Nanotechnology-based medicinal products for human use

EU-IN Horizon Scanning Report

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Table of Content

1. Introduction

Nanotechnology is a rapidly evolving scientific research field with a wide applicability. It is showing successful and beneficial uses in the fields of diagnostics, disease treatment and prevention.

In the context of medical science, it is expected that nanotechnology will contribute to unlock a broad range of applications for innovative medicinal products such as controlled drug release, targeted cancer therapies, medical imaging including theranostics, tissue engineering, etc. and will most likely be disruptive for the diagnosis and therapy of diseases in unforeseen ways.

Nanotechnology has found widespread application across various fields. In biomedical research, its utilization primarily evolves around designing and developing drug delivery systems and medical diagnosis. Nanotechnology-based drug delivery systems offer numerous advantages, including enhanced targeting of therapeutic drugs, protection against degradation during *in vivo* transport and controlled release at specific sites or cells in response to signals. This not only improves the therapeutic efficacy but also minimizes side effects (e.g. liposomal doxorubicin) (1). Among other advantages, the utilization of nanotechnologies in medicine can help minimizing the dosage regime (and thus mitigate adverse effects) and improve stability of active ingredients, as demonstrated by the approved mRNA COVID-19 vaccines in the form of lipid nanoparticles (2).

The European Commission (EC) first adopted a definition of a nanomaterial in 2011 (3) and a final recommendation on the definition of nanomaterial was published on 14th of June 2022 (4). According to this definition, 'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50% or more of these particles in the number-based size distribution fulfil at least one of the following conditions:

(a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm;

(b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm;

(c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm. In the determination of the particle number-based size distribution, it is not necessary to consider particles with at least two orthogonal external dimensions larger than 100 µm. However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial.

The EU definition of nanomaterial is also mentioned in Regulation (EU) 2017/745 on medical devices. Nevertheless, it is important to notice that while some European legislations (e.g. REACH, Biocidal Products Regulation and Medical Devices Regulation) follow the above-mentioned definition of nanomaterial, such general legal definition is not strictly binding for medicinal products (3).

Nanotechnology-based medicinal products, nanomedicine products or nanomedicines, the medical application of nanotechnology and nanoformulations, are typically medicinal products (fulfilling the definition of the medicinal product according to European legislation), in which at least one component is at nano-scale size (e.g. active substance or excipient), resulting in definable specific properties and characteristics, related to the specific nanotechnology application and characteristics for the intended use (route of administration, dose) and associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution). They are used in both systemic and topical use. Major therapeutic areas are: oncology, infectious diseases (e.g. vaccines), neurology, psychiatry and genetic disorders.

However, we would like to highlight that the definition of nanomedicines could vary slightly between regions and that there is not a unique definition of nanomedicines in EU.

2. Available support and information for researchers on nanomedicines

2.1. Regulatory framework

Nanomedicines are regulated under the existing regulatory frameworks of medicinal products and medical devices. The European Regulatory Framework for medicinal products for human use 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. There is no dedicated EU framework for nanomedicines. Nevertheless, some reflection papers related to different categories of nanomedicines (listed in Annex 1) have already been released in order to provide initial guidance on their pharmaceutical development, non-clinical and/or clinical studies. Based on the unique characteristics of nanomaterials, further guidance documents should be developed.

2.1.1. EMA Guidelines and FDA guidelines on nanomedicines

The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have published reflection papers and guidelines, respectively, to researchers and stakeholders on the development of nanomedicines (See Annex 1).

2.2. Available support for researchers on nanomedicines

Development of new medicines, such as certain nanomedicines, always carries the risk of high uncertainty for product developers. The aforementioned guidelines serve as one of the tools which may help the developers to conduct the relevant studies and generate the necessary supporting data to demonstrate regulatory compliance. However, the regulatory guidelines must also reflect the current knowledge, which can only be improved through greater understanding of a range of innovative products, and through more data regarding their quality, safety, and efficacy.

Therefore, there is a need to break the vicious circle shown in Figure 1 (5), where it is stated that the regulator's knowledge gaps produce incomplete guidance documents leading to developer's uncertainty and inadequacy of evidence datasets, thus raising regulatory objections on quality and safety assessment. The brake of this gap can only be achieved by a close collaboration between regulators, product developers and researchers. The European Innovation Network (EU-IN) aims indeed to foster collaboration among these stakeholders and reduce the gaps (6).

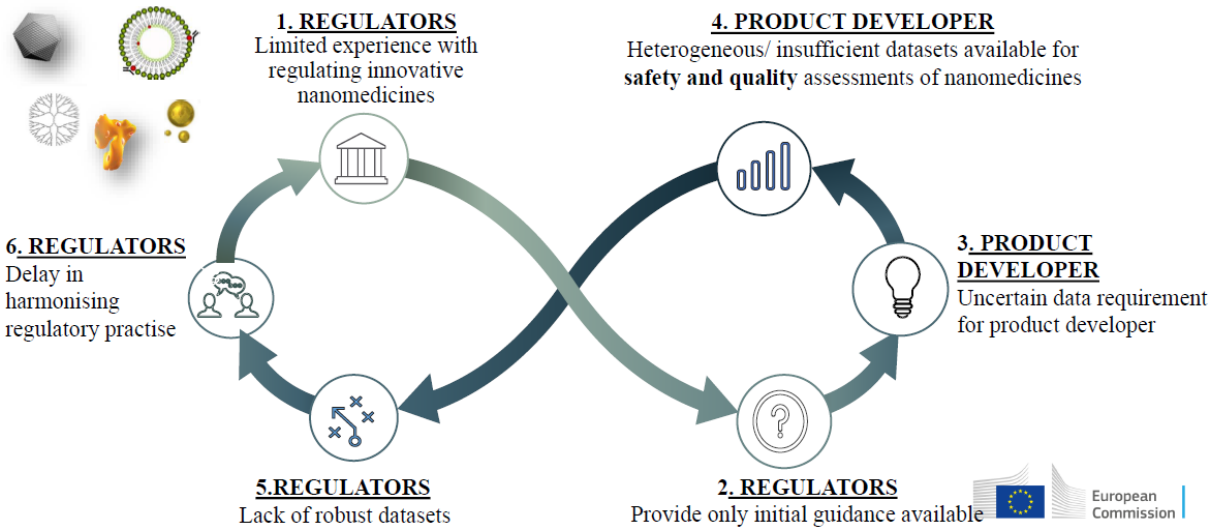

Figure 1. *Vicious circle showing the interdependence of availability of regulatory guidance and the generation of high quality and robust data related to the characterization of nanomedicines.*

Applicants are encouraged to contact the National Competent Authorities (NCAs) or EMA from the early stages of the development in order to obtain scientific and/or regulatory advice during the development of such products. In this regard, dedicated support is given by the NCAs (through National Scientific Advice or Innovation Offices) or by EMA (through the Innovation Task Force (ITF), Quality Innovation Group (QIG) or the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice Working Party (SAWP)) as follows:

- Through the Innovation offices within the NCAs. The contacts of the Innovation offices from the different NCAs can be found on the following link. Meetings are free-of-charge in some NCAs. These meetings have the aim of helping the researchers to advance on an appropriate and timely manner with their medicinal product development.
- EMA's early general regulatory guidance and orientation for academic developers (academia@ema.europa.eu).
- EMA ITF (ITFSecretariat@ema.europa.eu). The EMA ITF interacts with medicine developers through the so-called ITF briefing meetings which are free-of-charge, informal, brainstorming sessions of one hour and half where the applicant can ask questions to EU regulators and experts to receive an initial general guidance on their innovative product development.
- QIG. The QIG can support the development and registration of innovative technologies and products, by clarifying the regulatory requirements for manufacturing and control early on for stakeholders. Medicine developers may email qig@ema.europa.eu to:
    a) Request advice from the QIG
    b) Discuss plans for applying for an EMA scientific advice procedure on a topic covered by the QIG work programme
- SAWP (CHMP Scientific Advice Working Party) coordinates the provision of scientific advice and protocol assistance. It brings an integrated view forward to the CHMP and the Committee for Orphan Medicinal Products (COMP) on the quality, non-clinical, safety and efficacy related to the development of medicinal products and on the significant benefit of orphan medicinal products. Protocol assistance is a scientific advice dedicated to developers of designated orphan medicines.

- PRIority MEdicines (PRIME) scheme: PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise the development strategy and speed up evaluation so these medicines can reach patients earlier.

3. Current status and key emerging trends

3.1. Nanoparticle classification

Nanomedicines can be broadly divided into various categories depending on:

- Morphology (nanoparticles, micelles, nanofibres).
    - Nanoparticle: a nanoparticle is a nano-object with three external dimensions on a nanoscale. Nanoparticles are not all spheres but may have the shape of needles, extended rods, spring structures, etc. (7).
    - Micelles: an aggregate made up of molecules and/or ions, which is formed above a certain critical concentration in solutions of surface active agents (8).
    - Nanofibers: nanofibers are nanoscale in one dimension and are used frequently in electrospun polymer-containing drugs or alone, for example, as a wound-healing matrix (9)
- Structure (nanocapsules, nanospheres, nanocrystals).
    - Nanocapsules: nano-object (discrete piece of material with one, two, or three external dimensions in the nanoscale) with more than one chemically or structurally distinct wall layer enclosing a hollow or solid core and which is designed to carry analytical, therapeutic or image enhancing components (10)
    - Nanocrystals: nanoscale solid formed with a periodic lattice of atoms, ions or molecules (11).
    - Nanosphere: spherical nano-object (12), typically solid polymers with drugs embedded in the polymer matrix.
- Composition:
    - Lipid based nanoparticles (liposomes, solid lipid nanoparticles)
        - Liposomes: are classically described as artificially prepared vesicles composed of one or more concentric lipidic bi-layers enclosing one or more aqueous compartments. They include, but are not limited to, mono- and multi-lamellar liposomes, multi-vesicular-liposomes and polymer-coated liposomes (13).
        - Solid lipid nanoparticle (SLNs): comprise a solid hydrophobic core of lipids, such as mono-, di- and triglycerides or fatty acids with a monolayer of phospholipid coating. Like polymeric nanoparticles, they are capable of control release of up to several weeks and can also be coated or grafted with ligands for drug targeting (14). They are also stable and biodegradable under physiological conditions (15) with a high drug loading capacity for both hydrophilic and lipophilic drugs (16-17).
    - Polymeric nanoparticles (Polymer nanoparticles, polymer-protein conjugates)

- Polymeric nanoparticles: solid nanoparticles that consist of natural or synthetic polymers (18).
- 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.

- Protein nanoparticles
  - Nanoparticle albumin-bound (nab): uses albumin to shuttle hydrophobic therapeutics. Albumin is a ubiquitous serum protein that naturally carries molecules in the bloodstream, attached by reversible noncovalent binding (19).
- Inorganic nanoparticles
  - Colloid: e.g. 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.
- Carbon nanoparticles
  - Fullerenes: molecule composed solely of an even number of carbon atoms, which form a closed cage-like fused-ring polycyclic system with 12 five-membered rings and the rest six-membered rings (20).

3.2. Nanomedicines already authorised

Medicinal products containing nanoparticles have already gained approval within both the EU and the US under the existing regulatory frameworks. While the act of nanosizing does not inherently imply novelty, it is expected that the application of nanotechnology will yield innovative products (21).

The employed formulations may contain a nanoparticle (such as lipidic or polymeric) with a bound or encapsulated active substance or may be formed directly from the constituent drug in a nano-form (e.g. nanocrystals).

Most of the currently approved nanotechnology-based medicinal products are based on optimised formulations of active substances that had already been approved.

On the other hand, lipid nanoparticles (LNPs) have newly become a leading technology for the highly efficient in vivo delivery of exogenous mRNA, notably in the context of COVID-19 vaccines. LNPs have been thoroughly researched and effectively used in clinical setting for the delivery of numerous actives substances.

A non-exhaustive overview of authorised nanotechnology-based medicinal products approved via submission of full Marketing Authorisation applications, classified by their general physical and chemical properties, is provided as Annex 2.

It should be noted that EMA has published product-specific bioequivalence guidance for pegylated liposomal doxorubicin hydrochloride in 2019 (22) and in 2023 for liposomal amphotericin B (23).

3.3. Nanomedicines under development

3.3.1. Non-clinical developments using nanomedicines

Nanomedicines represent an active area of research in preclinical settings with a very diverse set of materials being developed, leading to increasing complexity of the therapeutic products.

As mentioned in section 3.2, most of the currently approved nanomedicines are based on active substances that have already been approved. However, in late-stage preclinical programs, new therapeutic modalities such as nucleic acids, peptides etc. are becoming more prominent. This is especially true with the rapidly expanding category of ribonucleic acid (RNA)-based products, which have a strong preclinical pipeline. These products are in the limelight owing to the success of mRNA vaccines against COVID-19, developed with unprecedented speed due to the collective urgency of the pandemic. Although late-stage preclinical programs still face the previously highlighted hurdles associated with translation of preclinical success of nanomedicines (discussed below) into clinical practice, nevertheless it is already foreseeable that a change in the landscape of approved products is set to come.

Research into reformulating previously approved active substances, using nano-based delivery systems, continues to advance as well, especially for well-known small molecules in oncology indications. At the preclinical stage, these novel formulations have demonstrated significant advantageous properties with respect to pharmacokinetics, safety and efficacy, when compared to their legacy counterparts (24-26).

While the majority of late-stage preclinical programs for nanomedicines still emphasise oncology indications, including prophylactic and therapeutic anti-cancer vaccines (27-28), there is a wide array of programs in other treatment areas such as autoimmune diseases, infectious diseases, and a variety of genetic and/or rare diseases (29-32). Examples of current late-stage preclinical products include:

- Lipid-based nanoparticles. Nanomedicines consisting of lipid-based nanoparticles continue to be a common class of investigated products. A large variety of lipid nanoparticle systems are being developed. Examples include hybrid delivery systems such as non-viral vector silicon-LNP delivery systems (17) and lipid bilayer (LB)-coated mesoporous silica nanoparticle (silicasome) platforms (33). Attempts are also made to further investigate simpler options such as lipoplexes (34) or optimize classical liposomal drug delivery systems.
- Protein and peptide-based nanomedicines. Proteins and peptides possessing self-assembling capabilities have been widely explored. Late preclinical development efforts include a 30 amino acid polypeptide (containing arginine-alanine-leucine-alanine repeats) as a delivery vehicle for nucleic acids (27-28), (35), iron oxide core nanoparticles that are coated with autoimmune disease-relevant peptide-major histocompatibility complexes EPT, and novel protein-only nanoparticles conjugated to an anti-tumor drug (T22-GFP-H6-FdU) (24).
- Inorganic nanomedicines. Nanoparticles in development that use inorganic elements are based on elemental metals, metal oxides, and/or metal salts. Hybrid nanomaterials are also common when inorganic nanomaterials are coupled with organic materials such as lipids, peptides or polymers (28-29). Examples include mesoporous silica nanoparticles coated with polyethylenimine and polyethylene glycol (PEG) that combine multiple therapeutic agents into a single nanoconstruct. This latter example aims to co-deliver CpG, a TLR-9 agonist, and STAT3 siRNA as a cancer nanotherapeutic (36).
- Cell-based formulations. Cellular nanoparticles represent an emerging biomimetic platform with the aim to deliver not only chemotherapy agents but also immunotherapy agents, or mRNA, examples include platelet membrane-coated nanoparticles (37). Exosome-based products are also being explored but are still in early to mid-stage preclinical development.
- Nanoparticles made with nucleic acids. As mentioned above, mRNA can be delivered using LNPs. Some companies are using the nucleic acids as the base nanoparticle, and RNA nanoparticles are being explored for the delivery of therapeutics (38).

Despite the significant interest in the field, a recent editorial in a prominent nanotechnology-based journal noted that translation of nanomedicines has not progressed as rapidly as the amount of promising preclinical results would have suggested (39). The reasons are multifaceted, and one can also include the existence of the "file drawer problem" in the nanomedicine literature, where authors report only strong and positive data, but results that are weak or even null are omitted. The editors concede that this behaviour is often in line with the aims of scientific journals that prefer to publish significant and breakthrough findings (40). Recent experience from peer-reviewed literature also suggests that, regardless of novelty, material choices and synthetic protocols often do not consider translatability into clinic. Researchers tend to focus on establishing the unique properties/novelty of the studied materials. The studies are designed from a material science perspective and often use a biological model system that highlights the uniqueness of the material instead of disease-relevant models. Additionally, individuals with the relevant expertise (e.g., clinical, pharmaceutical, immunological) are often not involved in the early to mid-preclinical stages (41).

As discussed above, there is a shift from using relatively "simple" nanoparticles, (e.g., conventional liposomes) containing previously approved active substances. Late-preclinical products now incorporate complex and multi-component materials with novel molecules. These composite products exhibit enhanced pharmaco-toxicological profiles that are quite different from the characteristics of the individual components. Considering that all components of the composite nanoparticle contribute to the final drug product's efficacy and safety profiles, a scientific argument can be put for designating the composite nanoparticle as the active ingredient. Therefore, from a regulatory standpoint, in very specific cases the active substance may include components that were previously considered as excipients. The associated challenges in characterisation and evaluation of nanomaterials are already recognised by regulators, as discussed in the EMA reflection papers and in section 4 below. It should be clearly outlined that in the EU a lipid nanoparticle itself is not considered as an active substance. In the case of a lipid nanoparticle, encapsulated with mRNA, the mRNA molecule is classified as the active substance. The lipids (also if used as novel excipients) as components of this lipid nanoparticles are considered excipients.

3.3.2. Ongoing clinical trials using nanomedicines

A literature search performed to identify publications focused on the use of nanomedicines in Clinical Trials (CT) has revealed that there is actually very limited information on this topic. The EU Clinical Trials Register does not contain structured data to identify which CT are conducted with nanomedicines. In depth analysis was not performed for the entire EU. Nevertheless, the Italian Medicines Agency (AIFA) carried out its own analysis (42). AIFA analysed Investigational Medicinal Product Dossiers (IMPDs) included in the Clinical Trial Applications (CTAs) authorised in Italy (43).

Information on CT involving nanomedicines can be found in Annex 3.

4. Challenges, opportunities and considerations from a regulatory perspective

4.1. Regulatory issues

In order to gain deeper insights into the regulatory needs and challenges from various stakeholder´s perspectives, the REFINE project organized a survey and series of workshops (42). The REFINE project is a Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices, funded by European Union's Horizon 2020 under Grant Agreement no 761104.

The findings revealed that around 50% of the respondents judged that current regulatory guidance is not clear and not easy to access. Moreover, there was a consensus on the necessity for additional guidance documents, in particular for novel nanomaterials and for a stepwise comparability approach for follow-on (generic) nanomedicines in order to reduce the uncertainty for product developers (44).

Due to their complexity, product marketing authorisation applications for future nanomedicines and their follow-on products are therefore anticipated to be submitted according to Article 8(3) and 10(3) of Directive 2001/83/CE rather than by Article 10(1). Therefore, relevant non-clinical and/or clinical data of appropriate CT must be provided, rather than data needed for a generic application.

An interdisciplinary approach should be adopted to apply the outcomes of biotechnology, nanomaterials, biomedical robotics, and genetic engineering combined under the broad category of nanomedicines.

Finally, international harmonization of nanomedicines-related definition and terminology stands as a crucial step in streamlining regulatory processes and ensuring clarity and consistency across the field.

4.2. Delivery systems/Borderline products

The classification of a product as a medicinal product or a medical device depends on the primary mode of action. So-called borderline products require special attention by the regulatory community (e.g. NBTXR3, a first-in-class radioenhancer for pancreatic ductal adenocarcinoma, has been classified in EU as medical device, however in USA is considered a medicinal product) (45). Since the regulatory pathways for marketing authorization of medicinal products versus the conformity assessment of medical devices are substantially different, it is very important for product developers to get into contact with both, the regulatory authority for medicinal products and the regulatory authority for medical devices, as early as possible (See section 2.2). Not all such novel products are covered by existing guidelines and therefore a tailored and risk-based approach is needed.

4.3. Quality / CMC (chemistry, manufacturing and control) issues

Specific challenges apply for the development, manufacturing and control of nanomedicinal products. Amongst others the following issues are relevant:

- Characterisation of the nanosystem with suitable analytical techniques.
- Defining critical quality attributes (CQAs) that have an impact on biological effects such as therapeutic effects, PK or safety profile, which the developers should be taking into consideration when developing new nanomedicines and guidance to choose those relevant critical quality attributes for each nanomedicine, considering the type of nanotechnology used, its mechanism of action and route of administration.
- Standardisation of analytical techniques for the most common quality attributes (e.g. drug loading/release, size/size distribution, surface chemistry) and biological effects (e.g. complement activation) are needed.
- Definition of drug substance *vs.* excipients.
- Establishing limits for degradation products during development (drug substance, nanosystem components).
- Challenges for reproducible and robust manufacturing, scale-up and stability of these products.
- Dealing from a regulatory perspective with possible platform technologies using prior knowledge if applicable (for example mRNA-LNP).

4.4. Non-clinical development

When it comes to non-clinical aspects, new drug products that contain nanomaterials should follow the same relevant guidelines as any other products containing novel components. Therefore, any component of the nanoformulation, which has not been previously classified as an active ingredient or an excipient, must undergo a comprehensive safety evaluation. In cases when a previously approved drug product is modified to include a nanomaterial, ADME (Absorption, Distribution, Metabolism and Excretion) and bridging general toxicology studies could be sufficient to characterize the pharmaco-toxicological profile of the new drug product. However, the final approach is highly dependent on the impact of the nanoparticle on ADME and toxicity. For example, additional reproductive toxicity studies with the new formulation may be warranted if the nanoparticle increases drug penetration through the placenta or if it is distributed to ovaries and testis.

The complexity of the non-clinical assessment often arises from the characterization of nanocomponents that function as carriers. As mentioned above, nanomedicines are often composite products and exhibit pharmaco-toxicological profiles that are more favourable than those of the individual components. Like any substance, if a novel nanocomponent used is then classified as an excipient, it will likely require a standalone characterization similar to the non-clinical evaluation required to support the approval of a new active ingredient (46). The safety evaluation of the nanocomponent alone is recommended when there is no non-clinical data available in order to characterize the toxicity profile and aid to stablish acceptable dosing to humans. When assessed separately from the intact nanomedicine it may however have a dissimilar pharmacokinetic profile. A standalone evaluation can thus lead to misleading scientific results as well as pose cost and time-related challenges. Since all components of the nanomedicine may contribute to the pharmaco-toxicological properties of the final drug product, then, in certain circumstances the nanocomponent should be characterized as part of the main toxicology studies performed with the nanomedicinal product. It would provide a safety margin in case of adverse events, even though it does not allow characterising the intrinsic risks of the molecule.

Nanoparticles in the final drug product to be administered to humans should also be considered in the non-clinical development plan to allow the determination of acceptable nanoparticle/drug product ratios, not only from a safety standpoint but also from a pharmacodynamic perspective. Nonetheless, if there is a relevant amount of safety data with the nanoparticle, proceeding directly to studies with the combination could be also considered acceptable. This approach would be aligned with the "3Rs principles" of animal experimentation - replacement, reduction, refinement.

Factors that require special attention in the development of nanoparticles and nanotechnology-based medicines are their interaction with the immune system, their hemocompatibility and their biodistribution due to surface coatings, targeting moieties and shape/size/morphology of nanomedicines. Thrombosis represents the most commonly reported blood toxicity during preclinical characterization of nanomedicines in vivo, followed by undesired complement activation and alterations on hematology (hemolysis, alterations of leukocyte count and leukocyte activation) (47-48). The interaction of nanoparticles with the immune system is not yet fully understood. Only the intravenous injection of a number of nanotechnology-based medicinal products (liposomal, micellar, polymer-conjugated) has been associated with a class of hypersensitivity reactions, in many cases caused by activation of the complement system (Complement activation-related pseudoallergy, CARPA syndrome). Animal species, particularly pigs and dogs, appear to be susceptible to CARPA syndrome and the *in vitro* assay for complement activation in human serum may help predict CARPA risk in humans (49-50). However, as the immune system is highly species specific, further research is needed on the predictive value of *in vitro* and *in vivo* assays to assess the risk of CARPA and to develop *in vitro* methods to assess the risk of immunogenicity.

4.5. Clinical

- Clinical outcomes on differences in biodistribution due to surface coatings, targeting moieties, shape/size/morphology of nanomedicines.
- Immune response may vary depending on the surface coatings, targeting moieties and shape/size/morphology.
- There is also need to clearly differentiate nanomedicine formulation from the corresponding conventional product at the level of INN (International Non-Proprietary Name) or medicinal product name, to avoid misuse of the medicinal product (e.g. in the past there was need to introduce wording "pegylated liposomal" into the product name of doxorubicin (to differentiate from conventional doxorubicin), or to introduce "lipid complex" or "liposomal" to differentiate two nanoformulations of amphotericin B from conventional amphotericin B). In the EU, rules have been in place since July 2019 (51) to establish a clearer distinction between liposomal and non-liposomal formulations of the same active substance, aimed at preventing medication errors.

4.6. Ethical issues

Ethical issues in nanomedicines are public trust, potential and unknown risks, issues of environmental impact, transparency of information, responsible nanoscience's and nanotechnologies research (52). Due to possible gaps in non-clinical and clinical development there is a need for precautionary principles as a basis for the regulation of nanotechnology. It is important to strengthen the public debate on benefits, risks and uncertainties of nanotechnology to increase understanding and awareness.

4.7. Environmental risk assessment (ERA)

There are limitations of existing environmental regulation in relation to nanomedicines. The same toxicology principles that apply to conventional molecules may not be applicable to nanoparticles. Factors that differ from conventional molecules may be different bioaccumulation, persistence in the environment and aggregation of nanoparticles (with possible binding of other molecules on their surface). Therefore, a risk-based approach should be employed when conducting ERA for nanomedicines (53). A new approach for ERA is considered within the revision of the EU pharmaceutical legislation (54), where strengthening of the requirements on the environmental risk assessment and conditions of use is suggested.

5. Regulatory preparedness

5.1. EU regulatory initiatives

There are several EU stakeholder initiatives requesting better harmonisation of the marketing authorisation requirements for nanomedicines. European Alliance for Access to Safe Medicines (EAASM) and the Regulatory Nanomedicines Coalition calls for robust centralised regulatory framework as essential step to enhance patients' safety (55). There are also ongoing activities within EDQM (European Directorate for the Quality of Medicines & HealthCare) which aimed to identify any gaps and opportunities for standards concerning nanoparticle-based formulations which can be filled by the European Pharmacopoeia (Ph. Eur.), notably by setting common quality standards across Europe and beyond (56). In March 2023, the European Pharmacopoeia Commission (EPC) agreed to intensify the work on standards on nanomedicines, to change the name of the Non-Biological Complex Drugs working party (NBC WP) to NANO WP (Nanomedicines) and to adjust the terms of reference

accordingly. Numerous additional experts from academia, research organisations, industry and regulatory agencies have been nominated as members of the NANO WP to further strengthen the expertise of this group.

In 2024 the European Pharmacopoeia (Ph. Eur.) Commission decided on two additions to the work programme of the NANO WP: Liposomal preparations (5.45) – general chapter and a monograph on Pegylated liposomal doxorubicin hydrochloride concentrate for infusion (3256). A monograph on Iron sucrose concentrated solution (2753) is at an advanced stage of drafting.

The ETP Nanomedicine (ETPN) is an initiative led by industry since 2005 and set up together with the European Commission, to address the application of nanotechnology in healthcare (57).

The EMA Regulatory Science to 2025 (58) identifies five strategic regulatory science goals for human medicines. One of these strategic goals is to integrate science and technology into the development of medicines. This also includes understanding and regulating nanotechnology and new materials in pharmaceuticals.

The European medicines agencies network strategy (EMANS) to 2025 (59) identifies six strategic focus areas to be achieved within the strategy period. Among these six strategies the innovation one is working on the safety of nanomedicines as one of the goals to be achieved.

There are also other groups further developing classification tools to foster nanomedicines development. The classification system proposed could allow regulators to monitor the regulatory state of the art of nanomedicines and it could also be useful to developers to link their technologies with the applicable regulatory guidelines (60).

Early dialogue and engagement between regulators and researchers need to be always promoted and encouraged in order to identify regulatory gaps and challenges that could hamper the development.

Additionally, the EC founded project Strengthening Training of Academia on Regulatory Sciences (STARS). The STARS project was a collaboration between 18 European NCAs/EU IN members, four associate countries and EMA. The project aimed to reach out to the medicine innovators in academia, to bridge the regulatory knowledge gap and enhance the dialogue between academia and regulatory authorities. Within the project different pilots were developed. The third pilot represented the implementation of a Comprehensive Curriculum for strengthening regulatory knowledge in health care professionals from academia which can be of interest for the audience of this HS report (61).

5.2. International regulatory initiatives

Facilitating the exchange of information among global regulators is crucial for addressing issues of mutual interest and fostering regulatory cooperation. This collaboration maximizes potential efficiencies within an ever-evolving and complex global regulatory landscape. The International Pharmaceutical Regulators Program (IPRP) was established in 2009 to achieve such purpose, aiming to promote regulatory collaboration and regulatory convergence, as well as facilitating the implementation of internationally harmonized technical guidelines for pharmaceuticals for human use. The IPRP Nanomedicine Working Group (NWG) https://www.iprp.global/working-group/nanomedicines was formed among a number of regulatory agencies to share non-confidential information on nanomedicines, nanomaterials in drug products, borderline and combination products, and on methodologies used during development and evaluation (62).

6. Recommendations

6.1. Improving knowledge and expertise

There is a clear need to enhance the knowledge of academia on regulatory requirements, as emphasized in the recommendations from the STARS project (63). These recommendations were derived from surveys, pilots and workshops carried out during the three-year project. Furthermore, it is crucial to improve the knowledge and expertise of regulators on nanotechnology in order to keep the regulators up-to-date about state-of-the-art methodologies, techniques and indications of nanomedicines. Therefore, fostering close collaboration and facilitating bidirectional training between academia and regulators is the optimal way to go forward.

To advance developments in the field of nanotechnology-based medicinal products, we recommend an early and continuous engagement with European regulators via existing support mechanism (as outlined in paragraph 2.2).

6.2. Changes to the regulatory framework

It is recommended to implement an efficient tracking system to identify nanotechnology-based medicinal products in clinical development such as the inclusion of an additional tick box in the CT Information System (CTIS) interface and regulatory submissions (scientific advice/protocol assistance applications, in applications for paediatric investigation plans and orphan designations or in the marketing authorisation applications).

The purpose of collecting qualitative and quantitative information through these means is to enable an EU-wide consistent assessment of nanomedicines, starting from the early development stages. This assessment will provide valuable quantitative insights over the development lifecycle of nanomedicines in the EU, which will help to facilitate the creation of more targeted support to nanomedicine developers during the stages where they face most challenges.

FDA has published more general guidance which addresses quality, nonclinical and clinical considerations for medicines containing nanomedicines throughout product development (Annex 1). It is recommended to consider reviewing and expanding the existing EU guidance and including consideration of requirements for both marketing authorisations and clinical trials.

6.3. Collaboration with stakeholders

As nanomedicines enter late-preclinical and clinical development, academic and industry investigators as well as external subject matter experts are encouraged to work collaboratively with regulatory authorities in the EU-IN network, to best inform and navigate the many regulatory considerations related to these complex products.

Exchange information on issues of mutual interest and enable regulatory cooperation, maximising potential efficiencies in an increasingly complex global regulatory environment is needed. The collaboration between stakeholders and regulators to accelerate drafting of EU guidance that could support the nanomedicine development is encouraged.

A European Platform for Regulatory Science Research will be launched to strengthen the collaboration between regulatory science researchers and regulators. Moreover, the participation of additional stakeholders is envisioned.

6.4. Harmonisation of classification of nanomedicine drug components

From a regulatory standpoint, the active ingredient, which provides pharmacological activity, in specific cases may include components that were previously considered as excipients. It is recommended to harmonise the classification of the different components of nanotechnology-based medicinal products (i.e., what is an active ingredient vs excipient). This clarity is crucial to avoid confusion for applicants arising from the use of varying classification standards in different regions. Early interaction with regulatory Agencies is strongly recommended, this will ensure that relevant quality, non-clinical and/or clinical data are generated and provided in the relevant sections of a regulatory application dossier.

7. Annexes

7.1. Annex 1: List of EMA and FDA guidelines on nanomedicines

EMA Guidelines on nanomedicines

1. Reflection paper on data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product.

This reflection paper discusses the data requirements for **nano-sized colloidal intravenous iron-based preparations** developed as a treatment for iron deficiency with reference to an innovator product.

https://www.ema.europa.eu/en/data-requirements-intravenous-iron-based-nano-colloidal-products-developed-reference-innovator

2. Reflection paper on data requirements for intravenous liposomal products developed with reference to an innovator liposomal product.

This document discusses the **principles** for assessing **liposomal products** developed with **reference to an innovator** liposomal product but does not aim to prescribe any particular quality, nonclinical or clinical strategy.

https://www.ema.europa.eu/en/data-requirements-intravenous-liposomal-products-developed-reference-innovator-liposomal-product-0

3. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products.

This reflection paper discusses the **general principles** for assessing **block copolymer micelle products** but does not aim to prescribe any particular quality, non-clinical or clinical strategy.

https://www.ema.europa.eu/en/development-block-copolymer-micelle-medicinal-products

4. Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products.

This paper highlights issues that require consideration during the development and lifecycle of **coated nanomedicine products** designed for **parenteral administration**.

https://www.ema.europa.eu/en/surface-coatings-general-issues-consideration-regarding-parenteral-administration-coated

5. Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications.

This paper provides a brief overview about the characteristics to be taken into account and the non-clinical studies to be carried out in order to compare, mainly, some **pharmacokinetic** and **toxicological** parameters between the **reference and generic nanoparticle-based products** (especially nanoparticle iron medicine products (**NPI**) for parenteral use).

The importance of quantifying the concentration of **total iron** and of the product in the most relevant compartments (**plasma**, reticuloendothelial system (**RES**) and pharmacological and toxicological **target tissue**) is stressed.

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-non-clinical-studies-generic-nanoparticle-iron-medicinal-product-applications_en.pdf

The principles outlined in these documents address general issues regarding the complexity of the nanosystems and provide basic information for the pharmaceutical development, non-clinical and early clinical studies of block-copolymer micelle, "liposome-like," and nanoparticle iron (NPI) medicinal drug products created to affect pharmacokinetic and stability of incorporated or conjugated active substances in vivo. Guidance documents on the validation of analytical, bioanalytical procedures as well as on *in silico* methods and *in vitro* methods were released by the Competent Authorities.

- Qualification of novel methodologies for drug development: guidance to applicants. EMA/CHMP/SAWP/72894/2008. (EMA/CHMP, 2014).
- Qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. EMA/CHMP/458101/2016 (EMA/CHMP, 2018)

FDA Guidelines on nanomedicines

1. FDA/CDER. Guidance for Industry: Drug Products, including Biological Products, that Contain Nanomaterials (FDA, 2022).
2. Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (FDA, 2018).
3. Guidance for Industry Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (FDA, 2014)
4. Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools (FDA, 2020)
5. Guidance for Industry: Bioanalytical Method Validation (FDA, 2018)
6. Guidance for Industry: Physiologically Based Pharmacokinetic Analyses — Format and Content (FDA, 2018).

7.2. Annex 2: Non-exhaustive overview of authorised nanotechnology-based medicinal products. The nanomedicines have been classified by their general physical and chemical properties

Lipid-based nanoparticles

Name (MAH*)	Payload	Pharmacological subgroup	Regulator (date of approval)
Spikevax (Moderna Biotech Spain, S.L.)	Elasomeran / COVID-19 mRNA vaccine (nucleoside-modified)	Vaccine	EMA Conditional approval (2021)
Comirnaty (BioNTech Manufacturing GmbH)	Tozinameran / COVID-19 mRNA Vaccine (nucleoside modified)	Vaccine	EMA Conditional approval (2020)
Arikayce liposomal (Insmed Netherlands B.V.)	Amikacin sulfate	Respiratory Tract Infections	EMA (2020)
VYXEOS liposomal (Jazz Pharmaceuticals Ireland Limited)	Cytarabine:daunorubicin (5:1 molar ratio)	Other antineoplastic agents	EMA (2018)

Name (MAH*)	Payload	Pharmacological subgroup	Regulator (date of approval)
ONPATTRO (Alnylam Netherlands B.V.)	Patisiran	Other nervous system drugs	EMA (2018)
Onivyde pegylated liposomal (Les Laboratoires Servier)	Irinotecan hydrochloride trihydrate	Plant alkaloids and other natural products	EMA (2016)
Marqibo (Talon Therapeutics Inc.)	Vincristine	Plant alkaloids and other natural products	FDA (2012; withdrawal 2022)
MEPACT (Takeda France SAS)	Mifamurtide	Immunostimulants	EMA (2009)
DaunoXome (InterGal Pharma Limited)	Daunorubicin	Cytotoxic antibiotics and related substances	DE/H/2810/001 (2005)
Definity (Lantheus Medical Imaging)	Perflutren	Ultrasound contrast media	FDA (2001)
Visudyne (CHEPLAPHARM Arzneimittel GmbH)	Verteporfin	Ocular vascular disorder agents	EMA (2000)
AmBisome Liposomal (Astellas)	Amphotericin B	Antimycotics for systemic use	FDA (1997) National Authorizations
Caelyx pegylated liposomal (Baxter Holding B.V.)	Doxorubicin	Cytotoxic antibiotics and related substances	EMA (1996)
Diprivan (Fresenius Kabi USA)	Propofol	Anesthetics, general	FDA (1989)

*MAH at the time of this overview

Protein nanoparticles/Albumin-bound nanoparticles:

Name (MAH*/Sponsor)	Payload	Pharmacological subgroup	Regulator (date of approval
Abraxane (Bristol-Myers Squibb Pharma EEIG)	Paclitaxel	Plant alkaloids and other natural products	EMA (2008)
Optison (GE Healthcare AS)	Perflutren	Ultrasound contrast media	EMA (1998)

*MAH at the time of this overview

Inorganic nanoparticles/Colloid

Name (MAH*)	Payload	Pharmacological subgroup	Regulator (date of approval)
Injectafer (Vifor)	Iron	Iron preparation	FDA (2013)
Ferumoxtran-10 Combidex Sinerem (AMAG)	Iron	Contrast media	Only available in the Netherlands (2013)
Feraheme (AMAG)	Ferumoxytol	Iron preparation	FDA (2009)
Resovist (Bayer Schering Pharma)	Iron	Magnetic resonance imaging contrast media	Some of Europe (2001)
Venofer (American Regent)	Iron	Iron preparation	FDA (2000) SE/H/1842/001/MR (2001)
Ferrlecit (Sanofi)	Iron	Iron preparation	FDA (1999)
CosmoFer INFeD Ferrisat (Pharmacosmos A/S)	Iron	Iron preparation	FDA (1992)

*MAH at the time of this overview

Nanocrystals

Name (MAH*)	Payload	Pharmacological subgroup	Regulator (date of approval)
Xeplion (Janssen-Cilag International N.V.)	Paliperidone palmitate	Schizophrenia	EMA (2011)
Zypadhera (Eli Lilly Nederland B.V.)	Olanzapine pamoate	Schizophrenia	EMA (2008)
Emend (Merck Sharp & Dohme B.V.)	Aprepitant	Antiemetics and antinauseants	EMA (2003)
Rapamune	Sirolimus	Immunosuppressants	EMA (2001)

Name (MAH*)	Payload	Pharmacological subgroup	Regulator (date of approval)
(Pfizer Europe MA EEIG)			

*MAH at the time of this overview

Polymeric nanoparticles

Name (MAH*/ Sponsor)	Payload	Active substance reported in the SmPC	Pharmacological subgroup	Regulator (date of approval)
Oncaspar (Les Laboratoires Servier)	PEGylated-L-asparaginase	Pegaspargase	Antineoplastic agents	EMA (2016)
Adynovate	Recombinant pegylated anti-hemophilic factor	Rurioctocog alfa pegol	Vitamin k and other hemostatics (Recombinant)	FDA (2015)
Cimzia (UCB Pharma SA)	PEGylated Fab' fragment binds to TNF-α	Certolizumab pegol	Immunosuppressants	EMA (2009)
Mircera (Roche Registration GmbH)	Epoetin β (EPO) conjugated to methoxy-PEG	Methoxy polyethylene glycol-epoetin beta	Other antianemic preparations	EMA (2007)
Neulasta (Amgen Europe B.V.)	PEGylated form of filgrastim	Pegfilgrastim	Immunostimulants	EMA (2002)
Pegasys (zr pharma& GmbH)	Peginterferon alfa-2a	Peginterferon alfa-2a	Immunostimulants	EMA (2002)
Somavert (Pfizer Europe MA EEIG)	PEGylated analog of human growth hormone	Pegvisomant	Anterior pituitary lobe hormones and analogues	EMA (2002)
Copaxone (TEVA)	Glatiramer acetate - Synthetic polymer consisting of L-alanine, L-	Glatiramer acetate	Immunostimulants	Europe (2001) UK/H/0453

Name (MAH*/ Sponsor)	Payload	Active substance reported in the SmPC	Pharmacological subgroup	Regulator (date of approval)
	glutamic acid, L-tyrosine and L-lysine			
Renagel (Genzyme Europa B.V.)	Sevelamer	Sevelamer hydrochloride	All other therapeutic products	EMA (2000)

*Marketing Authorization Holder (MAH) at the time of this overview

7.3. ANNEX 3: Information about Clinical Trials with nanomedicines

In the Table below the Clinical Trials are filtered from databases ClinicalTrials.gov and ClinicalTrialsRegister.eu, using key words "nano", "nanoparticle", "nanocarrier", "liposomal", "nanolipid" and "complex" and from input received from individual Member States. Date of the search 20th of April 2023.

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
DEX-NANO	Rectal Dexmedetomidine Niosomes	Egypt	N	Anastaesiology
mRNA-0184-P101	mRNA-0184, a lipid nanoparticle (LNP)-encapsulated mRNA	PL	C	Cardiology
Voriconazole	Voriconazole Self Nano Emulsifying Drug Delivery System Intermediate Gel	Egypt	D	Dermatology
Itraconazole	Itraconazole Self Nano Emulsifying Drug Delivery System Intermediate Gel	Egypt	D	Dermatology
TPM203	Non-biological complex drug (NBCD) TPM203 is a mixture of four Topas Particle Conjugates (TPC0002, TPC0003,TPC0005 and TPC0012)	DE	L	Dermatology

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
5-aminolaevulinic acid nanoemulsion	5-aminolaevulinic acid nanoemulsion	FI	D	Dermatology
methylaminolevulinate and aminolevulinic acid nano emulsion	methylaminolevulinate and aminolevulinic acid nano emulsion	FI	D	Dermatology
BF-200 ALA	a nanoscale-lipid vesicle formulation and the prodrug 5-aminolevulinic acid (5-ALA)	FI	D	Dermatology
NanoVitD	Oral nano form of the calciferol	CZ	A	Gastroenterology
NTLA-2001	CRISPR/CAS formulated in a lipid nano particle	SE	N	Genetic disorder
Progerinin	Progerinin, nano-suspension for oral use	USA	A	Genetic disorder
UX053 mRNA	mRNA encoding the human glycogen debranching enzyme formulated in a lipid nanoparticle delivery	FR, IT, ES	A	Genetic disorder
Nanoparticulate estradiol + progesterone	Nanoparticulate estradiol + progesterone	Brazil	G	Gynecology
ND L02 s0201	Vitamin A-coupled Lipid Nanoparticle Containing siRNA Against HSP47	BG	A	Hepatobiliary disorders
AguIX	Gadolinium-chelated polysiloxane nanoparticles	FR	V	Imaging techniques
Ferumoxtran-10	Ultrasmall superparamagnetic iron oxide (USPIO)	FI, NL	V	Imaging techniques
ICG - 99mTc - nanocolloid	Hybrid indocyanine green (ICG)-99mTc-nanocolloid	IT	V	Imaging techniques

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
Nano-Carbon	Nano carbon dye	China	V	Imaging techniques
Carbon Nanoparticles Suspension	Carbon Nanoparticles Suspension	China	V	Imaging techniques
mRNA-1345	mRNA-1345 is a lipid nanoparticle (LNP) encapsulated mRNA-based vaccine to prevent disease associated with RSV infection	PL, FI	J	Infectious diseases
Adjuvanted RSV F Vaccine	respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine with Aluminum	UK, ES	J	Infectious diseases
Nano-COVID19	Methotrexate Associated to LDL Like Nanoparticles	Brasil	J	Infectious diseases
NANO-efavirenz and NANO-lopinavir	Efavirenz and Lopinavir Nano-formulations	UK	J	Infectious diseases
MK-1439	Nano formulation of doravirine	NA	J	Infectious diseases
Topical Nano-liposomal Meglumine Antimoniate (Glucantime) or Paromomycin	Topical Nano-liposomal Meglumine Antimoniate (Glucantime) or Paromomycin	Iran	D	Infectious diseases
CAMB/MAT2203	Lipid crystal nano-particle formulation of amphotericin B	USA	J	Infectious diseases
CD24-Exosomes	natural nano-sized vesicles secreted by human cells	Israel	J	Infectious diseases
Nano-S1	Colloidal silver	Tunisia	J	Infectious Diseases
RNS60	electrically stimulated H_2O molecules	AT	N	Nervous System Diseases

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
CBD-THC-Piperine-PNL capsule	self-emulsifying drug delivery system termed Piperine-Pro-Nano-Lipospheres (P-PNL) for enhancing the oral bioavailability of tetrahydrocannabinol (THC) and cannabidiol (CBD)	Israel	N	Nervous System Diseases
BNT113/RNA-LPX	lipid-based nanoparticles	AT	L	Oncology
nano particle albumin-bound paclitaxel (nab-paclitaxel)	nano particle albumin-bound paclitaxel (nab-paclitaxel)	DE	L	Oncology
Imaradenant (AZD-4635)	AZD-4635 nano-suspension	UK	L	Oncology
C6 Ceramide Nanoliposome (CNL)	C6 Ceramide Nanoliposome (CNL)	USA	L	Oncology
Nano-liposomal irinotecan	Nano-liposomal irinotecan	USA, EU	L	Oncology
NAb-paclitaxel	NAb-paclitaxel	USA, EU, China	L	Oncology
SNB-101	novel nano-particle formulation of SN-38, the active metabolite of irinotecan (CPT-11)	China, Republic of Korea	L	Oncology
RXDX-107	dodecanol alkyl ester of bendamustine encapsulated in human serum albumin (HSA) to form nanoparticles	USA	L	Oncology
BPM31510	oral nanosuspension formulation of BPM31510 (ubidecarenone, USP)	USA	L	Oncology
IG-001 Cb-paclitaxel (Sorrento)	Paclitaxel (the next generation nanoparticle paclitaxel)	USA	L	Oncology

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
Genexol –PM (Samyang Biopharmaceuticals)	Paclitaxel (a polymeric NP micelle formulation of paclitaxel)	Republic of Korea, USA	L	Oncology
NC-6004 Nanoplatin (Nanocarrier)	Cisplatin: NC-6004 is a cisplatin nanoparticle developed using a cutting-edge micelle nanotechnology. Cisplatin is encapsulated into approximately 30 nm size polymeric micelles through the polymer-metal complex formation between polyethylene glycol poly (glutamic acid) block copolymers (PEG-P(Glu))	EU, USA, China, Japan	L	Oncology
NC-4016 (Nanocarrier)	Oxaliplatin: polymeric micellar nanoparticles incorporating 1,2-diaminocyclohexane platinum	USA	L	Oncology
CRLX101 (Cerulean)	cyclodextrin-based polymer (CDP) and an anti-cancer compound (camptothecin)	USA	L	Oncology
CRLX301 (Cerulean)	Docetaxel: Nanoparticle drug conjugate with docetaxel covalently conjugated to a cyclodextrin-polyethylene glycol co-polymer	USA	L	Oncology
ABI-009 (Celgene)	Nab-Rapamycin	USA	L	Oncology

Investigational Medicinal Product	Short Description	Member State / CountryI	ATC	Therapeutic indication
ABI-011 (Celgene)	Thiocolchicine analog: a novel thiocolchicine dimer with antitubulin and topisomerase 1 inhibitor	USA	L	Oncology
ITI-1001	DNA vaccine represents a multi-antigen nucleic acid cancer immunotherapy encoding 3 CMV antigens	USA	L	Oncology
Dexamethasone	dexamethasone nanoparticles eye drops	FI	S	Ophtalmology
Cyclosporine	Cyclosporine ophthalmic nano-emulsion 0.08%	Republic of Korea	S	Ophtalmology
3% Diclofenac Nano-Emulsion Cream	3% Diclofenac Nano-Emulsion Cream	Israel	M	Orthopaedics (osteoarthritis)
Nano-vesicles of Salbutamol Sulphate		Egypt	R	Pneumology
Paliperidone Palmitate 100mg/ml nano suspension	Paliperidone Palmitate 100mg/ml nano suspension	AT	N	Psychiatry
APH-1501	Nanoencapsulated Cannabidiol Time Released Capsules	NA	N	Psychiatry
GNPG	Biogenic Gold Nano Particle From Pelargonium Graveolens Leaves Extract	Iraq	A	Stomatology

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