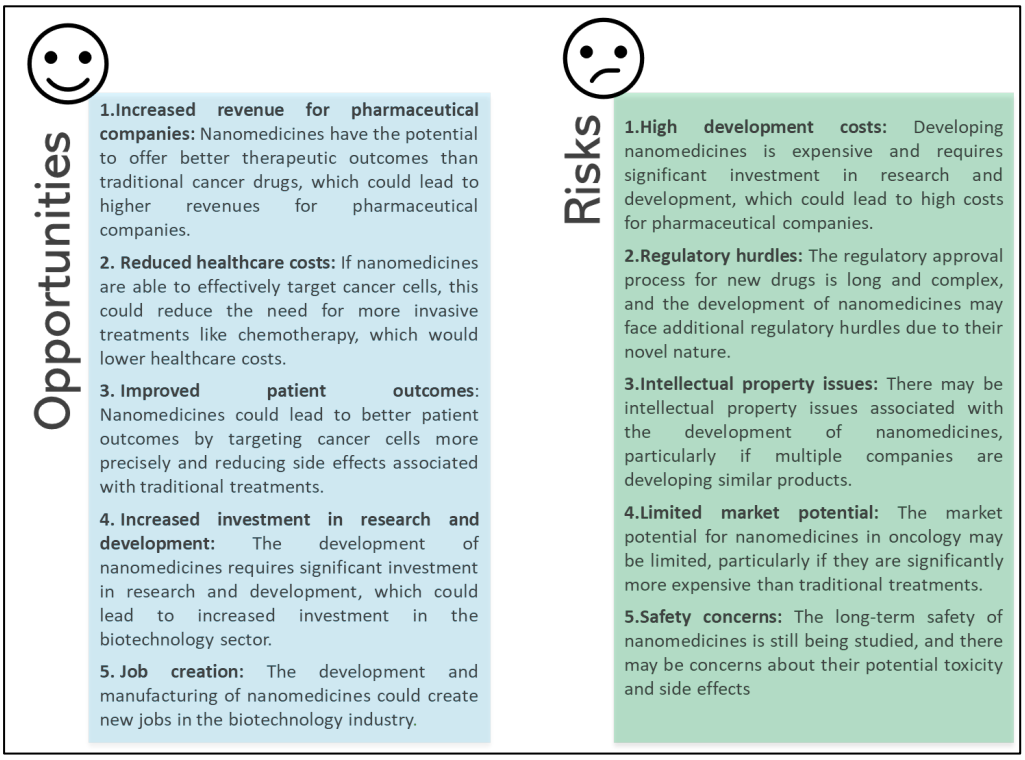
A fair assessment of the risks of any new technology must also consider positive contributions to increased safety. The basic innovations that come from nanotechnologies have the potential to contribute to human health in many ways. The potential of nanotechnologies regarding economic benefits, the potential to create jobs, wealth and well-being is very high. At the moment, public awareness about nanotechnology is limited. What happens over the next few years will determine how the public comes to view it. A transparent discussion of benefits and risks will help people reach a considered, balanced view. This will enable a greater public acceptance, which, in turn, will enable society as a whole to profit from these fundamental technological developments while, at the same time, the risks are kept under control.

Especially in the field of medicine there are quite a few technological developments that promise enhanced diagnostic possibilities, new ways to monitor patients, new ways to treat diseases like cancer and to reduce side effects. To give a few examples:

- Nanoparticles can be used as carriers for targeted drug delivery. Their ability to penetrate certain protective membranes in the body, such as the blood brain barrier, can be beneficial for many drugs. This could open the way for new drugs from active substances that have not been able to pass clinical trials due to less precise delivery mechanisms,
- Nanosensors and lab-on-a-chip-technologies will foster early recognition and identification of diseases and can be used for continuous monitoring of patients with chronic diseases,
- New therapeutic methods for the treatment of cancer with the help of nanoparticles are investigated.

[29] www.nano.gov
[30] http://www.cordis.lu/nanotechnology/

Figure. Economic opportunities and risks associated with the development of nanomedicines in oncology.



4.2.4. Underscoring the possible environmental impact due to nanoparticules manufacturing and application

For what concerns nanomedicine development and amelioration, it is necessary to verify that the production, synthesis, and diffusion of nanomaterials in the environment is limited and at the same time traceable. Nanoparticles and nanomaterials exhibit multiple properties with various applications and advantages, but at the same time, they have impacts and complications to the environment [31]. Many studies highlighted the possible ecotoxicity of nanomaterials despite the positive aspects, they should be considered a potential health risk declined in its various aspects [32]. Multiple aspects are involved in the estimation of environmental impact and prolonged release of nanomaterials such as nanoparticles, evaluating their life cycle, their environmental releasing capacity particularly on living beings.

The main classification to differentiate nanoparticulate, nanomaterials and nanopowders for their environmental impact is divided into three categories [33]:

1. Nanomaterials and nanoparticles accidentally and randomly formed that consist as a subsequent product derived from industrial or natural processes, such as combustions.
2. Nanomaterials produced with industrial and artificial methods designed using specific chemical and engineering procedures with determined properties and characteristics The big difference between accidentally formed nanomaterials in the environment is that these ones are intended to be formed with chosen sizes, specificities and composition.
3. Nanomaterials and nanoparticles derived from naturally products and biologics that can be found in living beings and nature (e.g., viruses, antibodies).

The potential risks and toxicities, determined by all those processes that control their release into the environment, the shipment between installations and zones or between organisms, due to the food chain, and the transformations, may arise by their ability to reach and invade the different environmental compartments that are available such as earth, water, air. This impact is directly correlated to the number of nanomaterials and nanopowders released to the biosphere [34].

The amount of released nanomaterial needs to be evaluated and quantified in this way it requires exhaustive research of its entire life cycle, starting from the nanomaterials production processes and ending with the recycling and disposal procedures, considering how they are incorporated into the final products and how they are utilized.

Nanoparticles can enter in the environmental life cycle with three possible emission scenarios: (i) release during production of raw material and nano-enabled products; (ii) release during use; and (iii) release after disposal of NP-containing products. NP emissions and residues can be either directly to the environment or indirectly via a technical system such as wastewater or landfills. The transformation processes of nanomaterials can be connected to the quantification of the released NPs that can be representative of the manufacturing stage.

The ability to predict the nanomaterials impact and applications for environmental purposes requires detailed comprehension of specific characteristics such as identification, physicochemical properties, environmental release, and their toxicity in living beings, and it plays a crucial role for this purpose to study the transformations and degradation of nanoparticles and nanomaterials in

[31] Hulla, J.E.; Sahu, S.C.; Hayes, A.W. Nanotechnology: History and future. Hum. Exp. Toxicol. 2015, 34, 1318-1321.

[32] Gottschalk, F.; Sun, T.; Nowack, B. Environmental concentrations of engineered nanomaterials: Review of modeling and analytical studies. Environ. Pollut. 2013, 181, 287-300.

[33] Gottschalk, F.; Sun, T.; Nowack, B. Environmental concentrations of engineered nanomaterials: Review of modeling and analytical studies. Environ. Pollut. 2013, 181, 287-300.

[34] Gottschalk, F.; Sun, T.; Nowack, B. Environmental concentrations of engineered nanomaterials: Review of modeling and analytical studies. Environ. Pollut. 2013, 181, 287-300.

order to have a real vision of what is really emitted to the biosphere. Key products containing nanomaterials are coatings, paints and pigments, catalytic additives, cosmetics, modified nanoparticulate materials that reach the environment early in the first stage of industrial applications.

Nanomaterials in the environment are susceptible to ageing processes such as chemical transformation, aggregation, and disaggregation. The interplay between these processes and the NP transport determines the fate and ultimately the ecotoxicological potential of nanoparticles [35].

Several analytical techniques can be exploited to determine and characterize metal-based nanoparticles in different environmental compartments. Concentration and size of metal-based NP such Au, Ag, Cu, TiO_2, in surface water and soils have been, for example, determined by single particle inductively coupled plasma mass spectrometry (sp-ICP-MS) or fractionation techniques in combination with light scattering and elemental detection. Structural information and information on particle size can be examined electron microscopy as a complementary technique. The NP surface chemistry including surface charge or functionalization controls NP fate [36]. Therefore, surface characterization methods are important to understand NP fate processes. For complex types of NP such as core shell structures a multi-element technique, such as sp-ICP-Time of Flight (ToF)-MS was developed and has recently been successfully applied to determine engineered nanoparticles' traces in the soil [37]. This approach can differentiate between engineered NP and natural NP by detecting impurities in natural NP which are not present in engineered NP. Such analyses will help to validate model outputs on environmental NP concentrations. NPs emissions during product employment can happen intentionally or accidentally and this paves the way to the origin or source and the number of nanoparticles released to the environment in intentional emissions are known and measurable and these parameters can only be estimated when it comes to accidental release caused by deterioration and alteration of products.

Thus, from fluid products, almost the entirety of nanoparticles is quickly released when the product is employed. However, from solid products, the contained nanomaterials are gradually released during the product employment (e.g., NPs used in pneumatic tires are released with attrition and friction). From spray products, the total emission of nanoparticles is immediate, while from suspensions, the total emission occurs in the first hours (e.g., cosmetics or sunscreens). Finally, NPs can remain stable for years in clothes and paint dyes [38].

Nanomaterials can interact with their abiotic surrounding, which influences their fate and ecotoxicological potential. The relevance of natural organic molecules attaching to NPs is a key-factor for prediction of environmental impact [39]. Dissolved organic matter (DOM) coats nanoparticles and their chemical processes are more effective with increasing hydrophobicity or aromaticity of the DOM, ultimately reducing their ecotoxicological potential based on reducing the availability of reactive surfaces. There are cases where artificial (poly-lactic-co-glycolic acid, polyvinylpyrrolidone, gum arabic or citrate) or natural organic matter coats specific nanomaterials and the release of potentially toxic ions into the surrounding environment or the NP bioavailability is reduced. It becomes apparent that soil properties influence the toxicity of NP to soil organisms [40].

[35] Mitrano, D.M.; Motellier, S.; Clavaguera, S.; Nowack, B. Review of nanomaterial aging and transformations through the life cycle of nano-enhanced products. Environ. Int. 2015, 77, 132-147.
[36] Mitrano, D.M.; Motellier, S.; Clavaguera, S.; Nowack, B. Review of nanomaterial aging and transformations through the life cycle of nano-enhanced products. Environ. Int. 2015, 77, 132-147.
[37] Mitrano, D.M.; Motellier, S.; Clavaguera, S.; Nowack, B. Review of nanomaterial aging and transformations through the life cycle of nano-enhanced products. Environ. Int. 2015, 77, 132-147.
[38] Gottschalk, F.; Nowack, B. The release of engineered nanomaterials to the environment. J. Environ. Monit. 2011, 13, 1145-1155
[39] Gottschalk, F.; Nowack, B. The release of engineered nanomaterials to the environment. J. Environ. Monit. 2011, 13, 1145-1155
[40] Gottschalk, F.; Nowack, B. The release of engineered nanomaterials to the environment. J. Environ. Monit. 2011, 13, 1145-1155

FINAL REMARKS

The vast majority of nanomedicines-approved in oncology until 2022 are still old/canonical drugs encapsulated into liposomes or micelles. In oncology, the nanomedicine field has shown that the vehicle "carrier" is new, the PK profile is new, while the mechanism of action that supports the antitumor activity is the same, it NPS are just creating a new PK/PD paradigm. NPs don't aim at primary objective to hit novel targets but aim to increase the specificity of the drug towards the tumor cell and increase the quantity of drug to be delivered to the tumor tissue. In this sense, expected clinical benefit is mostly based on the improvement of NPs PK profile, thus allowing a better therapeutic response and reduce side effects (improve the toxicity/efficacy ratio). Nanomedicine is a rapidly evolving field that offers promising solutions for cancer treatment and diagnosis. However, due to the unique properties of nanomaterials, there is a need for specialized regulations and guidelines to ensure their safety and efficacy. In this context, a unified set of global regulations for nanomedicines should be necessary to avoid regulatory inconsistencies and to facilitate their clinical translation. However, excessive regulation can affect the advancement of products in the marketplace, increasing costs to achieve regulatory approval and/or consuming a significant portion of the life of a patent.

Researchers should carefully follow these guidelines to ensure that their studies meet regulatory requirements and provide the necessary information to support the development of safe and effective nanomedicines for cancer treatment. In this very important to point out that regulatory authorities view nanomedicines on a case-by case basis. Early dialogue with regulatory agencies, knowledge and experience sharing, and the development of standardized methods for the characterization and evaluation of nanomaterials are essential to be constructive in our approach and focus on the gaps to be filled to accelerate nanomedicine translation into a more mature phase. Regulation of NPs is under the control of each country's regulatory authority. The regulations for nanoparticles in clinical trials are not specific for this type of drug and must follow the same rules as conventional drugs, and there are only certain specifications given in very specific guidelines by Agencies or governmental or academic initiatives.

The overview of achievements in nanomedicine during the last decade serves to reinforce our drive towards further expanding and growing the maturity of nanomedicine for healthcare and diagnostic, accelerating the pace of transformation of its great potential into bed-side medical breakthroughs.

Box 2. Major recommendations for the preclinical/clinical development of NPs in oncology
○ Use of realistic concentrations/doses and physiological conditions
○ Endotoxin-free samples
○ Selection of relevant animal species for Tox studies → canine models can display unusual sensitivities to NPs
○ "Classical" PK modelling can not correlate with PK behaviour of NPs
○ Prioritize methods with good in vitro / in vivo correlation
○ Prioritize the implementation of standardized bioanalytical methods and available standards
○ Analyze the method suitability for testing NPs
○ Personalized approach for the prediction of susceptibility/adverse effects in patients
○ Explore target engagement studies from early stages of the preclinical work
○ Evaluate possible mechanisms of action of the carrier and the drug triggering adverse effects
○ Integrated immunotoxicity testing approaches early in the program
○ Identify all of the potential risks that could impact your drug development program from early stages
○ Overall cost-effectiveness on nanomedicines respect to standard therapies
○ Analyse the external and internal economical / financial issues of your tecnology
○ Engage an early dialogue with the regulatory bodies from early stages → Preparation of the Target Product Profile

Annex 1. Roadmap of the translational strategy and regulatory aspects for Soft nanomedicines in oncology