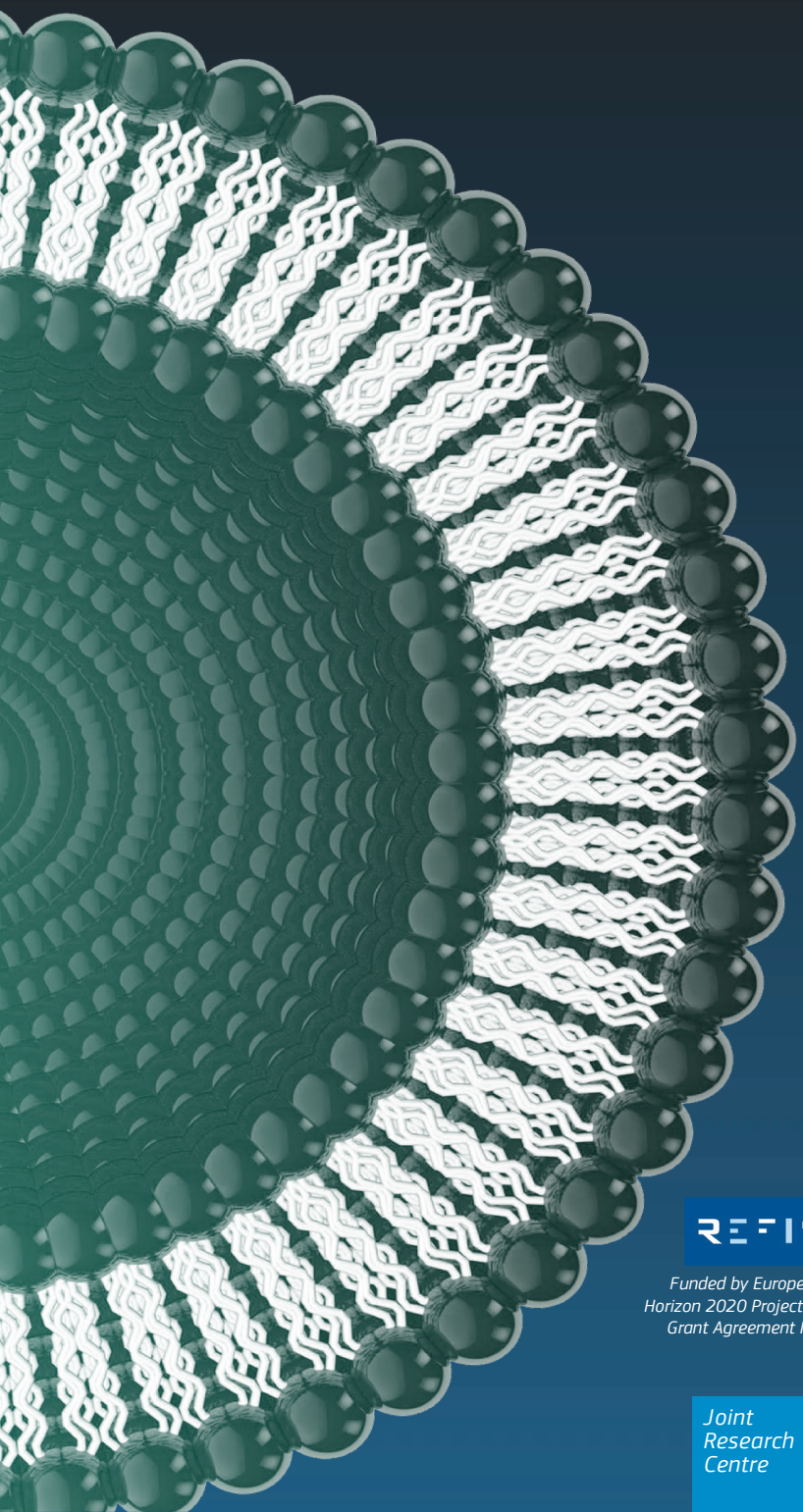
European Commission

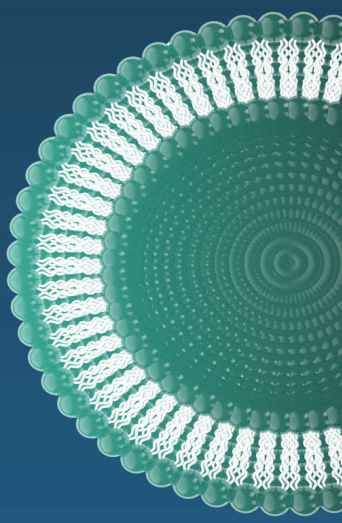
Anticipation of regulatory needs for nanotechnology-enabled health products

The REFINE White Paper

B. Halamoda-Kenzaoui, H. Box, M. van Elk, S. Gaitan, R. E. Geertsma, E. Gainza Lafuente, A. Owen, A. Del Pozo, M. Roesslein, S. Bremer-Hoffmann



2019



REFINE

Funded by European Union's Horizon 2020 Project REFINE under Grant Agreement No 761104

Joint Research Centre

EUR 29919 EN

This publication is a report by the Joint Research Centre (JRC), the European Commission's science and knowledge service. It aims to provide evidence-based scientific support to the European policymaking process. The scientific output expressed does not imply a policy position of the European Commission. Neither the European Commission nor any person acting on behalf of the Commission is responsible for the use that might be made of this publication. For information on the methodology and quality underlying the data used in this publication for which the source is neither Eurostat nor other Commission services, users should contact the referenced source. The designations employed and the presentation of material on the maps do not imply the expression of any opinion whatsoever on the part of the European Union concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Contact information

Susanne Bremer-Hoffmann
Via E. Fermi, 2749. TP 125, I-21027 Ispra (VA), Italy
susanne.bremer-hoffmann@ec.europa.eu

EU Science Hub

https://ec.europa.eu/jrc

Affiliation of authors

Blanka Halamoda-Kenzaoui
Susanne Bremer-Hoffmann
European Commission Joint Research Centre (JRC), Ispra, Italy

Helen Box
Andrew Owen
University of Liverpool, Liverpool, United Kingdom

Merel van Elk
Robert E. Geertsma
RIVM, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Angel Del Pozo
Eusebio Gainza Lafuente
Sandra Gaitan
BioPraxis Research, Miñano, Spain

Matthias Roesslein
EMPA, Swiss Federal Laboratories for Materials Science and Technology, St Gallen, Switzerland

JRC118190
EUR 29919 EN

PDF ISBN 978-92-76-12554-9 ISSN 1831-9424 doi:10.2760/596822
Print ISBN 978-92-76-12553-2 ISSN 1018-5593 doi:10.2760/599552

Luxembourg: Publications Office of the European Union, 2019

© European Union, 2019

The reuse policy of the European Commission is implemented by the Commission Decision 2011/833/EU of 12 December 2011 on the reuse of Commission documents (OJ L 330, 14.12.2011, p. 39). Except otherwise noted, the reuse of this document is authorised under the Creative Commons Attribution 4.0 International (CC BY 4.0) licence (https://creativecommons.org/licenses/by/4.0/). This means that reuse is allowed provided appropriate credit is given and any changes are indicated. For any use or reproduction of photos or other material that is not owned by the EU, permission must be sought directly from the copyright holders.

All content © European Union/ 2019, except: page 50 (© ASTM International), page 52 (© International Organisation for Standardisation)

Front page image: © clusterx / Adobe Stock

How to cite this report: Halamoda-Kenzaoui et al., *Anticipation of regulatory needs for nanotechnology-enabled health products*, EUR 29919 EN, Publications Office of the European Union, Luxembourg, 2019, ISBN 978-92-76-12554-9, doi:10.2760/596822, JRC118190

Anticipation of regulatory needs for nanotechnology-enabled health products

The REFINE White Paper

B. Halamoda-Kenzaoui, H. Box, M. van Elk, S. Gaitan, R. E. Geertsma, E. Gainza Lafuente, A. Owen, A. Del Pozo, M. Roesslein, S. Bremer-Hoffmann

JRC118190

2019

Funded by European Union's Horizon 2020 Project REFINE under Grant Agreement No 761104

Contents

Foreword

This white paper aims to launch a public debate on how the regulatory science in the field of nanotechnology-enabled health products can be further progressed (Box 1). The document summarizes and highlights the major regulatory needs that have been identified as a result of a number of communications with the regulatory community via questionnaires, workshops and bilateral discussions as well as a review of existing guidance, publications and other documents published by regulatory scientists. It also provides the context and underlying information related to challenges in regulating nanotechnology-enabled health products (Box 2).

Box 1. Definition of Regulatory Science (modified from the European Medicines Agency)

Regulatory science is defined as a range of scientific disciplines that are applied to the quality, safety and efficacy assessments of health products and that inform regulatory decision making throughout the lifecycle of a health product.

It encompasses basic and applied medicinal science and social sciences and contributes to the development of regulatory standards and tools.

Method developers, product inventors, academic groups, research funding organisations and regulators are considered as the major audience. The document intends to stimulate discussions related to necessary research activities within the community that can lead to scientific/technical solutions to address the challenges in regulating nanotechnology-enabled health products. Within the REFINE project, the presented analysis will provide guidance on the priorities to be addressed in the experimental work packages of the project. The annexes give an overview of the concerned regulatory and standardisation frameworks as well as on the involved key players, allowing the reader a better understanding of the context.

Box 2. Terms describing nanotechnology-enabled health products

A formal definition of nanomedicine does not exist and a variety of terms including *nanomedicines, nanotechnology-enabled health products, nanotechnology-based products, products containing nano(bio)materials* etc. are existing. For the purpose of this white paper the following terms are used:

“Nanomedicines”, describing products that are regulated as medicinal products

“Nanomedical devices”, describing products that are regulated as medical devices

“Nanotechnology-enabled health products” is an overarching term for both product classes.

Acknowledgements

The present report has been developed within the REFINE project: Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices, funded by European Union's Horizon 2020 under Grant Agreement no 761104 (Box 3).

The authors want to thank the REFINE consortium, in particular, Patrick Boisseau, Adriele Prina-Melo, Sven Even Borgos and Anne Weiler for constructive discussions and a critical review of the report, Valeria Amenta and Jacopo Piovesan for the additional support related to regulatory frameworks.

Many thanks to Heidi Olsson and Irina Defaranou for the technical and graphical assistance.

Box 3. REFINE consortium - Horizon 2020 project

Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices

http://refine-nanomed.com/

Timeline: 1 December 2017- 30 November 2021

13 partners

Grant no 761104

Objectives:

- Identification of the most pressing regulatory and scientific challenges for nano(bio)material-based medicinal products and medical devices
- Development of a Decision Support System for the regulatory assessment of product
- Development and validation of new analytical or experimental methods
- Addressing harmonization needs
- Bridging involved communities and synergies across the sectors

Executive Summary

The development of nanotechnology-based applications in the health sector offers innovative therapeutic and diagnostic opportunities to address medical needs. At the moment, no specific regulatory framework exists for nanotechnology-enabled health products but the current regulatory practice requires additional guidance in order to fully cover the particularities of such products. This white paper summarizes major challenges associated with regulating nanotechnology-enabled health products:

- Depending on their mode of action nanotechnology-enabled health products are regulated either as medicinal products or medical devices. However, due to the increased complexity of such products and their size-related properties, the **selection of the regulatory path** can become challenging since the primary mode of action might be difficult to determine.
- Due to the fast progress in the field and the lack of robust datasets, only **limited guidance on regulatory information** needs is currently available and the question remains whether the identified requirements in this initial guidance are sufficient for a reliable characterisation and assessment of all nanotechnology-enabled health products. In order to generate the required information on the quality, safety and efficacy of the products, **standardised testing methods** have to be available. However, many conventional methods may not be suitable or reliable for nanomaterial testing, for example due to the interference of nanomaterial with assay components. On the other hand, new state-of-the-art methods, instruments, approaches or tools have not yet sufficiently proven their reliability and relevance for the given purpose.
- As patents are expiring for certain nanomedicinal products, generic versions of the innovator products will require access to the market. Since the physicochemical characteristics can be very complex for nanotechnology-enabled products and achieved through sophisticated manufacturing processes, the current regulatory practice to assess the equivalence of the products may not be sufficient. More guidance is needed on how the **similarity of follow-on products** can be demonstrated and suitable standardised methods assessing the (bio) equivalence of such products need to be developed.
- The European definition of nanomaterials will apply for nanotechnology-enabled medical devices, outlining its classification and regulatory requirements. Yet, the i**mplementation of the definition and the classification rule**, introducing the need to define the internal exposure to nanomaterials, pose additional challenges.

The regulatory challenges highlighted in this white paper should guide the research projects and the involved communities willing to advance the regulatory science in the area of nanotechnology-enabled health products.

1 Introduction

Innovative nanotechnology-enabled health products are in the focus of an increasing number of research and development projects aiming to develop novel diagnostic and/or therapeutic concepts based on nanotechnology applications. However, such pioneering products can be very complex and might trigger regulatory concerns with regard to their quality and safety profile. In a communication to the European Parliament, the Council and the European Economic and Social Committee, the Commission confirmed already in 2008 that the Community legislative framework covers nanomaterials but the implementation of the legislation requires further elaborations e.g. when it comes to test methods and risk assessment methodologies.

For products such as medicinal products or medical devices that are subject to a pre-market control or pre-market notification, the assessment and management of risks in relation to nanomaterials are verified by competent authorities or Notified Bodies before placing them on the market (EC, 2008).

Nanotechnology-enabled health products follow current regulatory frameworks for medicinal products or medical devices.

Key reference:

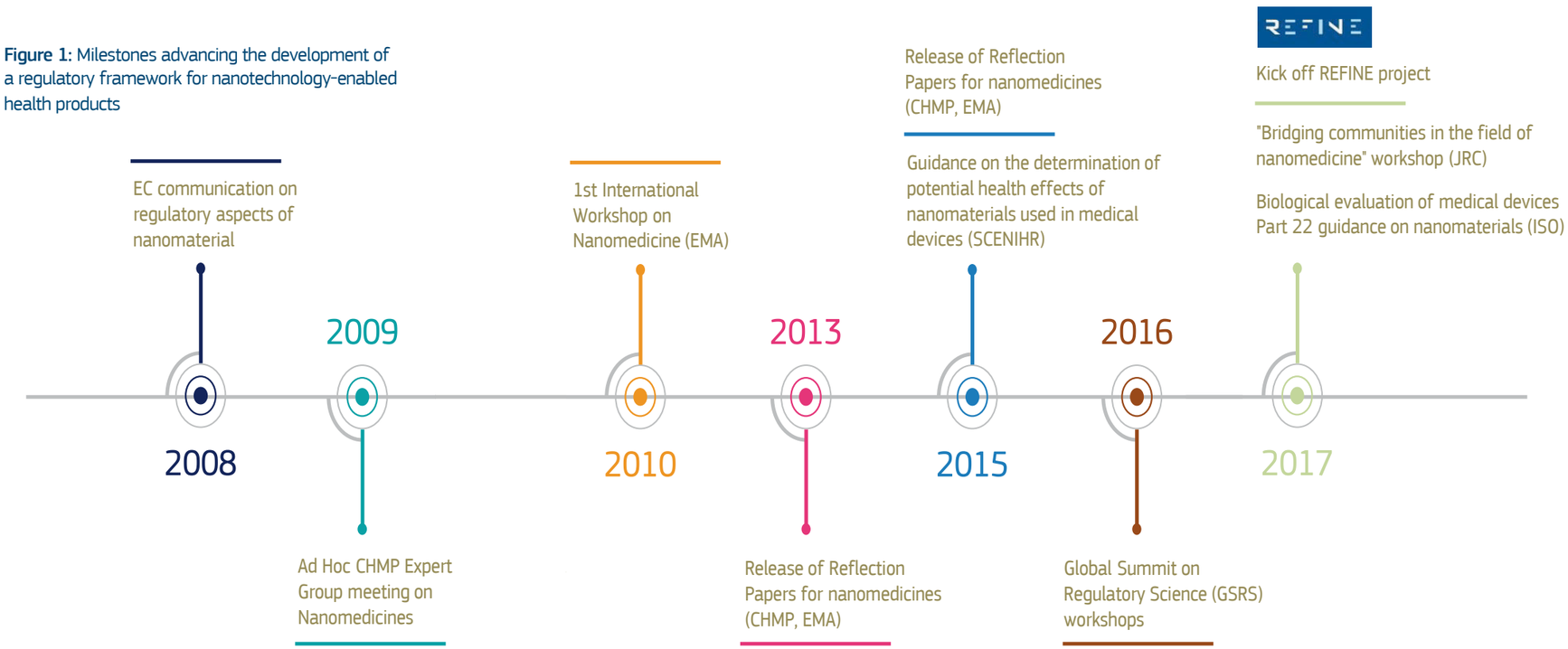
EC (2008). Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee- Regulatory aspects of Nanomaterials [SEC(2008) 2036]

In addition, a number of possibilities exist that can support the approval process of nanomedicines, such as the scientific advice procedures of national competent authorities and of the European Medicines Agency (EMA), the EU-Innovation Network (since 2015) and EMA's Innovation Task Force (ITF) (EMA, 2014). This task force brings together scientific and regulatory expertise to provide support on emerging therapeutic areas such as gene and cell therapy, regenerative and personalised medicines, pharmacogenomics, nanotechnology applied to medicines, biomarkers, and novel statistical models. In collaboration with regulatory authorities from US, Japan, Canada and Australia, the Committee for Medicinal Products for Human Use (CHMP) organised an expert meeting addressing specifically the development of nanomedicines. In 2010 EMA organised the 1st International Workshop on Nanomedicines aiming to share competencies and facilitate dialogue between regulators, academia, industry and patients (Figure 1).

Since then the CHMP Drafting Group on Nanomedicines released a number of Reflection Papers (EMA/CHMP, 2013a, 2013c, 2013b, 2015) related to different categories of nanotechnology based products. The Working Group on Nanomedicines of the International Pharmaceutical Regulators Programme (IPRP) discusses in biannual meetings upcoming regulatory challenges related to products containing materials in nanoscale.

The Global Coalition for Regulatory Science Research organised the Global Summit on Regulatory

Figure 1: Milestones advancing the development of a regulatory framework for nanotechnology-enabled health products



Key reference:

GSRS (2016). Nanotechnology Standards and Applications. Report.

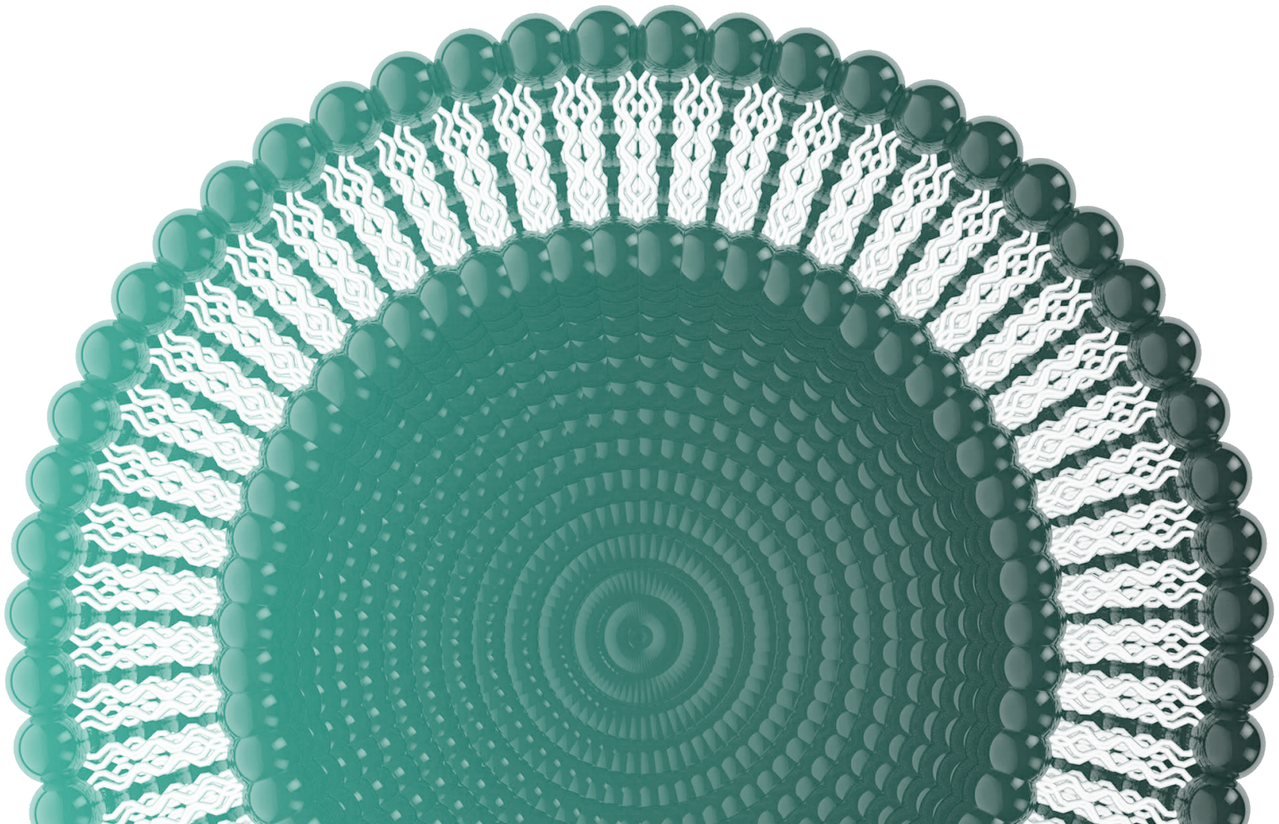
https://www.astm.org/COMMIT/GSRS16 Final Report.pdf

Science (GSRS) workshops in 2015 and 2016 dedicated to nanotechnology. In particular, participants of the workshop in 2016 identified the main standardisation needs including needs for nanotechnology-based biomedical applications (GSRS, 2016) which will be further updated in the GSRS 2019 on nanotechnology and nanoplastics.

In 2017, the EC Joint Research Centre organised a workshop on "Bridging communities in the field of nanomedicine" which gathered experts from research institutions, industry and regulatory bodies (Halamoda-Kenzaoui et al., 2019). The workshop resulted in a set of recommendations emphasising needs in immunological assessment of nanomedicines, quality attributes and standardisation. The recommendations of the experts were in particular relevant for the H2020 REFINE project which aims to advance the regulatory science in the field of nanomedicine.

For medical devices, the European Commission's Working Group on New and Emerging Technologies first flagged the need for special attention for nanotechnology-enabled medical devices in 2007. Since then, this working group has regularly provided input for regulatory (scientific) aspects related to this topic, especially during the development and implementation of the recently published new Medical Device Regulations. In 2015, the Scientific Committee for Emerging and Newly Identified Health Risks (SCENIHR) adopted their Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices (SCENIHR, 2015). Furthermore, in 2017 ISO published the ISO/TR 10993-22 Biological evaluation of medical devices, Part 22 Guidance on nanomaterials (ISO/TC 194, 2012).

The identified regulatory challenges, summarised in this report, now require a wider debate in the community on how the recognised challenges can be addressed. Tailor-made research strategies for the various product classes are necessary in order to fill identified knowledge gaps. In addition, necessary background information on the principles of the current regulatory frameworks of medicinal products and medical devices and a short description of the major players in the regulation of nanotechnology-enabled health products will support the reader in getting an overview on the highly complex regulatory frameworks at European and international level (see Annexes).



2 Regulatory and scientific challenges

2.1 Identification of regulatory information needs for nanotechnology-enabled products

Nanotechnology-enabled health products are regulated under the existing regulatory frameworks of medicinal products and medical devices but may require additional quality and safety assessments triggered by the unique characteristics of the nanomaterial. The identification and a general agreement on the regulatory requirements relevant for the assessment of a product is therefore a pre-requisite for a smooth approval process of a medicinal product or a medical device containing nanomaterial. Currently only limited guidance is available (Table 1) since robust datasets allowing a firm conclusion on information requirements needed for regulatory decisions are lacking. In addition, the increasing complexity and the huge variety of the next generation of nanomedicines and nanomedical devices (see Annex C) might even require more specific guidance.

This situation is leading to a high uncertainty for product developers and the lack of such guidance to prove compliance with the regulatory requirements may hamper the development and marketing of nanotechnology-enabled products. At the same time high quality data on safety, efficacy and quality for innovative products necessary for a better definition of regulatory requirements will not be generated (Figure 2). This vicious circle can only be broken in an iterative process that leads to the identification of physicochemical properties with clinical relevance.

Challenge 1:
Is the existing guidance sufficient for regulating the next generation of nano-enabled health products?

The identification and linkage of quality attributes to the safety and efficacy of the product is an important aspect within the quality-by-design approach (Bastogne, 2017).

Table 1: Regulatory documents specifically addressing nanotechnology-enabled health products*

Category of product addressed by the document	Initial guidance documents addressing nanotechnology-based medical products
All products including health care products	
Consumer products including medical products	• SCENIHR. Risk assessment of products of nanotechnologies; 2009
Products containing nano-silver	• SCENIHR. Nanosilver: safety, health and environmental effects and role in antimicrobial resistance; 2014
Medicinal products	
Medicinal products containing nanomaterials	• EMA Reflection paper on nanotechnology-based medicinal products for Human Use. EMEA/CHMP/79769/2006 • FDA/CDER. Guidance for Industry: Drug Products, including Biological Products, that Contain Nanomaterials: (2017) (draft guidance)
Liposomal products	• EMA/CHMP. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. London; 2013; EMA/CHMP/806058/2009/Rev.02. • FDA/CDER. Guidance for Industry. Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2018) • MHLW. Guideline for the development of liposome drug products (2016)
Block copolymer micelle products	• EMA/CHMP/ MHLW. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products. London; 2013; EMA/CHMP/13099/2013.
Iron based nano-colloidal products	• EMA/CHMP. Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product. London; 2015; EMA/CHMP/SWP/620008/2012.
Nucleic acid-loaded nanotechnology based drug products	• MHLW. Reflection paper on nucleic acids (siRNA)-loaded nanotechnology based drug products (2016)
Coated nanomedicine products	• EMA/CHMP. Reflection paper on surface coatings : general issues for consideration regarding parenteral administration of coated nanomedicine products. London; 2013; EMA/325027/2013.
Medical devices	
Medical devices containing nanomaterial	• SCENIHR. Opinion on the guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices; 2015 • ISO TR 10993-22: Biological Evaluation of medical devices – Part 22: Guidance on nanomaterials.

**EMA: European Medicines Agency, FDA: Food and Drug Administration (USA), MHLW: Ministry of Health, Labour and Welfare (Japan), SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks.*

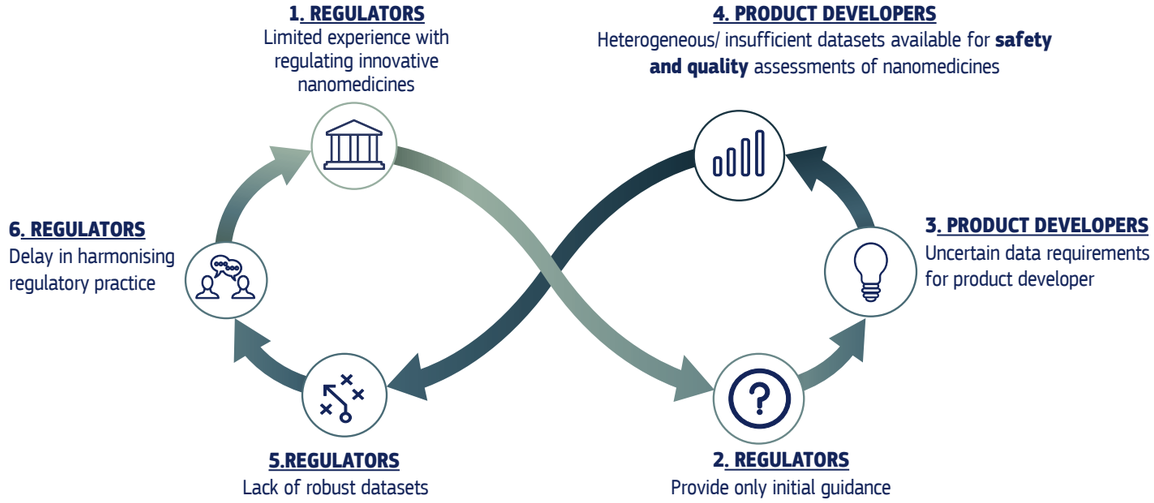


Figure 2: The vicious circle showing interdependence of availability of regulatory guidance and the generation of data related to the characterisation of nanomedicines

In order to get an overview on the current status of the regulatory requirements, the characterisation needs addressed in currently available regulatory documents (Table 1) were extracted and categorised (Table 2). Such exercise may help to identify standardisation needs, raise regulatory awareness on safety concerns reported in the scientific literature and recognise harmonisation opportunities between the regions.

Table 2: Quality and nonclinical information needs relevant for all categories of nanotechnology-based medical products

Physicochemical parameters (if applicable)	Biological characterisation
▪ Detailed description of all components ▪ Chemical composition ▪ Chemical structure ▪ Structural attributes that relate to function (e.g., lamellarity, core-shell structure ▪ Crystal form ▪ Impurities ▪ Particle size and size distribution ▪ Shape and morphology ▪ Surface properties (e.g., surface area, surface charge, chemical reactivity, ligands, hydrophobicity, and roughness); ▪ Particle concentration ▪ Porosity (if it relates to a function) ▪ Degradation path, kinetics and degradation products ▪ Stability, both physical and chemical ▪ In-use stability studies at clinically relevant concentrations and under relevant storage conditions **Drug delivery systems** • Drug loading efficiency • Assay and distribution of any active ingredient associated with the nanomaterial and free in solution (e.g., surface bound or liposome encapsulated versus free active ingredient) • Physical state of the active substance • In vitro drug substance /siRNA release rate in physiologically/clinically relevant media	**Bioburden control** ▪ Sterility and endotoxin levels **Pharmacokinetic parameters** ▪ Stability in blood and serum ▪ Biological fate ▪ Accumulation issues ▪ ADME ▪ Plasma Protein Binding (formation of PC over time) ▪ In vivo degradation/solubilisation rate and place of degradation **Pharmacodynamical parameters** ▪ Biocompatibility with blood and serum ▪ Additional risks associated with the exposure route: topical application: skin penetration, distribution in lymph nodes, subcutaneous administration: sensitisation to allergens, inhalation: effect on the respiratory system, iv: hemocompatibility ▪ In vitro uptake and cytotoxicity of nanomaterials to the phagocytes ▪ Interaction with enzymes e.g. Cytochrome P450 ▪ Immunogenicity (ICH S8) ▪ Complement activation

based on FDA and EMA regulatory guidance (EMA/CHMP, 2006; FDA, 2017) or included in at least three different guidance documents addressing specific categories of nanomedicines; ADME: Absorption/distribution/metabolism/elimination profile, PC: protein corona

The characterisation needs addressed in regulatory documents (Table 2) are not claimed to be compulsory information to provide by product developers but should rather be considered as suggested endpoints for quality and safety assessments. In addition, the specific guidance for nanotechnology-enabled products should be seen in connection with the applicable ICH guidelines or CEN/ISO standards, for medicinal products and medical devices, respectively.

Among the extracted physicochemical parameters, a major part refers to the nanoscale properties specific for or associated with the materials under investigation. Some of these are size, shape, morphology, chemical structure and structural attributes, surface properties and coating description. Others, refer to standard regulatory requirements for medicinal products, but were specifically addressed in the guidance documents to emphasize the risk of potential concerns when dealing with nanomaterials. For instance, stability, although required for all medicinal products, can be particularly complex to assess in case of nanomaterials, as several physical and chemical processes need to be considered (e.g. aggregation and agglomeration or separation, degradation, drug leakage or release etc.). Sterility and endotoxin levels are specifically mentioned in the FDA guidance (FDA, 2017), since

the contamination of nanoparticulate products with the endotoxin is a frequently encountered issue, requiring specifically adapted detection methods. Interestingly, binding of the plasma protein and the formation of the protein corona should be investigated for nanoparticle-based products that will enter the blood circulation. Identification of the major proteins that will bind to NP surface and the amount of proteins that will bind over time can give some insights into the circulation time, biodistribution and risk of the immunological effects. Immunotoxicity is not automatically tested for all medicinal products but may be triggered as a result of standard toxicity studies if showing alterations in routinely tested parameters that may indicate the risk of adverse immune effects.

However, these studies, performed in animal models, may not always be predictive for effects in humans, due to inter-species variability of the immune system, and may not always detect more subtle immune reactions induced frequently by nanomaterials (Giannakou, Park, et al., 2016; Halamoda-Kenzaoui & Bremer-Hoffmann, 2018).

Therefore the evaluation of potential immunogenicity issues was addressed in several documents addressing nanotechnology-enabled products requiring suitable methods to provide the requested information.

In addition to the already identified characterisation requirements, there is a need to monitor the information that becomes available through research activities or (pre)clinical studies pointing to any kind of safety concern that require regulatory awareness.

Additional understandings on the correlation of physicochemical properties and the biological effects of products require particular attention.

In frame of REFINE an attempt will be made to screen the scientific literature using advanced tools in order to identify eventual safety issues of nanotechnology-based products, that are not covered yet in the existing regulatory guidance (Table 1).

2.1.1 Example of regulatory and scientific issues: Pharmacokinetics of nanotechnology-enabled medicinal products

Nanomedicines to date have demonstrated an enhanced bioavailability, efficient penetration into the lymphatic system, persistence in the circulation, increased binding capacity to biomolecules and an improved penetration into target tissues. These effects are a result of significant differences in the absorption, distribution, metabolism and elimination (ADME) profiles of nanomaterials in comparison to small-molecule counterparts. Several nano-formulations have been developed for the purpose of increasing efficacy and reducing adverse events by altering the pharmacokinetic properties of an already licensed drug. In particular, increased oral bioavailability or prolonged terminal half-life for orally

Key reference:
Giannakou et al (2016). A comparison of immunotoxic effects of nanomedicinal products with regulatory immunotoxicity testing requirements. Int. J. Nanomedicine 11, 2935–2952.

administered nanomedicines have been successful in reducing dosage, frequency of administration and toxicity (Irby, Du, & Li, 2017; Maranhão, Vital, Tavoni, & Graziani, 2017). Efforts to develop these characteristics are likely to provide novel platforms for the treatment of specific diseases that have previously been a challenge using conventional small-molecule drugs. In particular, they will provide tools for the implementation of personalised medicine (Theek, Rizzo, Ehling, Kiessling, & Lammers, 2014) and will be instrumental for treating orphan diseases. However, the differences in pharmacokinetics or distribution can give way to persistent and elevated drug concentrations in plasma or tissues and may present additional safety concerns related to nano-specific effects (Wu & Tang, 2018).

European guidelines for the preclinical and clinical assessment of pharmacokinetics for medicinal products have been developed before nanomedicines became more common. An expanded dataset might be needed to address the specificities of the pharmacokinetic profiles of nanomedicines. As the medical applications of nanotechnology utilise innovations from multiple disciplines, this requires cross-citation between regulatory guidance documents developed for different sectors. There has been some uncertainty on the robustness of preclinical datasets necessary to provide adequate pharmacokinetic information for regulatory approval from different bodies.

Also, the current Food and Drug Administration (FDA) final guidance documents, other than those that are product-specific, do not provide a comprehensive review of what is required in terms of the pharmacokinetic evaluation of nanomedicines. However, the recently released draft set of guidelines provide some nano-specific considerations for ADME. This document takes into consideration the potentially harmful clinical adverse events, such as accumulation in off-target sites that are not necessary to consider for small-molecule compounds. A panel of preclinical pharmacokinetic assessments for the delineation of safety and toxicity depending on their route of administration is presented that may aid nanomedicine researchers in structuring their preclinical evaluation of these compounds to accelerate submission (FDA, 2017).

2.2 The selection of the regulatory framework

The unique opportunities of nanomaterials used in health products might lead to challenges when it comes to the selection of the regulatory path. The classification of a product into a medicinal product or a medical device depends on the primary mode of action (Box 4) but the decision is not always easy.

Such products are called borderline products and require special attention by the regulatory community. Since the regulatory pathways for market authorization of medicinal products versus medical devices are substantially different, it is very important for product developer to get into contact with the regulatory authority as early as possible. Regulatory agencies have set up several mechanisms that provide scientific advice and support innovation in health care e.g. EMA's Innovation Task Force, the scientific advice procedure offered by EMA and the national competent authorities as well as EMA's PRIME scheme for priority medicines targeting unmet medical needs[1]. A Borderline and Classification Expert Group is established and coordinated by the European Commission in order to discuss and assist in the classification of the borderline products.

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, light etc. (Figure 3). 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 have to follow primarily the regulatory framework of medicinal products or medical devices, while the component with the ancillary action has to comply with the other framework.

Challenge 2:
Can we always clearly define the primary mode of action of nano-enabled health products?

Box 4. Regulatory definitions

Medicinal Products	Medical Devices
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. (Directive 2001/83/EC)	any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. The following products shall also be deemed to be medical devices: — devices for the control or support of conception; — products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point. (Medical Device Regulation (EU) 2017/745)

[1] *EMA PRIME: Priority medicines: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines*

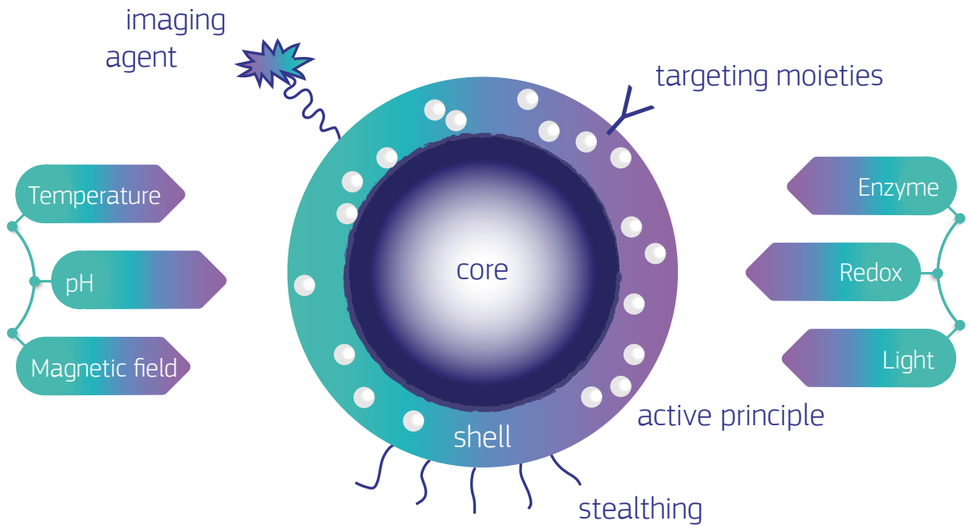


Figure 3: Theoretical example of a borderline product

Hybrid structure combining physical stimuli with pharmacologically active substances require special attention and may need the navigation between several directives and frameworks

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.

In addition, the increasingly overserved convergence of nanotechnology with other key enabling technologies is leading to highly innovative products combining e.g. a medicinal product with a device. Such combination products can pose now additional challenges in their governance. Depending on their primary mode of action they have to be compliant with the regulatory frameworks of medicinal products or medical devices. Recently, EMA has released a draft guideline on the quality requirements for drug-device combinations providing more information on such complex products (EMA, 2019).

2.3 The European definition of nanomaterial and its implication for nanotechnology-enabled health products

In 2011 the European Commission published a recommendation on the definition of a nanomaterial, which is not mandatory, however Member States, the EC agencies and economic operators are invited to use it (EU, 2011).

Whereas the recommendation has no implications for nanomedicines since the EMA has developed its own working definition, the medical device regulation has almost entirely adopted the EU definition of nanomaterials (Box 5) with two differences:

1. the definition in the medical device regulation does not contain the possibility to adjust the 50% number size distribution threshold for specific cases

2. nanomaterials cannot be identified via the specific surface area.

Challenge 3:
How to implement classification rule 19 and the EC definition of nanomaterial as used in medical devices regulation?

Box 5. Nanomaterial and other related definitions in the medical device regulation (EU 2017/745)

(18) 'nanomaterial' means a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm;

Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials;

(19) 'particle', for the purposes of the definition of nanomaterial in point (18), means a minute piece of matter with defined physical boundaries;

(20) 'agglomerate', for the purposes of the definition of nanomaterial in point (18), means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components;

(21) 'aggregate', for the purposes of the definition of nanomaterial in point (18), means a particle comprising of strongly bound or fused particles;

Key reference:
EU (2011). Commission Reccomendation of 18 October 2011 on the definition of nanomaterial. Off. J. Eur. Union L275, 338–40.

However, there is an ongoing confusion how to interpret the various terms used in the EC definition as well as in the medical device regulation, in particular in combination with classification rule 19 which is referring to medical devices containing nanomaterial.

In addition, technical and scientific discussions on how to measure the different parameters mentioned in the legislative texts are still ongoing. An overview of concepts and terms, which might help solve the confusion, has recently been published (Rauscher et al., 2019).

2.4 Challenges in assessment of follow-on products (“nanosimilars”)

Since patents protecting some of the first marketed nanomedicines have expired or are close to expiry, new opportunities for the development of generic nanomedicines also known as “follow-on nanomedicines” or “nanosimilars” occur. The term “nanosimilars” has been derived from the term “biosimilars” which faced comparable challenges to demonstrate their similarity and bioequivalence to the innovator products. Currently no specific regulatory pathway is designed for nanosimilars and the level of comparability with the innovator product has to be demonstrated following the legislative/regulatory path of generic products. The legislation states in its Article 10 (1) of Directive 2001/83/EC: *... the applicant is not required to provide the results of preclinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorized under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Union...* (EC, 2001)

A generic medicinal product is defined as a medicinal product that has:

- the same qualitative and quantitative composition in active substance(s) as the reference product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.(EC, 2001)

In order to support product developers the EMA has released a Reflection Paper (RP) for liposomal formulations which also includes indications on regulatory needs for nanosimilars. The RP concluded that differences in liposome characteristics might not be detectable by conventional bioequivalence testing alone, and additional studies are needed. A regulatory approach similar to the one established for similar biological medicinal products (biosimilars) that requires the stepwise comparability approach for quality, safety and efficacy between the reference product and the biosimilar was considered, highlighting that differences between the product claimed to be similar (follow-on) and the authorised reference medicinal product with regard to manufacturing process steps and formulation may substantially modify efficacy/safety. The design of clinical studies is crucial for nanosimilars.

A better understanding is necessary whether clinical trials can be limited to pharmacokinetics (PK)

Key reference:

Rauscher et al (2019). An overview of concepts and terms used in the European Commission’s definition of nanomaterial. JRC Sci. Policy Rep. EUR 29647.

studies or whether a more detailed and more expensive clinical trial is needed, including a full set of clinical efficacy and/or safety studies (Mühlebach, Borchard, & Yildiz, 2015).

This recommendation is driven by observations that apparently similar structures, with similar PK profiles have shown different safety and efficacy outcomes. The establishment of therapeutic equivalence, based on the existing methods and tools, is challenging.

Clinically significant quality attributes need to be identified with a known and understood influence on disposition, safety and/or efficacy of the product.

Such knowledge is decisive to define the need for additional clinical research, and the design of clinical trials. If molecular and functional similarities are not fully demonstrated, reduced requirements for clinical studies cannot be implemented. This may imply the need for Phase I-IIA clinical trials, including healthy volunteers (safety) but also patients (efficacy).

Some examples demonstrating the regulatory challenge already exist: an application for a generic version (Lipodox) of Caelyx was not accepted by the EMA. The assessment report pointed out that “there are outstanding major nonclinical and clinical objections which preclude a recommendation for marketing authorisation at the present time". However, the compound was accepted as generic version of Doxil by the US FDA.

Challenge 4:
Is the existing regulatory framework for assessing the equivalence of generic products sufficient for follow-on nanomedicinal products?

Key reference:

Mühlebach et al (2015). Regulatory challenges and approaches to characterize nanomedicines and their follow-on similars. Nanomedicine 10, 659–674.

2.5 Methods addressing regulatory information needs

Appropriate characterization as well as the assessment of quality, safety and efficacy of nanotechnology-enabled health products requires the availability of reliable methods that can address identified regulatory needs. Due to the specific properties of the materials at the nano-scale level, not all conventional testing methods might provide reliable results (Box 6).

A recent review (Halamoda-Kenzaoui et al., 2018) provided an overview on the existing standardised methods in the nanotechnology area that could be of relevance for nanotechnology-enabled health products.

For the characterisation of nanoscale-specific physicochemical parameters such as particle size, shape, surface charge, several methods were developed and standardised by the ISO Technical Committee on Nanotechnologies. In addition, other standardised methods, mainly from the material science area, might be suitable to measure additional chemical and physical parameters. However, some particular functionalities of nanotechnology-enabled delivery systems such as drug loading, drug release from the carrier, surface functionalisation or targeting capabilities need very specific, sophisticated methods, that are still under development. In addition, depending on the material properties, dispersion characteristics and method principles, the applicability of methods to a given nanomaterial can vary. Choosing inadequate methods can lead to unprecise or unreliable results requiring regulatory attention.

Another aspect is the interaction of medical products with biological fluids, where the presence of proteins and biomolecules can strongly impact the stability of dispersions and provoke immunological reactions. Therefore, the characterisation should ideally be performed not only in pristine state, but also in a biological medium of relevance.

Several challenges persist also regarding the toxicological evaluation of nanomaterials. Due to their specific physicochemical characteristics such as optical properties they can interfere with biological assays and their detection systems, e.g. increasing/decreasing the optical density or adsorbing proteins on their surface (Guadagnini et al., 2015).

In addition, particle contamination with bacterial endotoxin is very challenging to measure and can highly impact results of toxicological studies (Giannakou, Geertsma, et al., 2016). Therefore, existing methods should be reviewed for their suitability to test nanomaterials and, where necessary, suitable, adapted for nanomaterials, methods need to be developed (Giannakou et al., 2019).

Currently, only a few *in vitro* standardised methods are specifically developed for nanotechnology-enabled health products (Table 3).

Most of them were published by ASTM International Committee E56 on Nanotechnology (see Annex A.10). However, ASTM standards are not legally binding in the European frameworks for nanotechnology-enabled health products.

Guidance related to the biological evaluation of medical devices, containing nanomaterials has been released in 2017 by ISO, as a part of ISO/TR 10993 multi-part guidance. Additional *in vitro*

Key reference:

Halamoda-Kenzaoui et al (2018). Mapping of the available standards against the regulatory needs for nanomedicines. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. e1531.

Challenge 5:
Can existing standards provide the information needed for regulatory decision making?

Box 6. Methodological challenges:

- Limited reliability for heterogeneous materials
- Material dependent applicability
- Measurements in biological environment
- Nanomaterial interference with assay components

Table 3: Overview on available standardized methods and guidance addressing biological evaluation of nanotechnology-enabled medical applications

Test method/guidance	Endpoint	Reference	Comments
Biological evaluation of medical devices- Part 22 Guidance on nanomaterials	Physicochemical and biological evaluation	ISO/TR 10993-22:2017	Intended for medical devices; probably partly useful for medicinal products as well
Determination of silver nanoparticles potency by release of muramic acid from Staphylococcus aureus	Antimicrobial efficacy	ISO/TS 16550:2014	Not only medicinal products but also textile products, other consumer products
Standard Test Method for Analysis of Hemolytic Properties of Nanoparticles	Biocompatibility, hemolytic properties	ASTM E2524 - 08(2013)	Similar to Practice F756 but modified to accommodate nanoparticulate materials
Standard Test Method for Evaluation of Cytotoxicity of Nanoparticulate Materials in Porcine Kidney Cells and Human Hepatocarcinoma Cells	Cytotoxicity assessment using MTT and LDH assays	ASTM E2526 - 08(2013)	
Standard Test Method for Evaluation of the Effect of Nanoparticulate Materials on the Formation of Mouse Granulocyte-Macrophage Colonies	Immunological response	ASTM E2525 - 08(2013)	

toxicological test methods for nanomaterials were published by ISO (Halamoda-Kenzaoui et al., 2018). Nevertheless, their applicability to health products is not fully understood.

Several characterisation methods suitable for nanomedicinal product assessments have been developed by laboratories such as the NCI-NCL[2] and the EUNCL[3]. A large fraction of these protocols is probably also relevant for the assessment of nanomaterials released from medical devices. Such expert laboratories support the translation of nanotechnology-enabled applications providing technical know-how and scientific expertise necessary for a detailed physicochemical characterisation, as well as *in vitro* and *in vivo* safety testing of candidate products. In addition to providing the services of the characterization of nanomedicines, they actively develop and optimise protocols relevant for nanomedicinal product assessments. As such those protocols provide a good starting point for the standardisation of methods (see Annex B4).

Finally, one of the main REFINE's objectives is to develop and standardise those methods that are relevant for the regulatory assessment of nanotechnology-enabled health products. For this reason current regulatory requirements will be identified and available methods will be compiled allowing gap analysis. REFINE will focus on methods for the immunotoxicity assessment having potential to detect adverse effects of nanomedicines early in the preclinical stage.

The development of new methods claiming to characterise reliably nanomaterial is constantly increasing. However, an independent verification of the reliability and relevance of such methods for regulatory purposes is often not possible in a short time-frame. Another hurdle is the availability of reference materials (RMs) relevant for nanotechnology-based health products. Primary purpose of such RMs is to provide the confidence in measurements ensuring the quality of results. Lack of widely available, fit for purpose RMs can be an obstacle for the development of reliable methods for nanomaterial characterisation.

2.6 Terminology

A harmonised terminology and established definitions are essential in any field of science and technology for a mutual understanding among different communities of stakeholders including scientific experts and regulators.

An emerging technology, such as nanomedicine, is usually stimulating the generation of new terms, concepts and definitions, which may be used ambiguously by various stakeholders having diverse interests and coming from different backgrounds.

Currently a formal definition of nanomedicines does not exist. EMA has established a working definition for nanomedicines, based on following considerations (Pita, Ehmann, & Papaluca, 2016):

- Purposely designed systems for clinical applications
- At least one component at nano-scale size that should not exceed 1000 nm
- Resulting in definable specific properties and characteristics

[2] *Nanotechnology Characterization Laboratory (NCI-NCL): https://nanolab.cancer.gov/*
[3] *European Nanomedicine Characterisation Laboratory (EUNCL): http://www.euncl.eu/*

Box 7. Consideration of the US FDA on the application of nanotechnology (FDA, 2014a)

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);

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, even if these dimensions fall outside the nanoscale range, up to 1 µm (1000 nm).

Also the FDA has not established a regulatory definition of nanomaterials. In the guidance "Considering whether an FDA-Regulated Product involves the Application of Nanotechnology" (FDA, 2014a) it recommends to consider specific questions which are applied broadly to all FDA-regulated products including medicinal products and medical devices (Box 7).

The Nanomedicines Working Group of the International Pharmaceutical Regulators Programme (IPRP) (see Annex A.4) acknowledged the relevance of terminology for the harmonisation activities and included this topic in its work programme. The European Commission's Joint Research Centre (JRC) is a member of the working group and took up the challenge to compile and analyse nanomedicine-related terms and definitions used in regulatory context (Quiros-Pesudo et al., 2018). For this purpose websites of 13 regulatory authorities, all members of the IPRP Nanomedicines WG (see Figure 4) and international clinical trials registries have been crawled and text-mining tools were used to extract relevant information.

Challenge 6:
Do we need to harmonise the terminology between the involved stakeholders?

Key reference:

Pita et al (2016). Nanomedicines in the EU—Regulatory Overview. AAPS J. 18, 1576–1582.

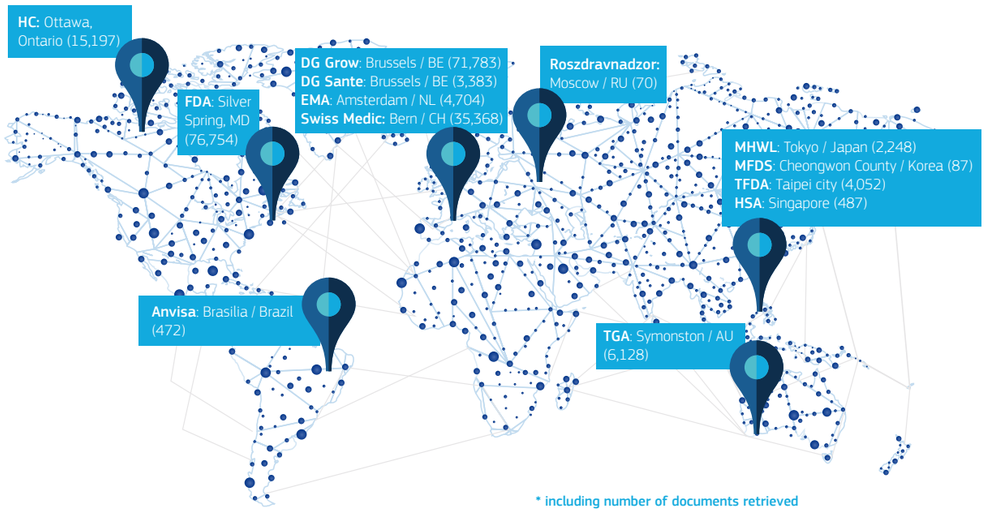


Figure 4: Location of 13 regulatory authorities included in terminology study

The study demonstrated differences in number and type of terms used by regulatory authorities to describe nanomaterials used in health products. General terms such as nanomedicine(s), nanotechnology, nanomaterial, nanoscale and nanostructure were used by nearly every agency, in particular by EMA and FDA (Figure 5).

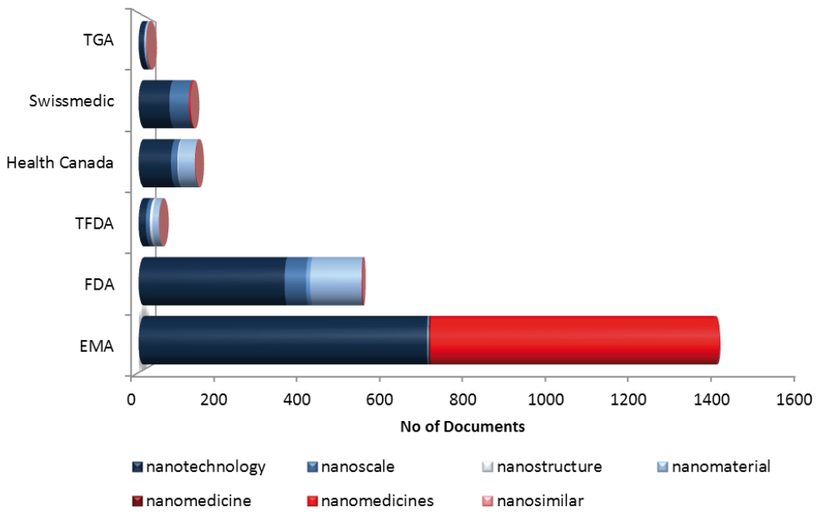


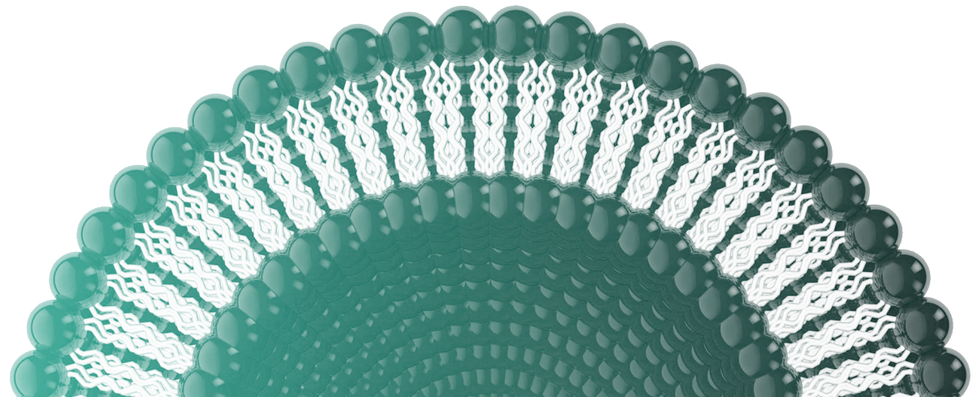
Figure 5: Frequency of general terms in selected regulatory authorities' websites

The analysis showed the existence of very specific terms used uniquely by certain regulatory authorities. Interestingly, the term "nanomedicines" was almost exclusively found in EMA's documents to describe the application of nanotechnology in medicinal products, whereas other expressions, often related to terms like "nanomaterial" or "nanotechnology", were preferred by several regulatory bodies (Table 4).

The term "nanosimilar" was a specific term extracted from EMA's website to describe the concept of nanomedicines that are claimed to be similar to a reference nanomedicine. Altogether, the JRC report showed geographical and sectorial differences in frequency and type of nanomedicine-related terms and compiled a set of most frequently employed terms to enable discussion and understanding among the stakeholders. However, further harmonisation of terminology between the regulatory authorities is needed to support marketing of nanotechnology-based products.

Table 4: Compilation of terms used by selected regulatory authorities (Quiros-Pesudo et al., 2018)

Source	Main terms used to describe the application of nanotechnology to medical products
Australia **Therapeutic Goods Administration (TGA)**	Nanomedicines Therapeutic products containing nanomaterials Nanotechnology-based drug products
European Union **European Medicines Agency**	Nanomedicines Medicinal products containing nanoparticles Nanomedicinal products Nanotechnology-based medicinal products
Japan **Pharmaceuticals and Medical Devices Agency, Japan (PMDA)**	Nanotechnology-based medicines Nanodrug delivery systems, Nanomedical devices Nanopharmaceuticals Nanosized drug
United States **US Food and Drug Administration (FDA)**	Nano-sized drug products Nanotechnology products Products that involve the application of nanotechnology Drug Products that Contain Nanomaterials
Canada **Government of Canada TERMIUM Plus®21**	Nanodrug



2.7 Harmonisation of regulatory practice

There is a general agreement in the international regulatory community that nanotechnology-enabled health products can be regulated according to existing legislative/regulatory frameworks. However, such frameworks might substantially vary in different geographical regions. Currently regulatory authorities are collaborating and seeking for the harmonization of regulatory practices in order to support the mutual acceptance of data in various regions.

EMA (EU), FDA (USA) and MHLW (Japan) have released specific guidance on data requirements for certain classes of nanotechnology-based products (Table 1). The Taiwan authority (TFDA) has added annexes to their current regulations for Registration of Medicinal Products related to: i) liposomal new drugs, ii) liposomal generic drugs. Health Canada provides some general considerations for nanomaterial-based products on their website and strongly recommends product developers to request a pre-submission meeting with the regulatory authority to discuss in details the information requirements that may be needed for the product seeking for regulatory approval.

The recommendation on the early dialogue with the regulators is shared by the majority of regulatory agencies world-wide. Annex B.3 provides a short comparison of the regulatory frameworks in EU and US (Table B.2) that illustrates the various steps to be taken when seeking access to different markets (Marques et al., 2019). 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.

The Nanomedicines Working Group of the IPRP has been created as a platform to further facilitate an exchange of information and regulatory cooperation of the pharmaceutical regulatory bodies in different regions. A survey addressing the regulatory experience with liposomal products was performed among the members of the WG. The respondents have confirmed that a number of liposomal products have been approved under the current regulatory framework suggesting that no specific regulation is needed for this class of products. The most critical issues related to the regulation of liposomal products included:

- Approaches for regulation of follow on/generic liposomal medicines
- Correlation of *in vitro* and *in vivo* data
- Limitations of analytical methodology
- Identification of quality attributes that are critical during the manufacturing process
- Selection of reference standards

The most common challenge, as recognised by respondents, is related to the regulation of generic liposomal products and, in particular, the comparability of data obtained with different measurement methods. Sharing of the submission data among the regulators could be of benefit in the identification of critical quality attributes. Developing a common definition of liposomes that would be acceptable for all regulators was suggested by the survey coordinators (IPRP, 2018b).

Challenge 7:
How can we harmonise regulatory practices at international level?

3 Conclusions and perspectives

Nanotechnology-enabled health products have no particular legislative or regulatory framework and follow the current regulation of medicinal products or medical devices. 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 (Figure 6). The present white paper highlights the major regulatory needs that require the development of additional guidance, methods and approaches in order to accommodate the particularities of nanotechnology-enabled products.

1. Unclear information needs for innovative nanomedicines

Innovative products often challenge the regulatory framework since robust datasets guiding the regulatory needs for quality, safety and efficacy evaluation are lacking. A close monitoring of the scientific literature by e.g. using automated text mining tools, and in depth analysis of safety issues reported in real world databases, as well as a better balance on the need for information and a proactive pharmacovigilance/post-market surveillance coupled with a rapid reporting on adverse effects could be ways forward to break the vicious cycle of regulating innovative products.

2. Suitability and availability of methods, tools and approaches

The increasing complexity of innovative nanomedicinal products and their sophisticated manufacturing processes often require additional physicochemical characterisation steps or safety assessment in order to ensure the quality and safety of the products. However, existing characterisation methods are often not suitable to assess different types of nanomedicines or are not sufficiently standardised to be employed for the generation of the regulatory information. For certain specific areas no suitable methods are available at all, generating methodological gaps. Development and standardisation of lacking methods has been taken on board by the REFINE project and aims to benefit from the joint efforts of the method developers and standardisation communities. In addition, transferability of methods and standards from other sectors should be considered.

3. Follow-on nanomedicines

Follow-on nanomedicines or "nanosimilars" are receiving more and more attention since patents of reference products are expiring but their complexity often does not allow a full comparability of physicochemical characteristics demonstrating the equivalence of the products. This group of products might require a new initiative that develops a regulatory framework allowing a demonstration of the

equivalence of the innovator products and the nanosimilars. The framework for assessing biosimilars could serve here as an example.

4. Borderline and combination products

The regulatory path for nanotechnology-enabled products is not easy to determine when their primary mode of action is not obvious or when they are composed of two or more components that are regulated under various frameworks.

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 increasingly complex innovative health products.

5. Harmonisation

As any other highly innovative product class also nanomedicines challenge the regulatory systems worldwide and the development of harmonised governance ensuring quick access to therapeutic solutions for medical needs should be considered. Under the umbrella of the International Pharmaceutical Regulators Programme representatives of competent authorities, the Nanomedicines Working Group has taken up the challenge. The group meets regularly in order to exchange the non-confidential information regarding the regulation of nanomedicines, organise related workshops and training, support the efforts of the harmonisation of the terminology, and discuss methodologies used during the development and evaluation of nanomedicines.

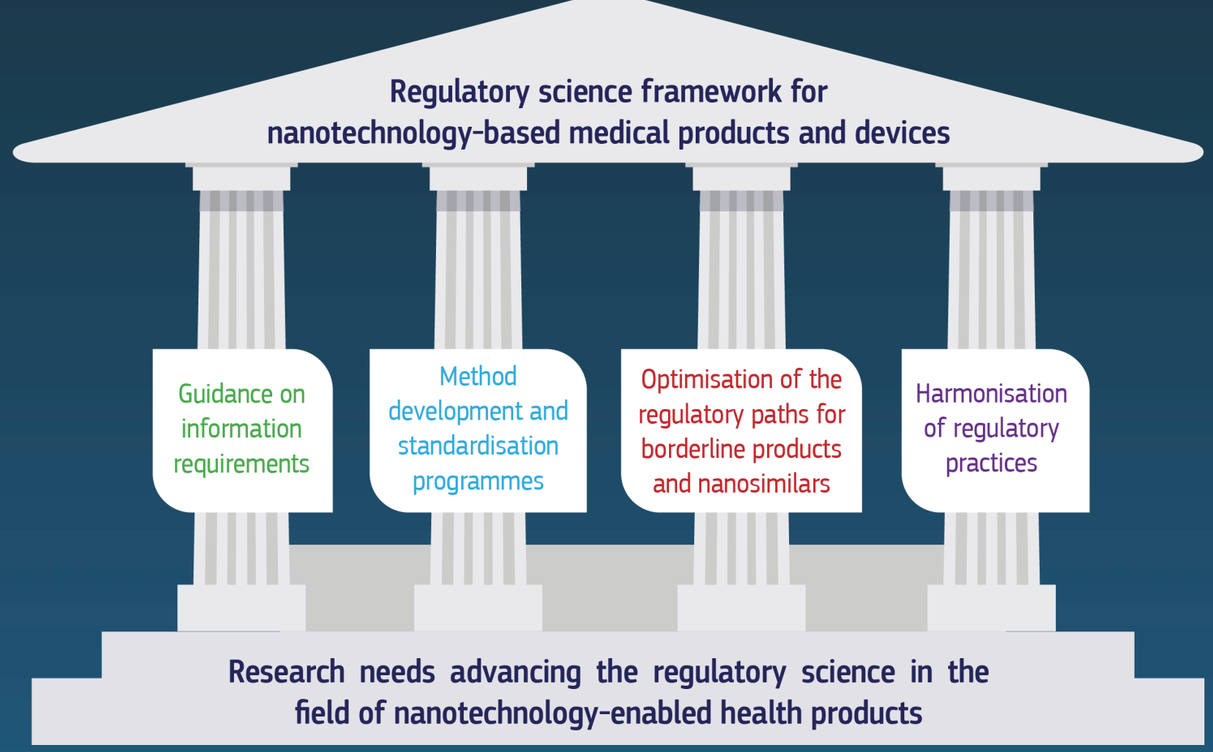


Figure 6: Research needs for the advancement of the regulatory science in nanomedicine

References

Bastogne, T. (2017). Quality-by-design of nanopharmaceuticals – a state of the art. Nanomedicine: Nanotechnology, Biology, and Medicine, 13(7), 2151–2157. https://doi.org/10.1016/j.nano.2017.05.014

CAMD Implementation Taskforce. (2018). Medical Devices Regulation/In-vitro Diagnostics Regulation (MDR/IVDR) Roadmap. Retrieved from https://www.camd-europe.eu/wp-content/uploads/2018/05/NEWS_171107_MDR-IVDR_RoadMap_v1.3-1.pdf

Caster, J. M., Patel, A. N., Zhang, T., & Wang, A. (2017, January). Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. https://doi.org/10.1002/wnan.1416

Council of the European Communities. (1976). Council Directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC). Official Journal of the European Communities.

EC. (2001). Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Union, L311, 67–128.

EC. (2008). Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee - Regulatory aspects of nanomaterials [SEC(2008) 2036] - Safety and health at work - EU-OSHA.

EMA/CHMP. (2006). Reflection paper on nanotechnology-based medicinal products for Human Use. EMEA/CHMP/79769/2006.

EMA/CHMP. (2011). Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009 Rev. https://doi.org/EMEA/CHMP/EWP/192217/2009

EMA/CHMP. (2013a). Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products., EMA/CHMP/13099/2013.

EMA/CHMP. (2013b). Reflection paper on surface coatings : general issues for consideration regarding parenteral administration of coated nanomedicine products., EMA/325027/2013.

EMA/CHMP. (2013c). Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, EMA/CHMP/806058/2009/Rev.02.

EMA/CHMP. (2014). Qualification of novel methodologies for drug development: guidance to applicants, EMA/CHMP/SAWP/72894/2008.

EMA/CHMP. (2015). Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product, EMA/CHMP/SWP/620008/2012.

EMA/CHMP. (2016). Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches, EMA/CHMP/C.

EMA/CHMP. (2018). Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation, 44(July), 16.

EMA. (1995). ICH Topic Q2 (R1) Validation of analitical procedures: Text and Methodology, 2, CPMP/ICH/381/95. https://doi.org/10.1136/bmj.333.7574.873-a

EMA. (2014). Mandate of the EMA Innovation Task Force (ITF), EMA/484400/2014.

EMA. (2019). Guideline on the quality requirements for drug-device combinations.

EU. (2011). Commission Reccomendation of 18 October 2011 on the definition of nanomaterial. Official Journal of the European Union, L275, 338–340.

EU. (2017). Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE. Official Journal of the European Union, L117, 1–175. https://eur-lex.europa.eu/eli/reg/2017/745/oj

FDA. (2013). Guidance for Industry Bioanalytical Method Validation - Draft 2013, (September). https://doi.org/http://www.labcompliance.de/documents/FDA/FDA-Others/Laboratory/f-507-bioanalytical-4252fnl.pdf

FDA. (2014a). Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, (February), 1–14. https://doi.org/10.1089/blr.2011.9814

FDA. (2014b). Guidance for Industry: Qualification Process for Drug Development Tools, (January), 35.

FDA. (2015). Analytical procedures and methods validation for drugs and biologics, (July). https://doi.org/http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

FDA. (2016). Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry, (December).

FDA. (2017). Drug Products, Including Biological Products, that Contain Nanomaterials. Guidance for Industry.

Geertsma, R. E., Park, M. V. D. Z., Puts, C. F., Roszek, B., van der Stijl, R., & de Jong, W. H. (2015). Nanotechnologies in medical devices. RIVM Report 2015-0149.

Giannakou, C., Park, M. V. D. Z., De Jong, W. H., Van Loveren, H., Vandebriel, R. J., & Geertsma, R. E. (2016). A comparison of immunotoxic effects of nanomedicinal products with regulatory immunotoxicity testing requirements. International Journal of Nanomedicine, 11, 2935–2952. https://doi.org/10.2147/IJN.S102385

Giannakou, C., Geertsma, R. E., De Jong, W. H., van Loveren, H., Vandebriel, R. J., & Park, M. V. (2016). Immunotoxicity testing of nanomedicinal products: possible pitfalls in endotoxin determination. Current Bionanotechnology, 2(2), 95–102. https://doi.org/10.2174/2213529402666160601115600

Giannakou, C., Aimonen, K., Bloois, L. Van, Catalán, J., Geertsma, R. E., Gremmer, E. R., … Park, M. V. D. Z. (2019). Sensitive method for endotoxin determination in nanomedicinal product samples. Nanomedicine, 14(10), 1231–1246. https://doi.org/10.2217/nnm-2018-0339

GSRS. (2016). Nanotechnology Standards and Applications. Report. Retrieved from https://www.astm.org/COMMIT/GSRS16 Final Report.pdf

Guadagnini, R., Halamoda Kenzaoui, B., Cartwright, L., Pojana, G., Magdolenova, Z., Bilanicova, D., … Boland, S. (2015). Toxicity screenings of nanomaterials: challenges due to interference with assay processes and components of classic in vitro tests. Nanotoxicology, 9(Suppl 1), 13–24.

Hafner, A., Lovrić, J., Lakǒ, G. P., & Pepić, I. (2014). Nanotherapeutics in the EU: An overview on current state and future directions. International Journal of Nanomedicine. https://doi.org/10.2147/IJN.S55359

Halamoda-Kenzaoui, B., Baconnier, S., Bastogne, T., Bazile, D., Boisseau, P., Borchard, G., … Bremer-Hoffmann, S. (2019). Bridging communities in the field of nanomedicine. Regulatory Toxicology and Pharmacology, 106, 187–196. https://doi.org/10.1016/J.YRTPH.2019.04.011

Halamoda-Kenzaoui, B., & Bremer-Hoffmann, S. (2018). Main trends of immune effects triggered by

nanomedicines in preclinical studies. International Journal of Nanomedicine, 13, 5419–5431.

Halamoda-Kenzaoui, B., Holzwarth, U., Roebben, G., Bogni, A., & Bremer-Hoffmann, S. (2018). Mapping of the available standards against the regulatory needs for nanomedicines. Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology, e1531. https://doi.org/10.1002/wnan.1531

Hartung, T., Bremer, S., Casati, S., Coecke, S., Corvi, R., Fortaner, S., … Zuang, V. (2004). A modular approach to the ECVAM principles on test validity. ATLA Alternatives to Laboratory Animals, 32(5), 467–472.

ICCVAM. (1997). Validation and Regulatory Acceptance of Toxicological Test Methods. A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods.

ICH. (2002). Guideline M4 : The Common Technical Document. https://doi.org/https://www.ich.org/products/ctd.html

ICH. (2005). Validation of Analytical Procedures : Text and Methodology. Q2 (R1). https://doi.org/http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

IPRP. (2018a). Mandate Document: Nanomedicines Working Group (NWG). Retrieved from http://development.iprp.backend.dev6.penceo.com/sites/default/files/2018-12/IPRP_NWG_MandateDocument_2018_1005.pdf

IPRP. (2018b). Mapping and exchange of requirements for nanomedicine / nanotechnology in drug product class specific guidance (liposomal formulation). Retrieved from http://development.iprp.backend.dev6.penceo.com/sites/default/files/2018-09/IPRF_NWG_LiposomalResults_HC_Survey_Summary_Final.pdf

Irby, D., Du, C., & Li, F. (2017). Lipid–Drug Conjugate for Enhancing Drug Delivery. Molecular Pharmaceutics, 14(5), 1325–1338. https://doi.org/10.1021/acs.molpharmaceut.6b01027

ISO/TC 194. (2012). Biological evaluation of medical devices- Part 22: Guidance on nanomaterials. ISO /TR 10993-22., 2012.

Maranhão, R. C., Vital, C. G., Tavoni, T. M., & Graziani, S. R. (2017). Clinical experience with drug delivery systems as tools to decrease the toxicity of anticancer chemotherapeutic agents. Expert Opinion on Drug Delivery, 14(10), 1217–1226. https://doi.org/10.1080/17425247.2017.1276560

Marques, M. R. C., Choo, Q., Ashtikar, M., Rocha, T. C., Bremer-Hoffmann, S., & Wacker, M. G. (2019). Nanomedicines - Tiny particles and big challenges. Advanced Drug Delivery Reviews. https://doi.org/10.1016/J.ADDR.2019.06.003

Mühlebach, S., Borchard, G., & Yildiz, S. (2015). Regulatory challenges and approaches to characterize nanomedicines and their follow-on similars. Nanomedicine, 10(4), 659–674. https://doi.org/10.2217/nnm.14.189

Noorlander, C. W., Kooi, M. W., Oomen, A. G., Park, M. V., Vandebriel, R. J., Geertsma, R. E., & Agnes, G. (2015). Horizon scan of nanomedicinal products. Nanomedicine (London, England), 10, 1–10. https://doi.org/10.2217/nnm.15.21

OECD. (2005). Guidance Document on the validation and international acceptance of new or updated test methods for hasard assessment. ENV/JM/MONO(2005)14.

Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. del P., Acosta-Torres, L. S., … Shin, H.-S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology, 16(1), 71. https://doi.org/10.1186/s12951-018-0392-8

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

Quiros-Pesudo, L., Balahur-Dobrescu, A., Gottardo, S., Rasmussen, K., Wagner, G., Joanny, G., & Bremer, S. (2018). Mapping nanomedicine terminology in the regulatory landscape. JRC Technical Report, EUR 29291. https://doi.org/10.2760/753829 (online)

Rauscher, H., Roebben, G., Mech, A., Gibson, P., Kestens, V., Linsinger, T., & Riego-Sintes, J. (2019). An overview of concepts and terms used in the European Commission's definition of nanomaterial. JRC Science for Policy Report, EUR 29647.

Ritter, N., Advant, S. J., Hennessey, J., Simmerman, H., Mcentire, J., Mire-sluis, A., & Joneckis, C. (2003). What is test method qualification?

Robinson, K. J., Corrie, S. R., Thurecht, K. J., Islam, J., & Bobo, D. (2016). Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. Pharmaceutical Research, 33(10), 2373–2387. https://doi.org/10.1007/s11095-016-1958-5

SCENIHR. (2015). Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices. Final Opinion, (January), 1–77. https://doi.org/10.2772/41391

Theek, B., Rizzo, L. Y., Ehling, J., Kiessling, F., & Lammers, T. (2014). The theranostic path to personalized nanomedicine. Clinical and Translational Imaging, 2(1), 67–76. https://doi.org/10.1007/s40336-014-0051-5

Wu, T., & Tang, M. (2018). Review of the effects of manufactured nanoparticles on mammalian target organs. Journal of Applied Toxicology, 38(1), 25–40. https://doi.org/10.1002/jat.3499

Abbreviations

ADME	Absorption/Distribution/Metabolism/Elimination
ANDA	Abbreviated New Drug Application (FDA)
API	Active Pharmaceutical Ingredient
CAs	Competent Authorities
CAMD	Competent Authorities for Medical Devices
CEN	European Committee for Standardization
CHMP	Committee for Medicinal Products for Human Use (EMA)
CQAs	Critical Quality Attributes
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-Human studies
GSRS	Global Summit on Regulatory Science

ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILS	Inter-laboratory study
IMDRF	International Medical Device Regulators Forum
IND	Investigational New Drug (FDA)
IPRP	International Pharmaceutical Regulators Programme
ISO	International Organization for Standardization
ITF	Innovation Task Force (EMA)
JRC	Joint Research Centre
MAA	Marketing Authorisation Application
MDDT	Medical Device Development Tools
MDR	Medical Device Regulation
MHLW	Ministry of Health, Labour and Welfare (Japan)
NBs	Notified Bodies
NBMs	Nano(bio)materials
NPs	Nanoparticles
NDA	New Drug Application (FDA)
OECD	Organisation for Economic Co-operation and Development
PBPK	Physiologically-based pharmacokinetic
PC	Protein corona
Ph. Eur	European Pharmacopoeia
Ph. Int.	The International Pharmacopoeia
RMs	Reference materials
RP	Reflection Paper
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
USP	US Pharmacopeia
WG	Working Group
WHO	World Health Organization

List of boxes

List of figures

List of tables

ANNEX A. Major organisations involved in the regulation of nanotechnology-enabled health products

A.1 European Medicines Agency (EMA)

The European Medicinal Agency (EMA) is a decentralised body of the European Union (EU), acting as interface between the national competent authorities rather than a centralised organisation. The EMA and the Community procedures of authorization of medicines for human and veterinary use have been established with the Regulation EEC2309/93. In accordance to Article 57 of the EC Regulation 726/2004, EMA shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.

EMA's main responsibility is the protection and promotion of public and animal health by:

- Mobilizing the scientific resources available within the EU to guarantee a high qualitative level evaluation of medicinal products and to give advices on research and development programs;
- Defining efficient and transparent procedures for the marketing authorisation of both human and veterinary medicines;
- Checking upon the safety of medicines for human and veterinary use through a pharmacovigilance network.

EMA is structured in seven different scientific Committees:

- CHMP Committee for Medicinal Products for Human Use
- VMP Committee for Medicinal Products for Veterinary Use
- COMP Committee for Orphan Medicinal Products
- HMPC Committee on Herbal Medicinal Products
- PDCO Paediatric Committee
- CAT Committee for Advanced Therapies
- PRAC Pharmacovigilance Risk Assessment Committee

The EMA Committee responsible for the evaluation and registration of new medicines is the CHMP. It is composed of 58 members: one member and an alternate nominated by each of the 27 Member States, one member and an alternate nominated by Iceland and by Norway; up to five co-opted members, chosen among experts nominated by Member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area and a chair, elected by CHMP members.

A.2 Notified Bodies (NBs)

Notified bodies are organisations designated by EU countries to assess the conformity of certain products before being placed on the market. These bodies carry out tasks related to conformity assessment procedures set out in the applicable legislation. The competence of NBs is periodically controlled by the competent authority and the European Commission publishes a list of notified bodies. Medical devices are assessed by NBs. The manufacturers are free to choose the notified body which will carry out the assessment procedure of their products. The issue of an EC certificate of conformity by an NB allows the product to be commercialized in all EU Member States. The NB-MED group allows NBs to share experience and exchange views, drafts technical recommendations and creates consensus on matters relating to conformity assessment and advises the European Commission at its request[4].

A.3 Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is a US federal agency which has the role of protecting and promoting public health through the control and supervision of foods, drugs, vaccines, medical products and cosmetics. The agency is part of the United States Department of Health and Human Services which is one of the US federal executive departments.

Overall, the main roles of the FDA are:

- Promoting health by reviewing research and approving new products
- Ensure that food and drugs are safe and properly labelled
- Working with other nations/organization to avoid worldwide public health threats
- Regulation of the manufacturing, marketing and distribution of products which can affect public health

The agency is led by the Office of the Commissioner which reports directly to the secretary of Health and Human Services. The Office of the Commissioner hosts the chief scientist of the FDA who is responsible for the FDA Nanotechnology Task Force[5]. The mission of this Task Force is to identify and recommend ways to address any knowledge or policy gaps related to nanotechnology. All FDA offices and centres are contributing to the Nanotechnology Task Force which provides the overall coordination of FDA's nanotechnology regulatory science research efforts such as the Nanotechnology Core Facilities, training and professional development and opportunities for research excellence.

[4]EC DG Grow –NB-MED group: https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/dialogue-interested-parties_en
[5]FDA Nanotechnology Task Force: https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force

The Office of the Commissioner oversees four directorates:

— Office of Foods and Veterinary Medicine
— Office of Medical Products and Tobacco
— Office of Global Regulatory Operations and Policy (GO)
— Office of Operations

The first two directorates are responsible for the assessment of the safety of specific products while the other two supports their efforts by drafting guidance, legislation and other general services. More specific, the main mission of the Office of Foods and Veterinary Medicine is to promote public health by preventing foodborne illness, fostering good nutrition and improving safety and efficacy of animal health products. The Office of Medical Products and Tobacco provides advice to the Commissioner on all medical product related issues. Finally, the Office of Global Regulatory Operations and Policy and the Office of Operations, are in charge of supporting all the services across the FDA. The Office of Operations is also coordinating emergency involving FDA regulated products, such as post-marketing adverse events. The GO provides strategic leadership and oversight of the projects carried within the FDA, but also takes care of the global collaboration and the global data-sharing with other related agencies.

The Office of Medical Products and Tobacco provides coordination across the centers for drugs, biologics, medical devices, and tobacco products and oversees the agency's special medical programs. Following centers are a part of this directorate:

- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Tobacco Products (CTP)
- Office of Special Medical Programs
- Oncology Center of Excellence

Several of those centers have regulatory science research programmes related to nanotechnology. Research projects cover novel detection technologies for pathogen, effects on carbon nanomaterials on blood cells (CBER), limitations of current test methods assessing quality and safety of nanomaterials (CDER), biocompatibility of nanomaterials (CDRH) etc.

A.4 EC DG GROW and the Medical Devices Coordination Group (MDCG)

The European Commission's Directorate-General Internal Market, Industry, Entrepreneurship and SMEs (DG GROW) is responsible for coordinating the regulatory framework for medical devices.

The Medical Devices Coordination Group (MDCG) is an expert group and was established by Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices. Its members are experts representing competent authorities of the EU countries. The MDCG advises and assists the Commission and EU countries in the implementation of both Regulations.

The MDCG has 11 working groups[6]:

1. Notified Bodies Oversight (NBO)
2. Standards
3. Clinical investigation and evaluation (CIE)
4. Post-market surveillance and vigilance (PMSV)
5. Market surveillance
6. Borderline and classification (B&C)
7. New technologies
8. EUDAMED
9. Unique device identification (UDI)
10. International matters
11. In vitro diagnostic medical devices (IVD)

A.5 Competent authorities for medical devices (CAMD)

All European Competent Authorities (CAs) work together in the Competent Authorities for Medical Devices (CAMD) network to promote patient safety through the consistent development and application of the medical devices regulatory system[7]. The CAMD facilitates the implementation and the enforcement of the MDR and IVDR. It also provides training and exchange of best practices. The CAMD meetings are also networking events and may tackle medical device issues beyond the MDR and IVDR. As part of the implementation phase a consistent and harmonised approach in interpretation of the regulations across the network is fundamental to ensure consistency in the application of these regulations. The objective is to implement an effective, robust, predictable and secure regulatory system and ensuring better protection for public health in the medical devices sector. In order to achieve this, the CAMD developed a Roadmap (CAMD Implementation Taskforce, 2018).

A.6 International Pharmaceutical Regulators Programme (IPRP)

"The purpose of IPRP is to create an environment for its regulatory members and observers to exchange information on issues of mutual interest, enable cooperation and promote convergence of regulatory approaches for pharmaceutical medicinal products for human use"[8].

IPRP has been created as a platform to facilitate an exchange of information and regulatory cooperation of the pharmaceutical regulatory bodies in different regions. Its mission is to coordinate international efforts related to regulation of medicines, and to harmonise guidelines for pharmaceuticals for

[6] *EC DG Grow- MDCG Group: https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/dialogue-interested-parties_en*
[7] *CAMD: https://www.camd-europe.eu/*
[8] *IPRP: https://www.iprp.global/home*

human use. Several Working Groups (WGs) dealing with specific topics have been created within this regulatory platform. They include:

— Biosimilars WG
— Bioequivalence for Generics WG
— Cell Therapy WG
— Gene Therapy WG
— Information Sharing for Generics WG
— Quality for Generics WG
— Identification of Medicinal Products WG
— Nanomedicines WG

IPRP Working Group on Nanomedicines was established in 2009 to discuss regulatory challenges related to products containing materials in nanoscale (IPRP, 2018a). The objectives of the IPRP Nanomedicines WG include:

- Sharing of the non- confidential information and regulatory harmonization in the area of nanomedicines / nanomaterial in drug products and borderline and combination products
- Regulatory cooperation with other related international bodies, particularly in specific topics of nanomedicines / nanomaterial in drug products
- Collaboration in the area of training/experience sharing among international regulators
- Promotion of potential consensus finding on standards

Discussions among participating entities are organised in the form of 2-3 face-to-face meetings/ teleconferences per year. The specific topics of interest recently taken on board by IPRP Nanomedicines WG include:

o Terminology, definitions and classifications
o Regulation of generic nanomedicines ("nanosimilars")
o Critical quality attributes for nanotechnology-enabled medicinal products

Up to now the information exchange was practised among the members in terms of definitions and classification of nanomedicines, existence of specific guidance documents, legislation applicable to nanomedicines as well as workshops and training activities.

A.7 International Medical Device Regulators Forum (IMDRF)

IMDRF is a forum of medical devices regulators established to discuss the future directions of regulatory harmonisation in the field of medical devices. It was established in October 2011 and gathers currently the medical devices regulatory authorities from: Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and United States of America.

Several Working Groups operate on specific activities identified in the IMDRF work plan. IMDRF Management Committee provides guidance on strategies, policies, directions, membership and activities of the Forum and oversees the activities of WGs. Topics including: the improvement of the

quality of the international standards, good regulatory review practice and guidance for Personalized Medical Devices are among current activities of the WGs.

A.8 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Hence their main focus is the drafting of international harmonized guidelines, e.g. related to the requirements for the validation of an analytical procedure. The guidelines describe the general aim of a given analytical procedure and provide a set of acceptance criteria. However, they do not describe any method as a technical standard in any detail. The ICH guidelines often build the foundation of guidelines release by national regulatory bodies, which means that the basic principles are internationally harmonised. The harmonisation is achieved through development of the Guidelines on Quality, Safety and Efficacy as well as Multidisciplinary aspects of pharmaceutical product evaluation (Table A.1). The activities are divided into four categories:

1) Formal ICH Procedure, for new topics of the harmonisation
2) Q&A Procedure
3) Revision Procedure and
4) Maintenance Procedure,

The last three are related to the revision and maintenance of the existent ICH Guidelines. Furthermore, as a part of the harmonisation process and the implementation of developed guidelines, the training activities related to different technical/scientific aspects are organised for ICH members and managed by the ICH Training Subcommittee. The ICH guidelines are relevant for information requirements for all medicinal products including nanomedicines.

Multidisciplinary guidelines are related to cross-cutting topics which do not fit into one of the Quality, Safety and Efficacy categories. One of them (M4) is dedicated to the assembly of all collected data on quality safety and efficacy of the product into the common format called Common Technical Document (CTD), required for the submission to different regulatory authorities. The ICH M4 contains several parts related to the organisation (M4 (R4)), quality ((M4Q(R1)), safety (M4S(R2)) and efficacy (M4E(R2)) sections of the CTD. In addition M8 Guideline is dedicated to the constitution of CTD in electronic format (eCTD).

The Safety Guidelines cover different aspects of toxicity testing, covering specific health risks such as carcinogenicity, genotoxicity or reproductive toxicology. They address mainly nonclinical studies, discussing the suitability of *in vivo* and *in vitro* models. More general guidance on "Nonclinical Safety Studies" (M3) which supports the design and timely management of the nonclinical studies and helps to reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles is part of the Multidisciplinary Guidelines. The Efficacy Guidelines refer to design, conduct and reporting of clinical trials organised in 19 specific topics.

The Quality Guidelines cover different parts of the product development and manufacturing, use of the validated analytical methods and evaluation of the critical quality parameters such as stability

Table A.1: ICH Guidelines on Quality, Safety, Efficacy and Multidisciplinary topics

Quality Guidelines	Efficacy Guidelines
Q1: Stability Q2: Analytical Validation Q3: Impurities Q4: Pharmacopoeias Q5: Quality of Biotechnological Products Q6: Specifications Q7: Good Manufacturing Practice Q8: Pharmaceutical development Q9: Quality Risk management Q10: Pharmaceutical Quality System Q11:Development and Manufacture of Drug Substances Q12: Lifecycle Management	E1:Clinical Safety for Drugs used in Long-Term Treatment E2: Pharmacovigilance E3: Clinical Study Reports E4: Dose-Response Studies E5: Ethnic Factors E6: Good Clinical Practice E7: Clinical Trials in Geriatric Population E8: General Considerations for Clinical Trials E9: Statistical Principles for Clinical Trials E10: Choice of Control Group in Clinical Trials E11: Clinical Trials in Pediatric Population E12: Clinical Evaluation by Therapeutic Category E14: Clinical Evaluation of QT E15:Definitions in Pharmacogenetics / Pharmacogenomics E16: Qualification of Genomic Biomarkers E17: Multi-Regional Clinical Trials E18: Genomic Sampling E19: Safety Data Collection
Multidisciplinary Guidelines	**Safety Guidelines**
M1: MedRA Terminology M2: Electronic Standards M3: Nonclinical Safety Studies M4: Common Technical Document M5: Data Elements and Standards for Drug Dictionaries M6: Gene Therapy M7: Genotoxic Impurities M8: Electronic Common Technical Document (eCTD) M9: Biopharmaceutics Classification System-based Biowaivers M10: Bioanalytical Method Validation	S1: Carcinogenicity Studies S2: Genotoxicity Studies S3: Toxicokinetics and Pharmacokinetics S4: Toxicity Testing S5: Reproductive Toxicology S6: Biotechnological Products S7: Pharmacology Studies S8: Immunotoxicology Studies S9: Nonclinical Evaluation for Anticancer Pharmaceuticals S10: Photosafety Evaluation S11: Nonclinical Paediatric Safety

or purity. They include 12 main quality-related topics. No topics are related to evaluation of products containing nanomaterials.

The Q4 topic refers to the harmonisation of the pharmacopoeial standards in different regions. Three pharmacopeial organisations: American Pharmacopeia (USP), Japanese Pharmacopoeia (JP) and European Pharmacopoeia (Ph. Eur.) carry out their harmonisation efforts through a tripartite pharmacopeial harmonisation program known as the Pharmacopoeial Discussion Group (PDG). The work focuses mainly on the harmonisation of pharmacopoeial monographs, including excipient monographs and selected general chapters, in order to enable their recognition by regulatory authorities in the ICH regions.

A.9 National Pharmacopoeias and International Pharmacopoeia (Ph. Int.)

The pharmacopoeias are ensuring that marketed medicines are of good quality through:

- Quality standards for active substances
- General standards for dosage forms
- General standards for manufacture of medicines
- Monographs on finished products
- Standard terminology

Historically, all countries in Europe produced and maintained their own national pharmacopoeias. After World War II, the countries replaced their national pharmacopoeias with the European Pharmacopoeia. Other regions also retain their own common pharmacopoeias (for instance the United States Pharmacopoeia, USP). Since 1952, the World Health Organization (WHO) has published the International Pharmacopoeia with the aim to achieve a wide global harmonization of quality specifications for selected pharmaceutical products, excipients and dosage forms.

Today, the International Pharmacopoeia focuses mainly on the WHO list of essential medicines and priority medicines of major public-health importance.

A.10 European Directorate for the Quality of Medicines (EDQM) and the European Pharmacopoeia (Ph. Eur.)

"The European Pharmacopoeia is a single reference work for the quality control of medicines in the signatory states of the Convention on its elaboration. The official standards published within provide a legal and scientific basis for quality control during the development, production and marketing processes. They concern the qualitative and quantitative composition and the tests to be carried out on medicines, on the raw materials used in production of medicines and on the intermediates of synthesis. All producers of medicines and/or substances for pharmaceutical use must therefore apply these quality standards in order to market their products in the signatory states of the Convention"[9].

The European Pharmacopoeia contains a series of general monographs for the manufacturing of medicines, general methods of analysis of substances and medicines, and some general requirements for dosage forms (tablets, capsules, injections, etc.). The methods of analysis may also be used by the pharmaceutical industry for substances and medicines not described in the pharmacopoeia.

The bulk of the Ph. Eur. is made up of quality standards, which are noted both in the monographs and general methods sections. Quality standards contain analytical methods to identify the substance and evaluate its quality and quantitative strength.

The EDQM has established a concept named certificate of suitability (CEP). A manufacturer of an active substance may apply to the EDQM for such a certificate. The application should contain a full description of the chemical synthesis of the substance, any potential and actual impurities. If the

[9] *EDQM: www.edqm.eu/en/european-pharmacopoeia-background-50.html*

manufacturer can show that the quality of a substance is regulated by the Ph. Eur. monograph, the EDQM will grant a CEP. The CEP is included in the dossier for the Marketing Authorization Application (MAA). The regulatory authorities will accept the CEP as sufficient documentation that the Ph. Eur. monograph is fully capable of controlling the quality of the active substance.

A.11 US Pharmacopeia (USP)

USP develops and publishes standards for drug substances, drug products, excipients, and dietary supplements in the United States Pharmacopeia–National Formulary (USP–NF)[10]. These standards have been recognized in the Federal Food, Drug and Cosmetic (FD&C) Act since it was first enacted in 1938. The FD&C Act defines the term "official compendium" as the official USP, the official NF, the official Homeopathic Pharmacopeia of the United States, or any supplement to them. USP has no role in enforcement of these or other provisions that recognize USP–NF standards, which is the responsibility of FDA and other government authorities in the United States and elsewhere. Manufacturers and potentially affected parties are encouraged to contact FDA with questions about the specific applicability of USP standards to their products.

Specific Drug Categories and Topics:

- **Drugs:** USP's goal is to have substance and preparation (product) monographs in USP–NF for all FDA-approved drugs, including biologics, and their ingredients. Although submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance with a USP–NF monograph, if available, is mandatory in the following respects:
  - o *Nonproprietary Name*: under the relevant FD&C Act provisions, a drug will be deemed misbranded unless its label bears to the exclusion of any other nonproprietary name the "established" name.
  - o *Identity*: a drug with a name recognized in USP–NF must comply with the identity/identification requirements of its monograph, or be deemed adulterated, misbranded, or both.
  - o *Strength, Quality, Purity*: drugs also must comply with compendial standards for strength, quality, and purity (tests for assay and impurities), unless labelled to show all respects in which the drugs differ.
  - o *Packaging, Labeling*: drugs with a name recognized in USP–NF also will be considered misbranded unless they meet compendial standards for packaging and labelling.
- **Biologics:** In the United States, all biologics are considered a subset of drugs, approved by FDA. All biologics are subject to the drug regulatory requirements. They are required to comply with the adulteration and misbranding provisions.
- **Compounded Preparations:** Compounding means the preparation, mixing, assembling, altering, packaging, and labelling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. USP provides both general chapters and monographs for compounded preparations. Compounded preparation monographs include formulas (ingredients and quantities), specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH, beyond-use dates based on stability studies, and detailed assays (majority of monographs).

[10] *USP-NF: www.uspnf.com/*

A.12 ASTM International

ASTM International is a non-profit organisation that develops and publishes technical standards. Of particular relevance is the ASTM Committee E56 on Nanotechnology which includes 170 members from 17 countries. The main objectives of the Committee E56 are the development of standards and guidance for nanotechnology and nanomaterials as well as the coordination of existing ASTM standardization related to nanotechnology needs. Today already 19 active standards have been developed and 13 additional are drafted. The technical Subcommittee E56.08 on Nano-Enabled Medical Products[11] has released a number of different standards relevant for nanomedicines.

Generally, each member of ASTM International can propose a new standard following the ASTM process:

1. **Recognising the need**: contacting the ASTM
2. **Work Item Registration:** The proposal is approved by sub chair or at a meeting
3. **Task Group**: drafting of a documentary standard by a group formed typically out of 6-8 key stakeholders
4. **Subcommittee Ballot**: Bring in more experts: electronic ballot system to vote on the draft standard. Negative votes and comments must be addressed in order to proceed to the next stage.
5. **Main Committee (Society Review)**: voting on standard, addressing any negative feedback or comments, back to subcommittee if needed.
6. **ASTM International Committee on Standards**: Review and Approval
7. **Online and Print Publication**: the draft will be published 6 weeks after the approval
8. **Marketplace Use**: Manufactures, governments, trade associations, consumers

In order to support standardisation studies, ASTM has established an international Inter-Laboratory Study programme (ILS) (Figure A.1) that facilitates the production of data to develop precision and bias statements as well as offering administrative support for the ongoing projects.

Figure A.1: Steps in inter-laboratory study program to assess the precession of a newly developed documentary standard within ASTM International source: ASTM International https://www.astm.org/

[11] *ASTM Subcommittee E56.08: www.astm.org/COMMIT/SUBCOMMIT/E5608.htm*

A.13 Comité Européen de Normalisation (CEN)

"CEN, the European Committee for Standardization, is an association that brings together the National Standardization Bodies of 34 European countries. CEN is one of three European Standardization Organizations (together with CENELEC and ETSI) that have been officially recognized by the European Union and by the European Free Trade Association (EFTA) as being responsible for developing and defining voluntary standards at European level."[12]

The development of European standards and other technical documents in relation to various kinds of products, materials, services and processes will protect consumers and facilitates cross-border trade. European standards for medical devices developed under a special mandate provided by the European Commission, the so-called harmonized standards, provide a presumption of conformity with the regulatory requirements. Through their more than 20 Technical Committees dedicated to medical equipment, CEN and CENELEC develop European Standards setting safety, quality and performance requirements for medical devices that are placed on the European market[13]. A large number of them enable manufacturers to make their medical products compliant with the European legislation in the medical sector, for the ultimate benefit of all European citizens. The Technical Committee on Nanotechnologies (CEN/TC 352)[14] is coordinating the development of technical specifications in relation to various aspects on nanotechnologies. Standards are often developed in cooperation with ISO and IEC; the process of the standardisation is described in the paragraph on ISO (see annexe A.14).

A.14 International Organization for Standardization (ISO)

ISO is an independent, non-governmental international organization with a membership of 162 national standards bodies. Through its members, it brings together experts to share knowledge and develop voluntary, consensus-based, market relevant International Standards that support innovation and provide solutions to global challenges. The Technical Committee on Nanotechnologies (ISO/TC 229)[15] has been established in order to develop standards for terminology and nomenclature; metrology and instrumentation; test methodologies; modelling and simulations; as well as science-based health, safety and environmental practices. The Figure A.2 demonstrates the general process of developing a new ISO standard.

[12] *CEN: https://www.cen.eu/about/Pages/default.aspx*
[13] *CEN-CENELEC sectors- medical devices: https://www.cencenelec.eu/standards/Sectorsold/healthcare/MedicalDevices/Pages/default.aspx*
[14] *CEN/TC 352: www.cencenelec.eu/research/tools/horizon2020/industrialleadership/nanotech/pages/default.aspx*
[15] *ISO/TC 229: www.iso.org/committee/381983.htm*

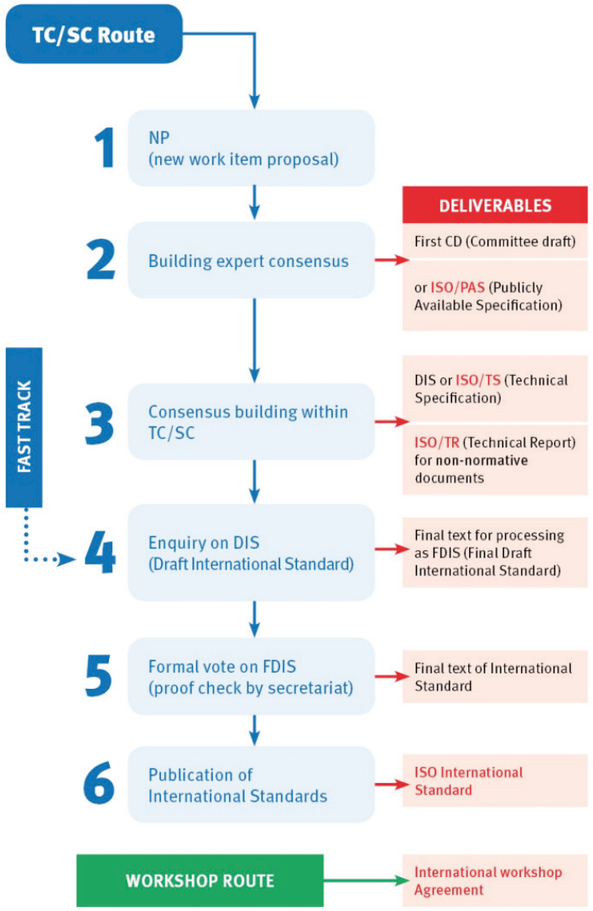


Figure A.2: Flow-chart illustrating main stages in the process developing a new ISO-standard
source: International Organisation for Standardisation: https://www.iso.org/developing-standards.html

A.15 Organisation for Economic Co-operation and Development (OECD)

Organisation for Economic Co-operation and Development (OECD) mainly focuses on the characterisation of chemicals and especially the determination of their toxicity. This series is well established and has a wide acceptance and usage for the general assessment of any given chemical. The standards are also reviewed, revised, withdrawn, if needed, or updated with new ones on a regular basis. In order to ensure the safety of manufactured nanomaterials, the OECD established the Working Party on Manufactured Nanomaterials (WPMN) and launched a strategic programme on the safety evaluation and risk assessment of manufactured nanomaterials[16] to assist countries in the implementation of national policies. Nevertheless, their main focus is on chemical products and not medical devices or medicinal produces. Therefore, these documentary and technical standards do not consider all the special requirements, which would be emphasised in the medical area. Even so they are well founded and often provide a good basis to develop an analytical procedure designed for medical products or devices.

[16] *Testing Programme of Manufactured Nanomaterials: http://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm*

A.16 Comparison of standardization requirements of ASTM and ISO

Some of the presented standardization bodies such as CEN or ISO will often focus on published procedures and results during the drafting of a new documentary standard, whereas others (e.g. ASTM International, OECD) will require more often testing of the draft technical standard in an inter-laboratory study (ILS). Such an ILS provides benchmarks for the within laboratory repeatability and between laboratory reproducibility. Especially the later process of ILS supports regulatory bodies in their assessment of new documentary standards. But even if the actual development process of the various standardisation bodies is quite different (Table A.2) the key principles are the same (Box A.1). Technical standards of ISO and ASTM International are reviewed every five years to either prolong them for another five years, to revise them, or to withdraw them, because they are outdated or not anymore in demand.

Box A.1 Common standardisation principles

- Standards respond to a need in the market
- Standards are based on expert opinion
- Standards are developed through a multi-stakeholder process
- Standards are based on a consensus

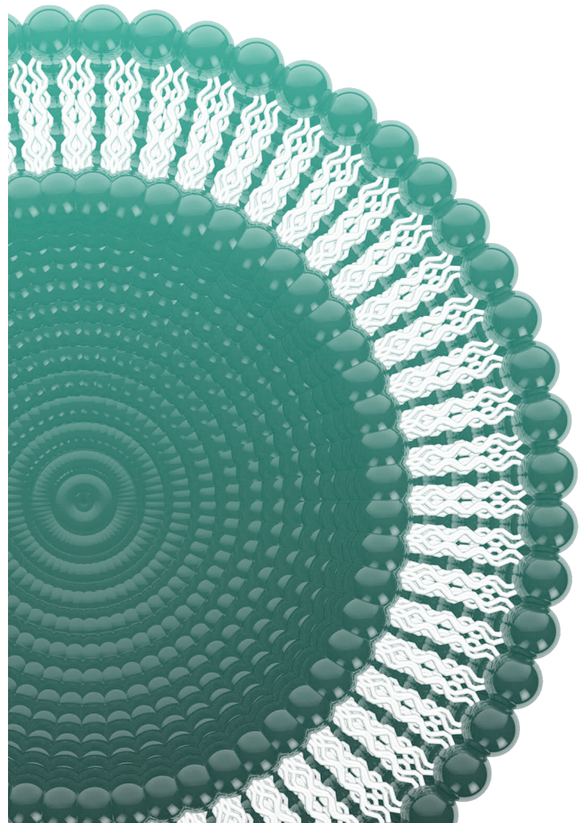


Table A.2: Comparison between ASTM international and ISO

	ASTM international	ISO
	A = American	I = International
How financed	Sales of standards	National members pay subscriptions that meet the operational cost of the Central Secretariat. The subscription paid by each member is in proportion to the country's Gross National Income
Membership	Open to all	Via country standards organization
Voting	One member = One vote	One country = One vote
Balance	Balance between producers, users, consumers	
Consensus	100% All negatives must be addressed	Majority based on stage of standard
Number of Committees	140	250
Number of members	32000 individual members	160+ countries
Number of Active Standards	12000	21000
Nanotechnology	E56 (2005)	TC229 (2006)
Meeting	Twice yearly	Twice yearly
Precision & Bias	Mandatory	Desirable
ILS	Yes	Use OECD and other groups and perform own ILS sometimes
Minimum Balloting time	30 days	3 months +
Meetings	International (1/4 must be outside the US)	International
Famous For	ASTM E11 Sieves	ISO9000+, ISO17025
Other	Collaboration spaces; Standardization News	
HQ	West Conshohocken, PA, USA	Geneva, Switzerland

ANNEX B. Regulatory frameworks relevant for nanotechnology-enabled health products

The following section gives an overview on the regulatory frameworks involved in the approval of nanotechnology–enabled health products. It needs to be pointed out that no dedicated framework for such products exists and products are regulated within the current regulatory frameworks of medical devices and medicinal products. However, products that are very similar to such health products can also fall under other sectorial legislations such as cosmetic products or novel foods. For such "borderline" products, their classification must be made on a case-by-case basis (Council of the European Communities, 1976; EC, 2001).

B.1 European regulatory framework for medicinal products

The European Regulatory Framework for medicinal products is based on *Directive 2001/83/EC on Medicinal Products for Human Use* (EC, 2001), which regulates the European marketing authorization and is supplemented with Directives, Commission regulations and several legal reference documents. Furthermore, this Directive is supported by a large number of scientific guidelines but none of them is related to nanotechnology-enabled medicinal products.

EMA has released a number of Reflection Papers related to different categories of nanotechnology-based products in order to provide initial guidance on the assessment of their quality and safety (see Table 1). EMA's Innovation Task Force is monitoring the field and organizes regulatory awareness sessions in order to update assessors on the progress in regulatory science in the field of nanomedicine. The scientific advice procedures offer individual support for the development of nanomedicines.

The successful development and commercialization of a nanomedicinal product depends on the complex interplay of actions by different actors: researchers, funders, pharmaceutical companies, regulators, standardisation bodies and institutions as for any other innovative health product. The development stage takes an average of 10-15 years and includes preclinical studies, clinical studies and the registration process (Figure B.1).

The final step of the drug development process, after successful completion of Phase 3 trial, is the request of registration of use of a compound for specific indication(s) in a specific market by a pharmaceutical company. Different types of registrations are possible within the existent regulatory

framework: National Procedure, Centralised Procedure and Mutual Recognition procedure. While the National Procedure enables an authorisation in one Member State, the Centralised Procedure allows the applicant to obtain an authorisation valid for all Member States of the European Union, after a positive evaluation of the EMA. If a medicinal product has already been authorised through National Procedure in one Member State and the industry wants to extend the marketing authorisation to other Member States the Mutual Recognition procedure can be used.

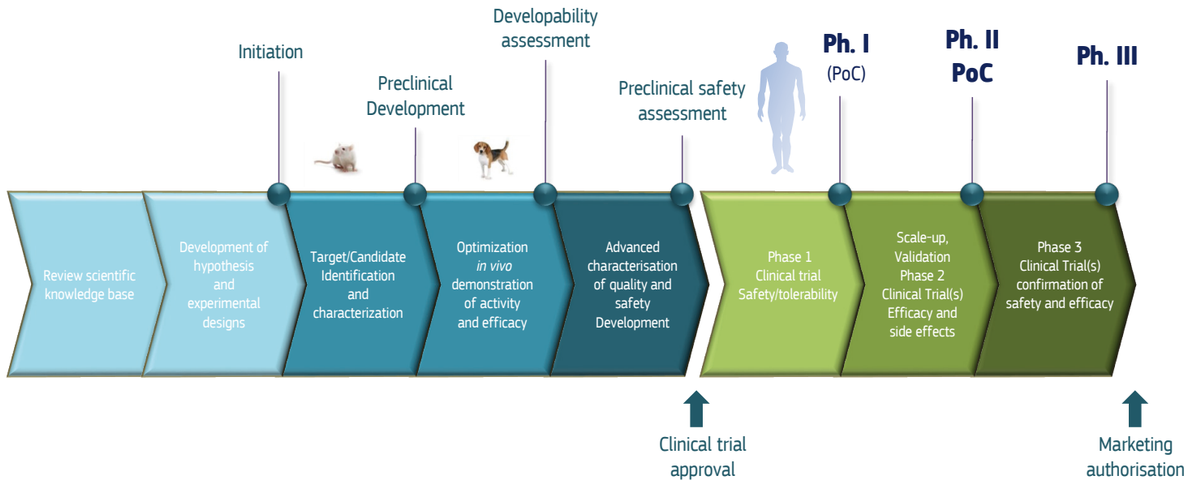


Figure B.1: Main phases of a drug development process, comprising the design phases (light blue), preclinical phases (dark blue) and clinical trial stages (green) leading to marketing authorisation

The compilation of dossiers for applications for European Marketing Authorisation should be made entirely in accordance with the rules of the Common Technical Document (CTD). The CTD is an international format, assembling all quality, safety and efficacy information, as described in ICH M4 guideline (ICH, 2002). In addition, applicants are obliged to take into account the Community guidelines relating to the quality, safety and efficacy of drug/medicinal products published by the Commission in "The rules governing medicinal products in the European Community", Volumes 3A, 3B, 3C: Guidelines on the quality, safety and efficacy of medicinal products for human use.

Once on the market, the product safety is to be continuously monitored as a part of the pharmacovigilance procedure, defined as "the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem". In the EU the EMA is responsible for the coordination of the pharmacovigilance system and supporting relating activities. In addition to EMA, marketing authorization holders and national competent authorities are involved in operating the pharmacovigilance system.

Reports of suspected adverse reactions seen in healthcare practice or clinical trials are stored in EudraVigilance system managing information on suspected adverse reactions to medicines which have been authorised or are being investigated in the European Economic Area (EEA). EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing and monitoring the safety of human medicines. It evaluates signals coming from EudraVigilance and may recommend a regulatory action.

B.2 Medical devices: European regulation and classification scheme

For many years, three Directives have covered medical devices, namely the Active Implantable Medical Devices Directive 90/385/EEC (AIMDD), the Medical Devices Directive 93/42/EEC (MDD) and the In-Vitro Diagnostic Medical Devices Directive 98/79/EC (IVDD). These Directives are supplemented by 15 amending or implementing legislative documents. This regulatory framework on medical devices does not contain specific requirements regarding nanomaterials.

On 5 May 2017, two new regulations on medical devices were published: the Medical Devices Regulation (EU) 2017/745 (MDR) and the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 (IVDR).

The IVDD will be replaced by the IVDR in May 2022, after a transition period of 5 years. This regulation does not contain any content specifically related to nanomaterials.

In May 2020, after a transition period of 3 years, the AIMDD and the MDD will be replaced by the MDR (EU, 2017). This regulation does contain several provisions on nanomaterials. It also contains a definition for nanomaterials, which will be discussed in a separate section below. This definition can be amended, reflecting technical or scientific progress as well as new European or international definitions.

According to article 5 (2) in the MDR, a device shall meet the general safety and performance requirements set out in Annex I. One of these requirements is that a device shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials. This requirement will most logically be addressed as part of the biological evaluation of medical devices. The EN ISO 10993 series of standards provides a framework on how to perform a biological evaluation. It includes a systematic approach to deciding which biological endpoints need to be addressed for a particular device. Furthermore, it prescribes methods for physicochemical characterisation of the devices and their potential degradation products. It also prescribes the relevant assays for the various biological endpoints. In 2017, a separate guidance document was added as part 22 to the series in order to specify how the EN ISO 10993 series can be applied to medical devices containing or consisting of nanomaterials.

The MDR contains a classification system, similar to the MDD. Devices are classified as Class I, IIa, IIb or III. The higher the class, the more stringent the conformity assessment route to prove compliance with the regulation. For Class I, self-certification can be applied. For the higher classes, involvement of a Notified Body (organization certified by a Member State Competent Authority) is required to obtain a CE certification that will allow the manufacturer to place the device on the market. In the MDR, a new rule was introduced related to nanomaterials, Rule 19. This rule specifies that a medical device containing nanomaterials is classified as Class IIa if the potential internal exposure is negligible. Class IIb applies to medical devices for which the potential internal exposure to the nanomaterials is low, while medical devices which have a medium or high potential of internal exposure are classified in Class III. The regulation does not clarify the meaning of negligible, low, medium or high and how this should be applied in practice. Currently, guidance is being developed for this purpose by the European Commission WG on New and Emerging Technologies.

An important document for the development of the guidance is the Scientific Committee on Emerging and Newly Identified Health Risks

Key reference:

SCENIHR (2015). Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices. Final Opinion. https://doi.org/10.2772/41391

(SCENIHR) opinion on the guidance on the determination of potential health effects of nanomaterials used in medical devices (SCENIHR, 2015), which introduced the concept of (external and) internal exposure.

According to this opinion the potential exposure is dependent on the type of device, type of contact, duration of the contact and type of application of the nanomaterial (Table B.1).

Table B.1: An estimation of potential internal exposure as starting point for a risk evaluation for medical devices containing nanomaterials

			Type of application of nanomaterials Internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	**Type of contact**	**Duration of contact**		**Weak (physisorb)**	**Strong (chemisorb)**	**In degradable materials***	**In non-degradable materials**
Surface device	Intact skin	≤ 24 h	N	N	N	N	N
		>24 h to 30 d	N	N	N	N	N
		>30 d	N	N	N	N	N
	Intact mucosal membrane	≤ 24 h	L	L	N	L	N
		>24 h to 30 d	M	M	L	M	N
		>30 d	M	M	L	M	N
	Breached or compromised surface	≤ 24 h	H	M	L	M	N
		24 h to 30 d	H	M	L	M	N
		30 d	H	M	L	M	N
External Communicating device	Blood path, indirect **	≤ 24 h	na	M	L	L	N
		>24 h to 30 d	na	M	L	M	N
		>30 d	na	M	L	M	N
	Tissue/bone/ dentin	≤ 24 h	H	M	L	L	N
		>24 h to 30 d	H	M	L	M	N
		>30 d	H	M	L	H	N
	Circulating blood***	≤ 24 h	na	H	H	L	N
		>24 h to 30 d	na	H	H	M	N
		>30 d	na	H	H	H	N
Implant device	Tissue/bone	≤ 24 h	H	H	L	L	N
		>24 h to 30 d	H	H	L	M	N
		>30 d	H	H	L	H	N
	Blood	≤ 24 h	H	H	L	L	N
		>24 h to 30 d	H	H	L	M	N
		>30 d	H	H	L	H	N

H=high, M=medium, L=low, N=negligible, na= not applicable;
* the exposure will depend on the degradation time of the medical device,
** contacting the blood path at one point. Examples of these types of devices are solution administration sets, transfer sets and blood administration sets (ISO 10993-4:2002),
*** Examples of these types of devices are: intravascular catheters, extracorporeal oxygenating tubing and dialyzers (ISO 10993-4:2002).

Source: (SCENIHR, 2015)

The type of device takes into consideration the application site. Devices that contact the skin are considered to lead to a lower potential internal exposure compared to external communicating devices (that come directly in contact with blood, tissue, bone or dentin) and implantable devices. The types of tissue contact considered in the risk assessment of the SCENIHR opinion include skin, mucosal membrane, breached/compromised surface, blood, tissue, bone and dentin. The longer the duration of contact with the body, the higher the potential for internal exposure with limited contact (≤ 24 hours) as the shortest exposure duration, followed by a prolonged contact (> 24 hours to 30 days) and permanent contact (<30 days). The internal potential exposure also depends on how the nanomaterials are incorporated in the medical device. Nanomaterials which are embedded in a non-degradable material possess a negligible potential for internal exposure, while the potential internal exposure is high if the nanomaterials are embedded in a degradable material. For nanomaterials that are used in coatings of medical devices, the potential internal exposure depends on how the nanomaterials are fixed. This potential is lower if the nano-coating is chemically bound compared to when weaker physical bounds are applied. Medical devices that contain free nanomaterials show the highest potential internal exposure.

B.3 Differences in the regulatory framework in Europe and US

Nanotechnology-enabled health products are regulated under existing regulatory frameworks for medicinal products and medical devices, which can substantially vary in different geographical regions. The short comparison of the regulatory frameworks in EU and US (Table B.2) should illustrate the various steps in the regulatory approval when seeking access to both markets. While in the US the FDA is the main actor involved in approval of preclinical and clinical studies and in the authorization of new medicines and medical devices, the situation in Europe is more fragmented and involves national competent authorities, Notified Bodies, expert panels, the EMA and European Commission (Table B.2). For example clinical trials are authorised by national competent authorities whereas the final market authorisations of innovative products such as nanomedicines are granted by the EMA. In contrary, the EMA is not involved in the regulation of medical devices, while FDA is the main responsible authority for medical devices commercialization in the US.

The manufacturer applies for the CE marking and Notified Bodies (NBs) (organizations certified by a Member State Competent Authority) are responsible for the conformity assessment. The EC, MDCG and CAMD all play their roles in this system (see Annex A). Furthermore, the classification into medicinal products and medical devices is crucial, since it determines the regulatory path the product should follow. However, as the definitions in different geographical regions can slightly differ, the products might be classified differently in various regions. The situation is even more complex for borderline products and combination products.

Both in Europe and US the determination of the primary mode of action (PMOA) is critical to decide which regulatory framework and which authority should be responsible for the product registration. However, in the US the primary responsibility for assigning combination products to a lead agency center is implemented by FDA Office of Combination Products (OCP). A formal request of determination of a combination product's classification may be submitted to OCP which will determine the PMOA and assign the review responsibility to the corresponding FDA center. In Europe, in case of uncertainty there is no clear procedure to follow and different regulatory authorities and NBs may be consulted by company in the early stage of the development process.

Due to regional differences certain nanomedicines might fall under different regulatory frameworks resulting in slightly different regulatory requirements.

Both EMA and FDA provide regulatory and scientific help for applicants during the product development phase, regarding performing of appropriate tests and studies. The EMA's scientific advice procedure has been often requested from companies developing nanotechnology-based medicines. Furthermore, a parallel EMA-FDA scientific advice can be requested by product developers, especially in case of products being developed for indications lacking development guidelines. This interaction should provide a better understanding of the regulatory framework.

Table B.2: Overview of major differences in the regulatory frameworks relevant for nano-enabled health products in EU and US

	EU	US
Regulatory framework for nanomedicinal products	Centralised marketing authorisation applications (MAA) to EMA Committee for Medicinal Products for Human Use (CHMP)	New Drug Application (NDA), Investigational New Drug (IND) or Abbreviated New Drug Application (ANDA) submitted to the FDA Center for Drug Evaluation and Research (CDER)
Regulatory framework for nanomedical devices	Applications are reviewed by Notified Bodies and in specific cases by expert panels. If the device meets regulatory requirements a CE mark is granted and the device can be commercialised in all member states.	Application to FDA Center for Devices and Radiological Health (CDRH). Class III medical devices require a premarket approval (PMA) based on the review of safety and efficacy of a device.
Classification of medicinal products and medical devices	Mechanism of principal intended action (pharmacological, immunological or metabolic action is distinctive for medicinal products)	Mechanism of action (chemical action or the fact of being metabolised by the body is distinctive for medicinal products)
Combination products	Several authorities (EMA ITF, national authorities, Notified Bodies) may be consulted in case of unclear regulatory pathway.	FDA Office of Combination Products (OCP) is responsible for the product classification as a drug, device, or biologic based on the PMOA.
Definition of nanomedicine	Descriptor as agreed with Intl. Nanomedicines WG: • Purposely designed systems for clinical applications • At least one component at nano -scale size (1-1000nm) • Resulting in definable specific properties and characteristics: -related to the specific nanotechnology application and characteristics for the intended use (route of admin, dose) -associated with the expected clinical advantages of the nano -engineering (e.g. preferential organ/tissue distribution)	No regulatory definition, but points to consider per FDA finalized guidance "Considering whether an FDA-Regulated Product involves the Application of Nanotechnology: - 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); - 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, even if these dimensions fall outside the nanoscale range, up to 1 µm (1000 nm).
Regulatory advice	**Scientific advice procedure**, which can be requested at any stage of development, helps to perform the appropriate tests and studies.	**Pre-IND meetings** provide help in preparation of an IND application, exploring possibilities to enhance and support development.

B.4 Requirements for gaining regulatory acceptance of methods

Methods, tools and approaches providing information that allow regulators to make decisions on the assessment of the quality safety and efficacy of medical products need to be checked for their reliability and relevance for the intended purpose. As a first step novel methodologies can seek for feedback on their suitability for regulatory purposes by following a **qualification process** developed by EMA and the FDA (Table B.3). Methods used in non-clinical or clinical studies, novel biomarkers, or models can undergo such a qualification procedure. Based on the submitted results and the recommendation of the Scientific Advice, the EMA CHMP can issue a qualification opinion on the acceptability of a specific use of a method. Alternatively it can provide a qualification advice supporting further development of a method towards its final qualification. Whereas the qualification process is an optional step, the following **validation procedure** is mandatory for gaining regulatory acceptance of a method. Guidance documents on the validation of analytical, bioanalytical procedures as well as on *in silico* methods and *in vitro* methods were released by the regulatory authorities (Tables B.3 and B.5) and will be briefly presented.

Table B.3: Guidance documents related to the qualification and validation of methods

	Organisation	References
Method qualification	EMA	EMA/CHMP: Qualification of novel methodologies for drug development: guidance to applicants. EMA/CHMP/SAWP/72894/2008.(EMA/CHMP, 2014)
	FDA	Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools (January 2015).(FDA, 2014b)
Method validation	EMA	EMEA: Validation of Analytical Procedures: Text and Methodology (June 1995).(EMA, 1995) EMEA/CHMP. Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** (21 July 2011).(EMA/CHMP, 2011)
	FDA	Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry (July 2015). (FDA, 2015) Guidance for Industry: Bioanalytical Method Validation. Draft Guidance (September 2013).(FDA, 2013)
	ICH	International conference of harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised Tripartite: Guideline Validation of Analytical Procedures: Text and Methodology Q2(R1) Current Step 4 version.(ICH, 2005)

Validation of analytical and bioanalytical procedures

Table B.4 describes a set of performance characteristics, which a given method has to achieve during validation. These parameters and their performance characteristics limits are independent of the investigated material or compound but are critical for the successful conduct of nonclinical and/or biopharmaceutics and clinical pharmacology studies. Existing guidance on the method validation (Table B.3) refers to analytical procedures, necessary for the characterisation of the drug, or to bioanalytical methods providing quantitative evaluation of drugs, their metabolites (analytes) and biomarkers in a given biological matrix (e.g., blood, plasma, serum, or urine).

The methods are further split into chromatographic and ligand binding analysis methods, which both have a full series of additional requirements and associated performance requirement limits. This results in a long list with further performance characteristic data, which also have to be reported in the validation report.

Table B.4: Set of method characteristics required for the qualification and validation of (bio)analytical and in vitro methods (Ritter et al., 2003)

Requirements	Qualification (all)	Validation (analytical)	Validation (bioanalytical)	Validation (in vitro)
Specificity/Selectivity	X	X	X	X
Linearity/Range	X	X	X	X
Accuracy	X	X	X	(X)
Precision (repeatability, intermediate precision, reproducibility)	X	X	X	X
Quantitation limit		X	X	
Dynamic range/Detection limit		X		X
Stability			X	
Robustness		(X)		X
Ruggedness				X

Qualification and validation of *in vitro* and *in vivo* methods for safety evaluation

As any other analytical methods also *in vitro* and *in vivo* methods can be subject to the qualification process of EMA. The qualification process requires information on the experimental approach including the selection of the biological model, positive and negative controls as well as a detailed description of the readout systems. The analytical/technological assay validation demands the assessment of **repeatability** (intra-run precision; intra-laboratory variability) and **reproducibility** (inter-lab precision) (Table B.4). In particular for sophisticated readout systems such as microfluidics, the sensitivity of assay parameter (**ruggedness**) has to be analysed and parameters such as e.g. on tubing, flow rate/sheer stress, cell number etc. have to be carefully controlled. Furthermore, the instrumentation as well as the statistical methodology has to be evaluated for their accuracy.

Key reference:
EMA/CHMP (2016). Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches.
EMA/CHMP/CVMP/JEG-3Rs/450091/2012

The **qualification of the proposed biological model** requires a review on components such as the intra- and inter-animal variability, difference between species and strains for *in vivo* experiments whereas for *in vitro* methods the source and identity of cells, the reproducibility of the source as well as the biological relevance are decisive. When assessing biological effects triggered by nanomaterial, interaction with reagents have to be excluded. The submission dossier should be supported by a systematic review on the assays as well as a description of remaining gaps (EMA/CHMP, 2014).

In the last decades in vitro methods were considered as a key component for the implementation of the 3Rs concept leading to a reduction of animal experiments. In this context stringent validation criteria have been developed in order to avoid an impact on safety and efficacy assessment. This is of particular importance when in vitro methods are considered as a replacement for an animal experiment and decision point in testing strategies and other regulatory decisions. In particular, the European Centre for the Validation of Alternative Methods (ECVAM) and its sister organisation the Interagency Coordination Committee on the Validation of Alternative methods (ICCVAM) have closely collaborated in order to develop harmonised criteria for method validation.

These criteria are widely accepted by different industrial sectors not only for alternative methods (EMA/CHMP, 2016; Hartung et al., 2004; ICCVAM, 1997; OECD, 2005).

Already today a number of *in vitro* methods were successfully validated following the criteria developed by ECVAM and its partner. However, their applicability domain is mainly in the field of industrial chemicals and it remains an open question whether they are also suitable for the assessment of nanotechnology-enabled health products.

Qualification and validation of *in silico* methods

Physiologically-based pharmacokinetic (PBPK) modelling is now routinely utilised to aid an efficient and quantitative understanding of the pharmacokinetic-pharmacodynamic relationship of small-molecule drugs and their metabolites. The tool has been increasingly recognised by regulatory bodies in recent years to facilitate drug development programs. In terms of nanomedicine development, the application of PBPK models for the informed simulation of first-in-human studies, drug-drug interactions, formulation changes and extrapolation to special populations can provide a substantial insight into the pharmacological behaviour of a nanomedicine compared to conventional drug. Although there are no specific guidelines on the use of PBPK in nanomedicine development, there is some guidance on the general use of PBPK analyses to support applications to regulatory bodies (Table B.5).

The EMA have drafted a guidance document describing the qualification and reporting of PBPK modelling and simulation approaches suitable for clinical development decision making (Table B.5). This document details the qualification of platforms suitable for PBPK and what is required in terms of model validation. For the general qualification of a PBPK platform i.e. a version of PBPK software for an intended purpose, this may be reviewed via a CHMP qualification procedure following the Qualification of novel methodologies for drug development guidelines (EMA/CHMP, 2014) (see section above). The predictive performance of the platform should then be further evaluated if it is to be used for an intended purpose (EMA/CHMP, 2018). This process should involve a detailed description of the model parameters, the equations used, how preliminary data was derived (if experimental) and a discussion on the source of any data collected from the literature. The requirements for qualification depend on the impending regulatory impact that data provided by the model may have if clinical decisions were to be made on its basis. This can be classified as high, moderate or low. The guidance recommends information should be provided on aspects of model structure, model performance in terms of sensitivity and level of confidence, and the final model results that should include a discussion of the simulation results and their regulatory consequences. There are a number of issues raised by academic and industry reviewers that mainly concern an uncertainty surrounding the qualification process where the regulators are advised to provide more detail in their requirements. For example,

Table B.5: Guidance documents related to PBPK modelling

Agency	Document	Scope
EMA/CHMP	Qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. EMA/CHMP/458101/2016(EMA/CHMP, 2018)	• Content of modelling and simulation reports • Qualification of PBPK platforms
FDA/CDER	Guidance for Industry: Physiologically Based Pharmacokinetic Analyses — Format and Content (Sep. 2018)(FDA, 2016)	• Structure and content of PBPK study reports • Does not address methodologies or best practices

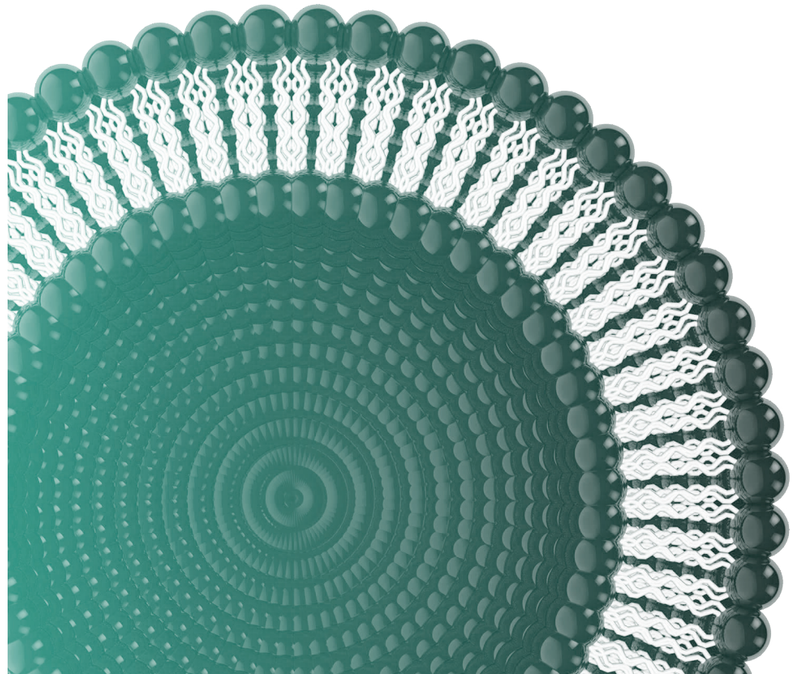
can a model be qualified to predict a pharmacokinetic parameter in general or does each model need to be drug-specific? These issues may be addressed before the final versions of the guidance are prepared.

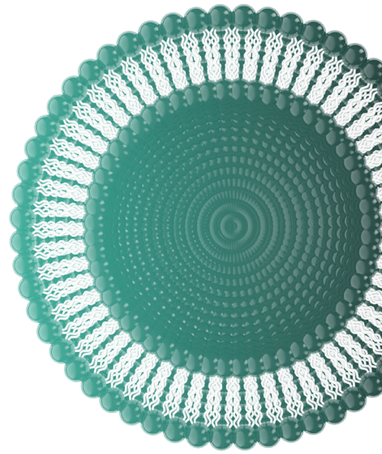
The FDA also provides final guidance on the recommended format and content for the submission of PBPK analyses to support various applications (Table B.5). A report should provide a comprehensive overview of what is known of the drug being investigated already and references to any PBPK analyses that have been performed previously, as well as a workflow for the construction and implementation of the model. This should include sufficient detail so that reviewers are able to duplicate the model to evaluate the integrity of the presented data. The methodology should also include the software used, but the FDA does not recommend the use of any specific software for PBPK modelling. Results should include data surrounding the model verification and any modifications that were made in order to demonstrate the model is appropriate for its application. The final application results should then be presented and discussed to address the original study question.

FDA procedure for medical devices methods

The Medical Device Development Tools (MDDT) program is an FDA's program for the qualification of tools that can be used in the development and evaluation of a medical device[17]. It applies to a method, material or measurement, which assesses the safety, efficacy or performance of a medical device. When a method after approval via the MDDT procedure, is used in a regulatory submission, the reviewers should accept the methodology without the need to reconfirm its suitability and utility. This can speed up and facilitate the development and evaluation of a new medical device which reduces costs and time and therefore makes new medical devices quicker available for the patient. The FDA recognizes 3 categories of MDDT based on how the parameters are measured: Clinical Outcome Assessments (which measure how a patient feels or functions), Biomarker tests (a laboratory test or instrument that detects or measures biomarkers) and Non Clinical assessment Models (a nonclinical test method or model that measures or predicts device function or performance in a living organism). The qualification process consist of several phases and starts with the proposal phase in which the FDA determines if the MDDT is suitable for qualification in the MDDT program. The proposals that have the strongest potential to meet a public health need will be prioritised. This phase might be followed by the incubator phase. In certain instances an MDDT with a high potential impact may be accepted while the MDDT is not fully developed. During the incubator phase, the FDA will foster the development of the tool. Also the pre-qualification phase in which the FDA provides feedback to the submitters is optional. The goal of the qualification phase is to determine whether the MDDT is qualified for the specific context based on scientific evidence and the provided justification. The FDA has released the first two MDDTs namely the Kansas City Cardiomyopathy Questionnaire (KCCQ) which qualifies patient health status and the Minnesota Living with Hearth Failure Questionnaire (MLHFQ) which measures quality of life for hearth failure patients.

[17]MDDT program: https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttools-mddt/





ANNEX C. Overview of products on the market

The number of nanotechnology-enabled health products that have reached the European market is constantly increasing. They can be regulated either as medicinal products or medical devices. Most widely used nanotechnological platforms and applications are described below.

C.1 Nanotechnology-enabled medicinal products

Most of the currently approved nanotechnology-enabled medicinal products are based on conventional active substances that had already been approved. The employed platforms may contain a nanoparticle (such as liposome or polymer) with a bound or encapsulated active substance or may be formed directly from the constituent drug in a nano-form. The remainder of investigational products demonstrate a trend toward agents using micelles, as well as the introduction of formulations using dendrimers (Caster, Patel, Zhang, & Wang, 2017; Robinson, Corrie, Thurecht, Islam, & Bobo, 2016). Among the approved products on the market (Figure C.1 and Table C.1) (Hafner, Lovrić, Lakǒ, & Pepić, 2014; Patra et al., 2018; Pita et al., 2016) the main nanotechnology platforms include:

1) Nanocrystals, consisting of pure active substance in form of particles in a nano-size. They offer better solubility and bioavailability of the drug;

2) Polymer-protein conjugates: the conjugation of protein with a polymer such as poly(ethylene glycol) (PEG) leads to a longer circulation in bloodstream and can be designed to influence the biological activity;

3) Amino-acid based polymers, biodegradable polymers allowing tailored functionalization and controlled drug delivery;

4) Nano-emulsions: dispersion systems consisting of oil, surfactants, co-surfactants, and aqueous phase, where the active substance is distributed in the lipid droplets of a nano-size;

5) Liposomes: vesicles encapsulating active substance in one or more lipid bilayers, protecting active substance from being metabolized early and delivering it to the site of disease;

6) Iron–carbohydrate complexes in a colloidal suspension, used in iron deficiency disorders. They provide high doses of iron in a stable, non-toxic form with a reduced risk of hypersensitivity reactions.

7) Virosomes, which consist of virus-derived proteins encapsulated in unilamellar phospholipid membrane which allows the virosomes to fuse with target cells. They act as a vaccine carriers and adjuvants (immunity enhancing) systems, combining high efficacy with the improved safety.

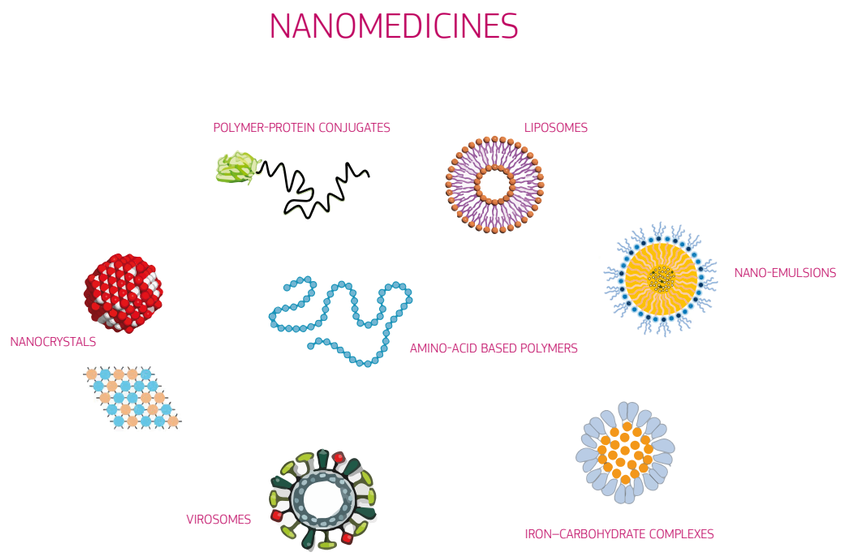


Figure C.1: Illustration of the diversity of nanotechnology-enabled medicinal products

In all cases the main advantages are related to the improved pharmacokinetic (PK) properties such as:

- Prolonged stability and blood circulation
- Improved transport across biological barriers
- Preferential distribution within the body
- Controlled and site specific release
- Improved solubility of hydrophobic drugs

Thanks to these properties the efficacy of a medicine is increased allowing the reduction of dosage and limiting the risk of side effects.

The anticancer and antimicrobial therapeutics are the most numerous categories among the approved and investigational products (Noorlander et al., 2015). But there are formulations being developed for autoimmune conditions, anaesthesia, metabolic disorders, ophthalmic conditions, neurological and psychiatric diseases, and others (Caster et al., 2017).

C.2 Nanotechnology-enabled medical devices

Nanotechnology applications in the field of medical devices span a wide range of extremely diverse products, technologies and application areas (Figure C.2) (Geertsma et al., 2015).

They are used for therapy, diagnosis, monitoring and prevention of diseases. Many different medical disciplines benefit from nanomedical devices.

Nanomaterials are used in coatings of various implants (Table C.2). Examples are coatings on stents

(cardiology), dental implants (dentistry) and hip implants (orthopedics). Coatings are used on these implants for various reasons. Nanocoatings can improve the biocompatibility and haemocompatbility by masking the surface of the implant to prevent pathological reactions. Nanomaterials in the coating can also improve the interaction between the implant surface and the surrounding bone or tissue, decreasing the risk that the implant loosens. Applying coatings to blood contacting surfaces reduces the risk of thrombosis. In addition, some nanomaterials like silver nanoparticles have antimicrobial properties preventing infections around the implant. Coatings may also form a barrier preventing the migration of heavy metal ions, which might provoke an allergic reaction. There are also nanocoatings that swell in time which induces a controlled drug release. In implantable pacing leads (cardiology) nanocoatings optimize the electrically active surface area.

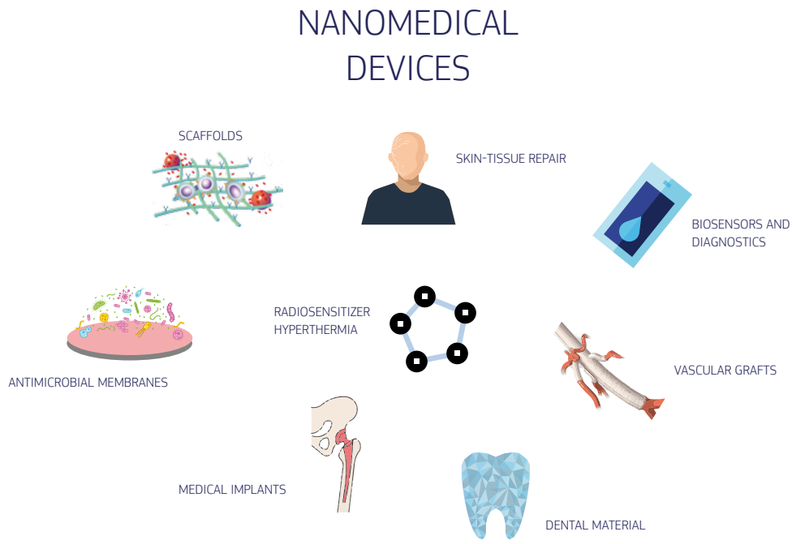


Figure C.2: Most spread nanotechnology applications in medical devices

Nanomaterials can also mimic natural tissues. With help of nanotechnology, optimal biological, physical and mechanical properties can be realized. In orthopaedics, nanomaterials are used as a matrix for bone regeneration. This matrix favours cell adhesion, stimulates bone growth and gives mechanical strength. Nanomaterials are also used in skin substitutes since these materials mimic the natural extracellular matrix to provide a microenvironment for wound healing and cell growth. In dentistry, nanomaterials are used in dental and root canal fillers to improve the physical and mechanical properties.

Nanotechnology has specific applications in oncology. Examples are diagnostic tests in which nanoparticles coated with an antibody detect cancer in an early stage or determine tumour boundaries or metastasis during surgical procedures. Nanomaterials can also increase the effect of chemotherapy and radiation by increasing the temperature locally (hyperthermia) or direct killing of local tumour cells (ablation).

Key reference:

Geertsma et al (2015). Nanotechnologies in medical devices. RIVM Rep. 2015-0149.

During surgery, suture needles and surgical blades can be used which are manufactured with nanomaterials. These nanomaterials make the surgical equipment stronger, lighter and extremely sharp which reduces tissue damage. Surgical gloves can be made of antibacterial textile containing nanomaterials.

Table C.1 Examples of nanotechnology-enabled medicinal products currently on the European market (non-exhaustive)

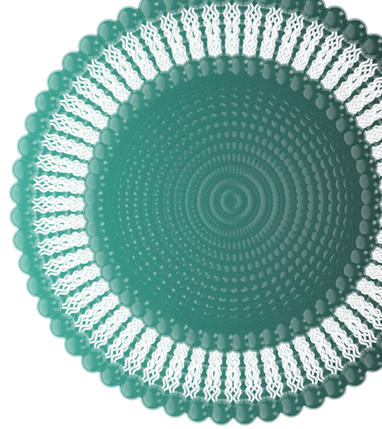
Nanotechnology platform	Advantage of nanotechnological approach	Active substance	Commercial name	Indication(s)
Nanocrystal	Increased dissolution velocity resulting in improved bioavailability	Fenofibrate/simvastatin	Cholib®	Dyslipidaemias
		Fenofibrate	Tricor® Lipanthyl® Lipidil®	Hyperlipidaemia
		Sirolimus	Rapamune®	Prophylaxis of organ rejection in renal transplant
		Aprepitant	Emend®	Nausea and vomiting
		Paliperidone palmitate	Xeplion®	Schizophrenia
		Olanzapine pamoate	Zypadhera®	Schizophrenia
Liposome	Drug delivery system, increased accumulation of the drug at the site of disease, protection of the drug from being metabolised too early, reduction of side effects	Doxorubicin hydrochloride	Caelyx® Myocet®	Breast neoplasms,/ Multiple myeloma / Ovarian neoplasms / Kaposi's sarcoma Metastatic breast cancer
		Irinotecan	Onivyde®	Metastatic adenocarcinoma of the pancreas
		Amphotericin B	AmBisome®	Fungal infection
		Daunorubicin	DaunoXome®	Advanced HIV-related Kaposi's Sarcoma
		Hepatitis A vaccine	Epaxal®	Active immunisation against hepatitis A
		Cytarabine	DepoCyte®	Lymphomatous meningitis
		Mifamurtide	Mepact®	Osteosarcoma
		Propofol	privan®/Propofol Lipuro®/Propofol®	Anaesthesia
		Verteporfin	Visudyne®	Degenerative myopia /age-related macular degeneration
		Morphine	DepoDur®	Pain
Albumin-bound drug nanoparticle	Increased site-specific delivery and solubility	Nab-paclitaxel	Abraxane®	Breast neoplasms /Carcinoma non-small-cell lung /Pancreatic neoplasm
Mixture of synthetic polypeptides		Glatiramer acetate	Copaxone®, Synthon®	Multiple sclerosis
Polymeric amine	Increased circulation and therapeutic delivery	Sevelamer	Renagel®/Renvela®	Dialysis/ hyperphosphatemia

Nanotechnology platform	Advantage of nanotechnological approach	Active substance	Commercial name	Indication(s)
Monoclonal antibody conjugated to radioactive isotope		Yttrium-90 radiolabelled ibritumomab tiuxetan	Zevalin®	Follicular Lymphoma
Polymer-protein conjugates	Improved pharmacokinetic properties, prolonged stability	Pegaspargase (mPEGasparaginase)	Oncaspar®	Acute lymphocytic leukaemia
		Peginterferon alpha-2b	PegIntron®	Chronic hepatitis C
		Peginterferon alpha-2a	Pegasys®	Chronic hepatitis B and C
		Pegfilgastrim	Neulasta®	Leukopenia by chemotherapy
		Methoxy polyethylene glycol-epoetin beta	Mircera®	Anaemia associated with chronic kidney disease
		Certolizumab pegol	CimziaTM	Rheumatoid arthritis
		Pegvisomant (PEGHGH antagonist)	Somavert®	Acromegaly
Nano-emulsion	Encapsulation and delivery of hydrophobic drugs, Improvement of pharmacokinetic properties	Ritonavir	Norvir®	HIV infection,
		Cyclosporine		Prophylaxis of organ rejection after transplantation
		Cyclosporine	Sandimmun Neoral®	Solid organ, bone marrow transplantation Endogenous uveitis Nephrotic syndrome Rheumatoid arthritis, Psoriasis Atopic dermatitis
Iron–carbohydrate complexes	Improved dose capacity improved tolerance	Ferumoxytol	Rienso®	Iron deficiency, anaemia in adult patients with chronic kidney disease
		Ferric carboxymaltose	Ferinject®	Iron deficiency
		Iron sucrose [iron(III)-hydroxidesucrose complex]	Visudyne®	Iron deficiency
		Iron(III) isomaltoside	Monofer®	Iron deficiency
		Iron(III)-hydroxide dextran complex	Ferrisat®/Cosmofer®	Iron deficiency
Virosome	High efficacy in enhancing immune response and improved safety	Adjuvanted influenza vaccine	Inflexal® V	Vaccine against influenza
		Inactivated hepatitis A virus	Epaxal®	Vaccine against hepatitis A
Gas dispersion in form of "microbubbles"	Enhances performance of the imaging technique	Sulphur hexafluoride	SonoVue®sulphur hexafluoride	Contrast agent for echocardiography and ultrasonography

Table C.2 Examples of nanotechnology-based medical devices currently on the market (Geertsma et al., 2015)

Product	Discipline	Application nanoparticle	Advantages	Example of product
Stents (bare metal and drug eluting stents)	Cardiology	Coating: improve biocompatibility and haemocompatibility	Due to hydrophobicity and smooth surface. Create barrier for migrating heavy metal ions. Mask stent surface which prevents pathological reactions. To trap drugs and release it slowly.	MOMO® Cre8™
(drug coated) Balloons	Cardiology	Coating: controlled release of drug during swelling		DIOR®
Ventricular assist device	Cardiology	Coating blood contacting surface: minimize thrombosis		VentrAssisst™
Implantable pacing lead	Cardiology	Coating: optimize electrically active surface area		(Biotronik SE&Co KG)
Pacemaker	Cardiology	Magnetoresistive sensor: more sensitive sensor to communicate and receive instructions faster		(St Jude Medical, Inc)
Dental composite	Dentistry	Dental filler: improve mechanical properties	Aesthetic properties, reduce working and setting times of resins	Ceram-X®
Dental implants	Dentistry	Coating: improve biocompatibility	Increase cell adhesion	
Bonding agent	Dentistry	Ensure product homogeneity and better mixing		
Dental material	Dentistry	Antimicrobial properties to prevent secondary caries		
Impression material	Dentistry	Filler: provide tear, distortion and heat resistance		
Root canal sealer/filler	Dentistry	Antimicrobial properties, better fit, improved physical properties		
Veneering material (tooth coating)	Dentistry	Prevent discoloration, increase wear resistance		
Diagnostics	a.o. Oncology	Nanoparticles coated with antibodies bind to biomarkers		
Immobilization device	Oncology	High strength and thinner material		
Hyperthermia/ablative devices	Oncology	Nanoparticles generate heat when exposed to alternating magnetic field. Inducing hyperthermia or ablation.		NanoTherm®
Tumour tracer	Oncology	Tumour localization by accumulate in lymph node and detection by the magnetic properties		Sienna+®

Orthopaedic implants (artificial knee, hip)	Orthopaedics	Coating: improve biocompatibility	Improve interaction between implant surface and surrounding bone or soft tissue.	
Bone filler/bone graft	Orthopaedics	Matrix for bone regeneration.	Favour cell adhesion and stimulate new bone growth. Adjustable degradation time and mechanical strength	
Suture needles	Surgery	Lighter, high strength and good ductility which reduces tissue damage		
Surgical blades	Surgery	Coating: extreme sharpness, low friction and low adhesion		
Sealing vessels	Surgery	Electrode consists of nanometer sized conductive particles for heat regulation		
Wound dressings	Wound care/healing	Antibacterial and antifungal (silver nanoparticles)	Mechanical support, tensile strength, stiffness, flexibility. Promote haemostasis thanks to Smaller pore size , larger surface area	
Skin substitutes	Wound care/healing	Mimic natural extracellular matrix to provide microenvironment for wound healing and cell growth		
Medical textiles	All disciplines	Antibacterial textile products such as patient dresses, bed lines, reusable surgical gloves		



GETTING IN TOUCH WITH THE EU

In person

All over the European Union there are hundreds of Europe Direct information centres. You can find the address of the centre nearest you at: https://europa.eu/european-union/contact_en

On the phone or by email

Europe Direct is a service that answers your questions about the European Union. You can contact this service:

- by freephone: 00 800 6 7 8 9 10 11 (certain operators may charge for these calls),
- at the following standard number: +32 22999696, or
- by electronic mail via: https://europa.eu/european-union/contact_en

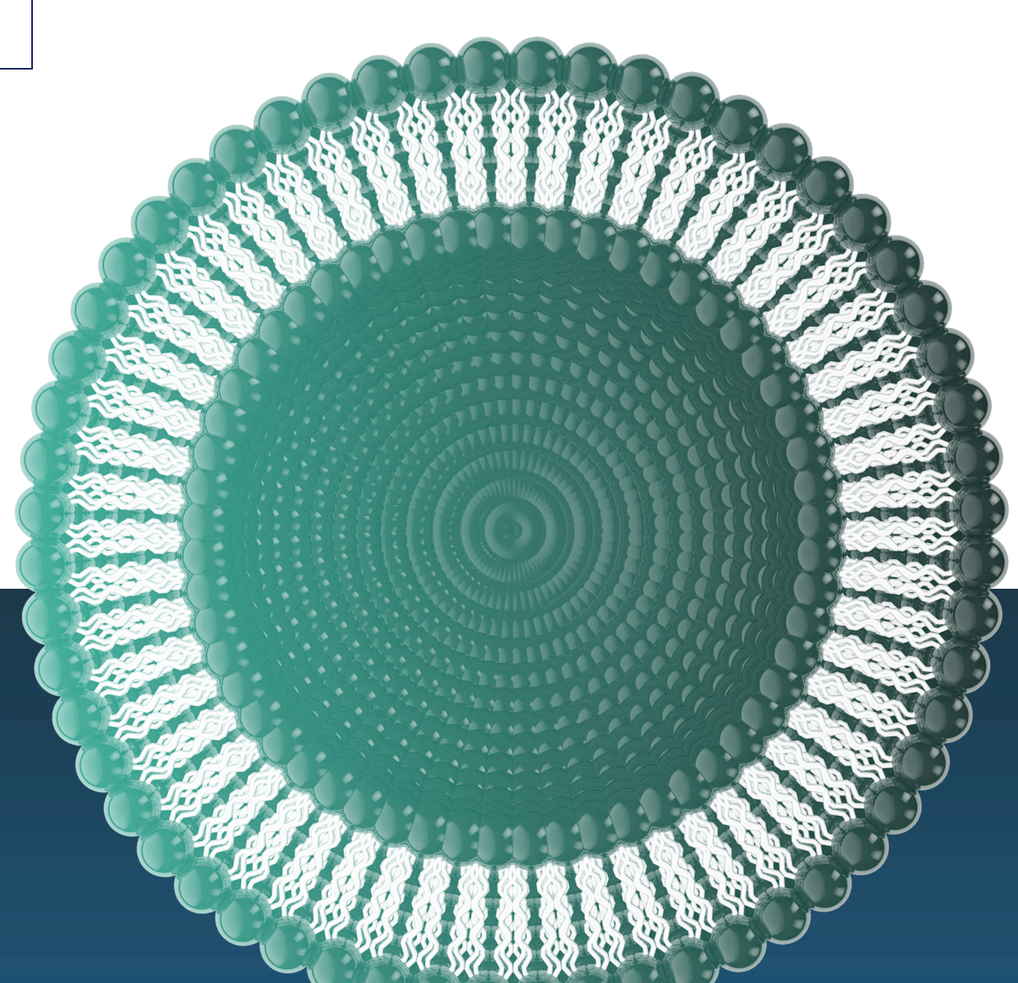
FINDING INFORMATION ABOUT THE EU

Online

Information about the European Union in all the official languages of the EU is available on the Europa website at:
https://europa.eu/european-union/index_en

EU publications

You can download or order free and priced EU publications from EU Bookshop at:
https://publications.europa.eu/en/publications
Multiple copies of free publications may be obtained by contacting Europe Direct or your local information centre: https://europa.eu/european-union/contact_en



KJ-NA-29919-EN-N

The European Commission's science and knowledge service

Joint Research Centre

JRC Mission

As the science and knowledge service of the European Commission, the Joint Research Centre's mission is to support EU policies with independent evidence throughout the whole policy cycle.

EU Science Hub

ec.europa.eu/jrc

@EU_ScienceHub

EU Science Hub - Joint Research Centre

EU Science, Research and Innovation

EU Science Hub

Publications Office of the European Union

doi: 10.2760/596822

ISBN 978-92-76-12554-9