Launching stakeholder discussions on identified regulatory needs for nanotechnology-enabled health products

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Box 1: Terms describing nanotechnology-enabled health products
A formal definition of nanomedicines does not exist. For this review, the following terms are used:
• “nanomedicines”: to describe products that are regulated as medicinal products
• “nanomedical devices”: to describe products that are regulated as medical devices
• “nanotechnology-enabled health products”: overarching term to describe both product classes

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Abstract

The development of nanotechnology-enabled health products offers innovative therapeutic and diagnostic opportunities to address medical needs. At the moment, no specific regulatory framework exists for such products since they can be covered by the existing frameworks for medicinal products and medical devices. However, these frameworks do require additional guidance to fully cover the particularities of nanotechnology-enabled products. After a detailed analysis of regulatory guidance documents, standards, and scientific publications originating mainly from Europe and the US, the European project “REFINE” has released a White Paper summarising the main needs in the field. The selection of the regulatory pathway, the identification of regulatory information needs, as well as the availability of standardised testing methods are among the identified regulatory challenges.

Furthermore, additional guidance is needed on how the similarity of follow-on medicinal products can be demonstrated. Also, challenges related to the classification and assessment of nanotechnology-enabled medical devices are presented. The project consortium is now collecting feedback on the identified challenges through a dedicated survey and published comments on this manuscript. The resulting discussions within the scientific community should help to advance the regulatory science in the area of nanotechnology-enabled health products.

Purpose and rationale

Sophisticated nanotechnology-enabled health products can bring solutions for medical needs but might also trigger challenges with regulatory approval. The main regulatory challenges have been summarised in the REFINE’s White Paper, calling for a stakeholder discussion on these issues and possible solutions. This common effort should help to advance regulatory science in the field and facilitate the development and commercialisation of these highly innovative products.

Introduction

The number of nanotechnology-enabled health products (see Box 1 for an explanation of terminology) used for therapeutic and/or diagnostic applications is constantly increasing. They can offer substantial improvements in terms of pharmacokinetic properties, such as prolonged stability and blood circulation, improved transport across biological barriers, or a preferential distribution within the body [1]–[4]. The applications of nanotechnology in medical devices are diverse and include coatings on implants for increased biocompatibility, bone, skin, or dental material substitutes with optimised properties; and diagnostic as well as therapeutic tools in oncology [5], [6]. Depending on their primary mechanism of action, nanotechnology-enabled health products are regulated under the existing regulatory frameworks for medicinal products or medical devices. Examples of nanotechnology-enabled health products that have successfully reached the market and the regulatory path they followed are provided in Table 1.

However, such pioneering products can be very complex and might trigger regulatory questions regarding the assessment of their quality and safety. The European Medicines Agency (EMA) Innovation Task Force (ITF), as well as the European Commission’s Working Group on New and Emerging Technologies (NET) support the development of nanotechnology-enabled health products with guidance and scientific advice. EMA’s Reflection Papers [7]–[11], as well as the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) opinion [12] provide initial guidance for specific categories of nanotechnology-enabled health products. Guidance for industry has also been released by the US and Japanese regulatory authorities [13]–[16]. Challenges related to the regulation of nanotechnology-enabled products are regularly discussed among the involved communities at regulatory science summits and workshops and resulted in expert recommendations on regulatory needs [17,18]. Furthermore, the Nanomedicines Working Group of the International Pharmaceutical Regulators Programme (IPRP) meets biannually to share experience and discuss upcoming regulatory questions related to products containing nanomaterials.
Table 1: Examples of nanotechnology-enabled health products approved under regulatory frameworks for medicinal products or medical devices

| Product description | Advantage of nanotechnology platform | Indication/Area of application | Mechanism of action | Regulatory path |
|---------------------|--------------------------------------|--------------------------------|---------------------|-----------------|
| Liposomal doxorubicin hydrochloride | Increased accumulation of the drug at the site of disease, reduction of side effects | Breast neoplasm, ovarian cancer, Kaposi’s sarcoma | Pharmacological | Medicinal product |
| Albumin-bound paclitaxel nanoparticle | Increased-site specific delivery and improved solubility | Breast neoplasms | Pharmacological | Medicinal product |
| PEGylated l-asparaginase | Prolonged stability, reduced side effects | Acute lymphoblastic leukemia | Pharmacological | Medicinal product |
| Fenofibrat nanocrystal | Increased dissolution velocity resulting in improved bioavailability | Hyperlipidemia | Pharmacological | Medicinal product |
| Iron-sucrose complexes | Improved dose capacity, improved tolerance | Chronic kidney failure with iron deficiency | Pharmacological | Medicinal product |
| Virosomal formulation of a hepatitis A vaccine | High efficiency in enhancing immune response and improved safety | Vaccine against hepatitis A | Immunological | Medicinal product |
| Superparamagnetic Iron oxide nanoparticles (SPION) | Hyperthermia cancer treatment | Brain tumour (EU) | Physical: heat production under alternating magnetic field | Medical device |
| Nanostructured hydroxyapatite | Bone substitute: mimics bone structure by cell adhesion and growth | Orthopedics | Physical | Medical device |
| Bare metal stents with a nano-level coating of diamond-like carbon | Coating: improve biocompatibility and haemocompatibility | Interventional cardiology | Physical | Medical device |
| Nano-ceramic dental composite | Improved mechanical and aesthetic properties | Dentistry | Physical | Medical device |
| Skin substitute composed of cellulose nanofibers | Mimic natural extracellular matrix to provide a microenvironment for wound healing and cell growth | Wound healing | Physical | Medical device |
| Wound dressing with silver nanoparticles | Antimicrobial and antifungal properties of silver nanoparticles | Wound healing | Both physical and antimicrobial | Combination product regulated under medical device regulation |

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The current status of identified regulatory challenges in the field of nanotechnology-enabled health products has been summarised in the frame of the H2020 project REFINE\(^1\), which aims to propose a regulatory science framework for nano(bio)material-based medical products and devices. REFINE’s White Paper [19] provides an overview of current regulatory challenges in the field of nanotechnology-enabled health products, calling for a broader debate in the community on how the recognised challenges can be addressed in upcoming research activities. In addition, REFINE’s White Paper contains information on the legislative/regulatory structure and the role of the different key organisations involved in the regulation of nanotechnology-enabled health products.

Selection of the regulatory framework

The classification of a product into a medicinal product or a medical device depends on its primary mode of action [20], [21] (see also Table 1), which can be blurry for certain nanotechnology-enabled health products. Examples are nanomaterials (mostly inorganic) exhibiting their therapeutic action via external stimuli (i.e., light, magnetic field, radiation) or acting as enhancing factors of energy sources (Figure 1).

Challenges are also presented by the classification of combination products, which combine a medical device with a medicinal product. Again, the determination of the primary mode of action is critical to decide which regulatory framework is applicable and which authority is responsible for the market regulation.

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\(^1\) H2020 Project REFINE; www.refine-nanomed.eu
authorisation. Since the regulatory pathways for medicinal products versus medical devices are substantially different, product developers to get into contact with the regulatory community as early as possible.

In Europe, the European Commission’s Borderline and Classification Working Group\(^2\), as well as EMA’s ITF\(^3\) and the EU-Innovation Network\(^4\), provide advice and can assist in the classification of borderline products and combination products. The EMA draft guideline on the requirements for drug-device combinations has recently been released [23]. Also, competent authorities of European Member States have established scientific advice mechanisms as a tool to provide regulatory guidance concerning questions on quality, safety, efficacy, and clinical requirements arising at different stages of product development. The Heads of Medicines Agencies (HMA) have recently proposed a new concept that allows asking for scientific advice from more than one national competent authority in a single step. The pilot project has started on 1 February 2020 [24].

In the US, the primary responsibility for assigning combination products to a lead agency centre is implemented by the Food and Drug Administration (FDA) Office of Combination Products (OCP). The OCP will classify the product as a drug, biologic, or device and assign the review responsibility to the corresponding FDA centre. However, also other concerned centres will be involved in the evaluation procedure. The principles of the classification of combination products and the corresponding regulatory paths have been presented in the recently released draft guidance of the FDA [25].

Identification of regulatory information needs

The identification of regulatory requirements relevant for the assessment of a product is a prerequisite for its regulatory approval as a medicinal product or a medical device. Nanotechnology-enabled health products are regulated under the existing regulatory frameworks for medicinal products or medical devices. Still, they may require additional quality and safety assessments triggered by the unique characteristics of the nanomaterials. Currently, only initial/draft guidance is available [19], including FDA draft guidance for drug products that contain a nanomaterial [13] and EMA Reflection Papers for certain classes of nanotechnology-enabled products used in medicine [7]–[10]. These documents reflect the current state of knowledge in the specific areas where the regulatory experience is limited and provide several different parameters which seem to be important for the characterisation of product quality and safety. However, there is no certainty about the relevance and impact of described parameters since robust datasets deriving from several submissions on the same product classes and the regulatory experience on emerging products are lacking. For such innovative products, a close collaboration of product developers and competent authority is crucial to ensure a successful translation to the market. In addition, the increasing complexity and the huge variety of the next generation of nanomedicines (Figure 2A) and nanomedical devices (Figure 2B) might require even more specific guidance. On the other hand, while such guidance should address specific properties of sophisticated products, it should not limit its applicability to other products in the same class/classes.

Unclear regulatory requirements may hamper the development, clinical translation, and marketing of nanotechnology-enabled health products, while at the same time, high-quality data on safety, efficacy, and quality for these products will not be generated (Figure 3).

This vicious circle can only be broken in an iterative process that leads to early identification of physicochemical and non-clinical properties

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\(^2\) MDCG Working Group 6: Borderline and Classification - Terms of reference. Available at: [https://ec.europa.eu/docsroom/documents/32069](https://ec.europa.eu/docsroom/documents/32069)

\(^3\) European Medicines Agency Innovation Task Force. Available at: [https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema%27s-innovation-task-force-(itf)-section](https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema%27s-innovation-task-force-(itf)-section)

\(^4\) EU Innovation Network. Available at: [https://www.hma.eu/495.html](https://www.hma.eu/495.html)
with clinical relevance. Close monitoring of the scientific literature, such as by using automated text-mining tools and in-depth analysis of safety issues reported in real-world databases, could be ways forward to identify the information needs for innovative health products.

Terminology and definitions of nanotechnology-enabled health products

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.

A:

B:

Figure 2: Nanotechnology-enabled platforms and applications marketed as medicinal products (A) or medical devices (B) [19]
An emerging technology, such as nanotechnology, 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.

The IPRP Working Group (WG) on Nanomedicines acknowledged the relevance of terminology for the harmonisation activities and included this topic in its work programme. The descriptions for nanotechnology-enabled medicinal products, as well as applicable legislative frameworks, were collected among the WG members [26]. The European Commission’s Joint Research Centre is a member of the WG and took up the challenge to compile and analyse nanomedicine-related terms and definitions used in a regulatory context [27].

The vicious circle showing the interdependence of availability of regulatory guidance and the generation of data related to the characterisation of nanomedicines [19].

For this purpose, websites of 13 regulatory authorities and international clinical trial registries have been crawled, and text-mining tools were used to extract relevant information. The study demonstrated differences in the number and type of terms used by regulatory authorities to describe nanotechnology-enabled medicinal products (Table 2). Furthermore, it showed geographical and sectorial differences in frequency and type of used terms and identified 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 the marketing of nanotechnology-enabled products.

Currently, a formal definition of nanomedicines or nanotechnology-enabled medicinal products does not exist. EMA uses a working definition containing the notion of specific size-related properties, which can also occur for sizes larger than 100 nm (Table 3) [4]. Likewise, also, the FDA has not established a regulatory definition of products containing nanomaterials. In the guidance “Considering Whether an FDA-Regulated Product involves the Application of Nanotechnology” [28], it recommends considering several aspects of size and related effects (Table 3), which should apply broadly to all FDA-regulated products including medicinal products and medical devices.

In 2011, the European Commission published a recommendation on the definition of a nanomaterial [29]. Whereas this recommendation in practice has no implications for medicinal products, the medical device regulation [21] has almost entirely adopted the EU definition of nanomaterials 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.

In general, there is an ongoing confusion on how to interpret the various terms used in the EC
definition, but an overview of concepts and terms, which might help solve the confusion, has recently been published [30]. This is, in particular, relevant for the classification Rule 19, which is specifying the exposure-based classification of nanomaterial-containing products. Guidance for the application of all classification rules is expected soon5. In addition, technical and scientific discussions on how to measure the different parameters mentioned in the legislative texts are still ongoing [31].

Table 2: Compilation of terms used by selected regulatory authorities [24]

| 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, Nanomedicine products, Nanotechnology-based medicinal products |
| Japan Pharmaceuticals and Medical Devices Agency, Japan (PMDA) | Nanotechnology-based medicines, Nanodrug delivery systems, Nanomedical devices, Nanopharmaceuticals, Nanosized drugs |
| United States US Food and Drug Administration (FDA) | Nanosized drug products, Nanotechnology products, Products that involve the application of nanotechnology, Drug Products that contain nanomaterials |
| Canada Government of Canada TERMIUM Plus®21 | Nanodrugs                                                                                              |

Challenges in the assessment of follow-on products

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. 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. However, it is not defined yet to what extent the characterisation and comparability of the follow-on product is required and how similar is sufficiently similar. In particular, the acceptability of differences in numerical values of quality attributes is relevant to define similarity. Nevertheless, already small differences in physicochemical characteristics can have an impact on the safety and efficacy of the product.

To support product developers, the EMA has released Reflection Papers for liposomal formulations [8] and iron-based nano-colloidal products [9], which include guidance on the current status of regulatory needs for

5 Ongoing Guidance development within MDCG Subgroups, https://ec.europa.eu/docsroom/documents/38862
nanosimilars. Also, the FDA guidance on drug products that contain nanomaterials [13] provides considerations for generic products intending to follow the pathway for Abbreviated New Drug Application (ANDA). These regulatory documents conclude that differences in product characteristics might not be detectable by conventional bioequivalence testing alone, and additional (non-clinical and clinical) studies might be needed. Particular challenges are presented by drug delivery systems where the active pharmaceutical ingredient (API) often exists in multiple forms, including nanomaterial-encapsulated drugs as well as released free drug and its metabolites, both in systemic circulation and at the target site [13]. In this case, the outcomes of the bioequivalence studies alone might lead to diverging regulatory decisions in different geographical regions, as shown in the example of liposomal doxorubicin hydrochloride formulation. To provide more clarity, the EMA and the FDA have released product-specific guidance that can help to assess the generic products of this formulation [32], [33]. Thus, a more harmonised regulatory approach that could be similar to the one established for generic biological products (“biosimilars”) might be a suitable way forward. This regulatory framework applies a stepwise comparability approach for quality, safety, and efficacy and highlights the differences between the follow-on product and the innovator product with regard to the impact of the manufacturing process. In any case, it requires a better understanding of whether clinical trials can be limited to pharmacokinetics (PK) studies or more detailed and expensive clinical trials are needed that will also include the assessment of efficacy and/or safety of the follow-on product [34].

Table 3: Working definitions and terms related to nanotechnology-enabled health products used by regulatory authorities

| Regulatory descriptions of nanotechnology-enabled health products | EU | US |
|---|---|---|
| Medicinal Products (EMA) | EMA Working definition of nanomedicines:  
• Purposely designed systems for clinical applications  
• At least one component at the nanoscale size (1–1000 nm)  
• 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 according to the FDA finalised 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 mm (1000 nm). |
| Medical devices (EC) | Medical devices regulation based on the EU definition of nanomaterial:  
‘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 (EU 2017/745) | |
Methodological challenges

The assessment of quality, safety, and efficacy of nanotechnology-enabled health products obliges the availability of reliable and relevant methods that are accepted by the regulatory authorities.

The specific properties of nanomaterials might need an adaptation of conventional testing methods or even the development and standardisation of new methods, tools, and approaches [35]. Both EMA and FDA propose mechanisms for the acceptability of new methodologies, tools, or models, including in silico methods [36]–[38]. Competent authorities in different regions (US FDA, EMA, and the Japanese PMDA) share the information related to new methods under confidentiality agreements supporting the international acceptance of methods.

However, formal standardisation, including method validation and regulatory acceptance, will highly facilitate the regulatory review process of health products. The ISO Technical Committees on Biological and clinical evaluation of medical devices (ISO/TC194) and on Nanotechnologies (ISO/TC229), as well as ASTM International Committee E56, have developed many standardised test methods for the physicochemical characterisation and biological evaluation of nanotechnology products [39] (Table 4).

Table 4: Standardised in vitro methods and guidance addressing the biological characterisation of nanotechnology-enabled health products [19].

| 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 the release of muramic acid from Staphylococcus aureus | Antimicrobial efficacy                                                   | ISO/TS 16550:2014   | Intended for medical applications but also 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) |                                                                                                   |

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. Also, for certain toxicological aspects such as evaluation of a contamination with bacterial endotoxin and immunotoxicity, the development of additional, reliable test methods is necessary [40]–[43][44][45].

In addition, the application of standards depends on the legal frameworks and geographical area. As an example, ISO standardised methods are used in different industrial sectors, including medical devices, whereas the official reference for standards applying to medicinal products is the
pharmacopoeia and ICH guidance documents. In the US, other methods such as those standardised by ASTM International can be subject to FDA’s standards recognition procedure.

Apart from the method recognition, several scientific/technical factors such as material properties, dispersion characteristics and method principles (Box 2) can influence the applicability of the methods for the nanomaterial under investigation and have to be considered when interpreting results.

The standardisation process and the confidence in the obtained data can also be hampered by a lack of appropriate reference materials relevant to nanotechnology-enabled health products [46]. Another important aspect is the interaction of nanotechnology-enabled products with biological fluids, which can strongly impact the stability of the dispersion, affect the pharmacological and toxicological profile or provoke unexpected immunological reactions. Therefore, before starting toxicological assessments, in-depth characterisation of the dispersion should be performed in a biological medium of relevance [47].

Several challenges also persist regarding the toxicological evaluation of nanomaterials. Due to their specific physicochemical characteristics such as optical properties, nanomaterials can interfere with in vitro assay components resulting in misleading data [48]. Therefore, existing methods should be reviewed for their suitability to test nanomaterials and, where necessary, suitable, adapted for nanomaterials, and methods need to be developed [49].

Several characterisation methods suitable for assessments of nanotechnology-enabled products have been developed by laboratories such as the NCI-NCL[6] and the EUNCL[7]. A large fraction of these protocols is probably also relevant for the characterisation of nanomaterials released from medical devices. Such optimised protocols provide a good starting point for the method standardisation.

The development and optimisation of lacking methods are the major objectives of the REFINE project. REFINE will focus on in silico methods for biodistribution and in vitro methods for toxicological assessment required early in the preclinical stage. In this context, REFINE will discuss with other communities the common challenges, the transferability of methods and standards between sectors as well as strategies to advance the regulatory science of nanotechnology-enabled products.

**Conclusions**

Like any other highly innovative product class, also nanotechnology-enabled health products challenge the regulatory frameworks worldwide. Challenges for nanotechnology-enabled health products are already recognised by regulatory authorities through the provision of initial reflection papers and guidance documents. REFINE’s White Paper highlights regulatory needs that require the development of additional guidance, methods, and harmonised approaches to accommodate the particularities of nanotechnology-enabled health products. The project consortium is now calling for stakeholder feedback on the identified challenges and would like to launch a debate in the nanotechnology community on how these challenges can be addressed efficiently. The project consortium will launch a dedicated survey allowing to comment on the identified challenges and collect information on relevant ongoing activities providing scientific solutions. Such information will complete the White Paper and can be seen as a starting point for common research activities supporting the translation of nanotechnology-enabled products to the market.

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6 Nanotechnology Characterization Laboratory (NCI-NCL): [https://nanolab.cancer.gov/](https://nanolab.cancer.gov/)

7 European Nanomedicine Characterisation Laboratory (EUNCL): [http://www.euncl.eu/](http://www.euncl.eu/)
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Disclaimer
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