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The Landscape of Nanomedicines: An Expert Perspective

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Abstract

The field of nanotechnology is at the forefront of a scientific revolution, where the term "nano" transcends mere size and opens the door to enormous possibilities.

In the context of drug development, the selection of a suitable drug delivery system (corresponding to a certain active pharmaceutical ingredient) is a pivotal decision. Accordingly, nanosystems have emerged as a promising avenue, offering innovative solutions, and gaining recognition for addressing healthcare issues.

While these products hold immense promise, they have faced certain complexities in their translation from the preclinical to the clinical setting, reflected in the lack of proper assessment protocols for quality and safety aspects and, consequently, an insufficiently defined regulatory environment. Since the groundbreaking US Food and Drug Administration (FDA) approval of liposomal doxorubicin in 1995, approximately 80 nanomedicine products have received regulatory approval so far. Recent attention has gravitated toward lipid-based nanomedicines, particularly in the development of mRNA vaccines during the COVID-19 pandemic, further highlighting their significance. However, the relatively modest number of approved nanomedicines compared to the extensive research efforts raises important questions and underscores areas of uncertainty.

This article provides an overview of the challenges in defining nanomedicines, their properties, the complexities of regulatory frameworks, and the imperative for standardized characterization protocols.

Key words: nanomedicines, nanoparticles, characterization protocols, regulation of nanomedicines

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Nanomedicines – a general overview

In the field of nanotechnology, we are entering into a fascinating area where matter is undergoing a profound transformation, where “nano” is not simply a dimension of size. At the nanoscale, materials and technologies defy the rules governing their macroscopic counterparts.

In the early stages of drug development, after the selection of an active pharmaceutical ingredient (API), it is important to opt for a suitable drug carrier / delivery system. In this context, nanosystems have been recognized as promising. Accordingly, nano-enabled medicinal products have been widely accepted in the field of biomedical innovation. Owing to their unique physicochemical properties, their development has been raising hopes to address specific health challenges, such as the diseases affected by insufficient diagnostic and/or therapeutic tools (1). Yet, regardless of these high aspirations, certain initial hypotheses, particularly in the context of pharmacokinetics and anticipated therapeutic outcomes, have encountered a more complex reality in clinical practice (2, 3, 4). Nevertheless, the value of nanomedicines remains indisputable. They confer stability to fragile APIs, transform insoluble actives, and navigate biological barriers, enhancing bioavailability while mitigating systemic side effects. Moreover, these nanosystems present an expansive canvas for advancements in diagnostics and regenerative medicine (1, 5, 6).

The European research area has recognised the potential offered by nanotechnology in the context of healthcare, including other innovative approaches, in addition to the delivery of medicinal compound, such as gene therapy and stem cell therapy. As an illustration, according to the CORDIS database (*Community Research and Development Information Service*), starting from 2008 and ending in August 2023, the European Commission has funded a total of 411 projects that have *nanomedicine* as one of their key words, through various project frameworks. Only through the last one – Horizon Europe (which started in 2021), as many as 36 nanomedicine-related projects have been approved for financing (7).

Even though the first nanoparticle-based formulation (irone-sucrose colloidal dispersion) was actually introduced into the market almost 50 years before the official recognition of the term “nanomedicines” (8), in more popular terms, the journey of nanomedicine finds its earliest start with liposomal formulation of the anticancer drug doxorubicin, which obtained market authorization in 1995 by the FDA, and the following year by the European Medicines Agency (EMA) (9). Since then, in the last decades, around 80 nanomedicine formulations have been approved by the FDA and/or EMA, and many more are currently in various stages of clinical trials (Figure 1). These nanomedicines, ranging from liposomes to lipid-based nanoparticles, nanocrystals to metal-based nanoparticles, protein-bound drugs and polymeric nanoparticles, have ushered in a new era of medical treatment (10, 11).

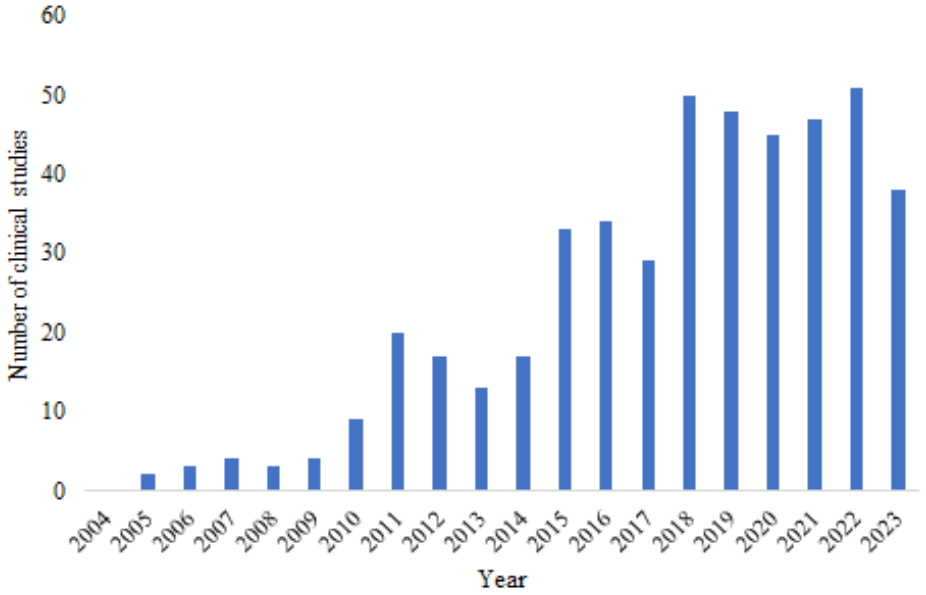

Figure 1. Clinical studies including the key word "nano" having a start date from January 1st, 2004, to August 31st, 2023 (12)

Slika 1. Kliničke studije koje uključuju ključnu reč „nano", a koje su započete sa datumom početka 1. januar 2004, zaključno sa 31. avgustom 2023. (12)

Very often, the development of nanomedicines relies on already known drug molecules, but transformed into nanostructured products which are superior in terms of safety and efficacy. One supporting example is the drug dantrolene, indicated in the treatment of malignant hyperthermia. Prior to the approval of nanosuspension of dantrolene-sodium (approved in 2014 by the FDA), usual treatment would require the engagement of more than 2 healthcare professionals, reconstitution of several vials per treatment and long-lasting i.v. application of a large volume preparation, while the nanoformulation is 150 times more concentrated compared to the previous dosage form, significantly reducing the total volume for injection, injection time (less than one minute), and preparation procedure (13).

On the other side, after the notable success of patisiran, a milestone in the therapy of genetic disorders, supported by nanotechnological innovation and the advent of mRNA vaccines during the COVID-19 pandemic, which strongly relied on lipid-based nanoparticle formulations (game-changers in nanomedicine development), the profound importance of lipid-based nanomedicines has been clearly highlighted (10).

However, it should be noted that, despite the undeniable advantages demonstrated by nanoparticle formulations, the clinical landscape remains somewhat limited in terms of the number of approved nanomedicines. This discrepancy between the considerable research efforts invested in nanomedicine and the comparatively modest number of successfully translated formulations raises pertinent questions and highlights specific uncertainties that merit closer examination.

Understanding a nanomedicine

Nanomedicines simultaneously pose a wide range of technological, scientific, and regulatory challenges, which require an early awareness, appropriate scientific and methodological expertise and consensus on the more appropriate regulatory requirements (14). Despite the growing expansion of nanotechnology and its application in various fields, including pharmaceutical applications (15), the scientific community has been struggling to define the term "nanomedicine" (16). Currently, a universally accepted or formal definition does not exist. Current terminology encompasses words such as nanomaterial, nanosystem, nanocarrier, nano-enabled medicinal product, nanomedicine, etc. Sometimes they overlap, but sometimes there are specific nuances that make a difference, which highlights their complexity (17).

It should be noted that the current EC definition refers to the nanomaterials that are solid, with clear and constant dimensions (18), while nanosystems used in the biomedical context are usually soft matter materials, with fluid edges, whose dimensions vary depending on the movement or pressure exerted on them. Therefore, official documents of European regulatory and scientific bodies, when they talk about nanomedicine and nanotherapeutics, refer to the dimensions that are on the nanoscale – below 1 micrometer. The European Nanomedicine Technology Platform (ENTP) defines nanomedicines as “systems of specific physicochemical properties” (due to their small dimensions), thus achieving new perspectives in diagnosis and disease prevention (19). Furthermore, clarifying the field of nanotherapeutics, in the *European Medical Research Councils Forward Look Report* it is stated that it is a field dealing with complex systems, typically but not exclusively with dimensions smaller than 100 nm (20). Apparently, it is not easy to impose strict size limits. Size matters, but is not a unique feature that makes the nanomedicine.

As a consequence of their physicochemical specificities, nanomedicine-related analytical challenges have a very significant impact on the applicability of these medicines in the clinical setting. There is a lack of established protocols for their proper characterization, so they very often fail in the early stages of preclinical development. Accordingly, the lack of standards (both reference materials and written standards) also creates an unclear regulatory environment (21).

As an illustration of nanomedicine-related regulatory ambiguities, in the latest expert opinion published in *Nature Nanotechnology* in April of this year (22), an important question was raised, reflecting on the approach to nanomedicines in the process of evaluation for market authorization. Namely, the approval process for drugs typically differentiates between active ingredients and excipients. Both categories undergo rigorous safety testing. However, in the realm of nanomedicines, there is an ongoing debate between manufacturers and regulatory authorities regarding whether the entire particle should be considered the active ingredient, or each component should be tested individually. The most glaring example of this dilemma is the case of lipid nanoparticles for mRNA delivery, used in COVID-19 vaccines. More precisely, in its application for

approval with the FDA, *Moderna* presented the entire nanoparticle in *Spikevax* as the active ingredient, while *Pfizer* submitted the four lipids individually as excipients for its *Comirnaty* vaccine. Surprisingly, the FDA accepted both applications, resulting in a paradoxical situation where two highly similar vaccines were authorized under completely distinct regulatory frameworks. In this expert opinion, it was suggested that the safety evaluation of individual components, as performed in the traditional approach, does not provide an accurate representation of the overall scenario. The complete nanoparticle plays a crucial role in its efficacy within the body, making it more prudent and meaningful to evaluate it as a unified entity.

Regulatory information requirements addressing all classes of nanotechnology-based health products are divided into physicochemical and biological (Table I), actually representing their critical quality attributes (CQAs). Theoretically, they should be within an appropriate range, ensuring the desired quality of the product. However, it is difficult to expect to define CQAs for nanomedicines when there is still no consensus on their definition (17), and in a situation where among certain categories and subcategories of these CQAs there are no recommendations or available standards (23). In these cases, researchers often engage with the procedures that are successful in acquiring results, but not necessarily the correct ones.

Several years ago, a survey was conducted among the regulatory authorities in which their representatives were asked to assign priority levels (high, medium, low) to certain recognized methodological gaps (Table II). As an illustration, size, size distribution and stability of nanoparticles in a biorelevant environment (as physicochemical parameters), and protein corona evaluation and immunotoxicity assessment (as biological parameters), were considered high priority areas. In addition, whether it was justified or not, size, size distribution and particle stability were considered to be the most important parameters for regulatory decision making (29).

Of course, when talking about nanomedicines, size is a universal feature to be assessed. Nonetheless, defining particle size represents a challenge in itself, as there is no unique definition of particle size. Multiple organizations, including the ISO, OECD, FDA, and EC have proposed various definitions for the nanoscale and nanomaterials. In these definitions, size often refers to one or more external dimensions or an internal structure falling within a specified size range. Commonly, an upper limit of 100 nm or approximately 100 nm prevails. Indeed, the appropriateness of a specific size value lacks scientific support. To capture the essence more accurately, several definitions in the field of nanomedicine incorporate reference to specific properties or nano-specific characteristics, emphasizing their significance over adhering strictly to a numerical size limit (16).

What complicates the situation even more is the fact that exact size can be applied to solid nanosystems, with defined edges, while nanomedicines are usually “soft matter systems,” with fluid/flexible edges. Moreover, the term “size” is quite general, having in mind all the possible “types of size” (30). Finally, not only is the size important, but also the size distribution.

It is worth highlighting that there is compelling scientific evidence demonstrating that a universal methodology or set of tests cannot be uniformly applied to all nanomaterials (16). The diverse nature of nanomaterials demands a tailored approach to characterization and evaluation. Here we have only presented some examples.

Considering size estimation (as, logically, the first association with regard to nanostructures), nanoparticle sizing techniques can be classified into: i) batch particle size measurements (dynamic light scattering, static light scattering, small and wide angle X-ray scattering), ii) single particle size measurements (nanoparticle tracking analysis, tunable resistive pulse sensing, transmission and scanning electron microscopy, atomic force microscopy, single particle inductively coupled plasma mass spectrometry, and iii) separation-based size measurements (asymmetric flow field flow fractionation, analytical ultracentrifugation; size exclusion chromatography) (31). However, each measurement depends on the underlying physical principle, providing a "different type of size" (e.g., hydrodynamic radius, radius of gyration, ferret radius, etc.). Therefore, the results of the same sample provided by different techniques may vary, which complicates the decision on the result validity (30). Therefore, in order to reduce the risk of unknown systemic errors and technique-related biases, the latest recommendations suggest the application of orthogonal techniques when assessing sample properties (techniques that measure the same parameter but rely on different physical principles) (32). Such an approach should support complementary measurements, which enable collecting different types of information to achieve a better understanding of the sample.

The same strategy should be considered in biological evaluation. For example, the anticipation of immunogenic potential represents a specific challenge, standing out as an important factor in the safety of nanomedicines (29). Moreover, interactions between the test reagents and the nanomaterial have been identified as one of the most important issues in toxicity testing that influence market authorization of nanomedicines (33). For instance, doxorubicin-loaded liposome formulation interaction in colorimetric cytotoxicity assessment has been reported. Consequently, it is not possible to detect the dose-response curve and, as a final outcome, false negative results are provided. It is also important to notice that this is not a unique case (34, 35). Therefore, the inclusion of several assays that have different readouts and rely on different biological principles is crucial.

Similarly, it could be difficult to detect endotoxin levels in nanomaterials intended for biomedical applications, as different nanomaterials can interfere with endotoxin detection systems at various levels (36). In that regard, convenient methods for endotoxin evaluation in nanomaterials samples, with proper controls, must be assessed. Nanomaterials are prone to endotoxin contamination during synthesis or handling, or through the use of laboratory glass or chemicals which are not endotoxin-free. Moreover, hydrophobic cationic surfaces of nanomaterials are sensitive to endotoxin binding, as endotoxins are negatively charged (37). In order to detect endotoxin

contamination in nanomaterials, four methods are accepted in the European and US Pharmacopeias (38, 39):

- Rabbit pyrogen test (RPT) as an *in vivo* test;
- *Limulus* amoebocyte lysate (LAL) assay, which has replaced the old i*n vivo* RPT test;
- Monocyte activation test (MAT), which is an animal-free method;
- Recombinant Factor C assay, which overcomes false-positive results of the LAL test in interaction with beta-glucans.

The LAL test is fast and sensitive, and three variants of the LAL assay are commercially available: the gel clot, turbidimetric and chromogenic assays. Depending on the characteristics of nanomaterials, different tests may be more suitable for endotoxin detection. For example, if the nanomaterial absorbs highly between 400 and 550 nm, turbidimetric and gel clot LAL assays and RPT may be more suitable than the chromogenic LAL assay, rFC or MAT method, due to potential interferences. If the nanomaterial contains beta-glucans, the use of a glucan inhibitory buffer in the LAL test is mandatory. Alternatively, the rFC assay may be used (37).

Having in mind all the difficulties that have been mentioned, leading EU and US scientific bodies have been working jointly since 2015 to establish a framework for reliable nanomedicine characterization. Their activities have delivered the so-called assay cascade protocol, defining three major aspects of potential nanomedicine to be assessed before entering clinical trials, and demonstrating quality and safety to the regulators: physicochemical, *in vitro* and *in vivo* (40). However, these protocols are not binding. With a similar goal, the REFINE H2020 EU project, gathering leading institutions and experts in the field, proposed a regulatory science framework for the risk-benefit assessment of medical products and medical devices that are based on nanomedicines and biomaterials (41). Even though intensive work has been performed so far, there are still unresolved methodological gaps.

Regulatory framework in the EU

As already mentioned, one of the challenging aspects in the field of nanomedicine is the definition of these complex structures. Taken together with the characterization challenges, it is not surprising that regulation is quite complicated, since there is no consensus on the basic aspects. However, whenever we are talking about a nanomedicine in general, there are 3 concepts to keep in mind (8, 14):

- it is a structure, not a simple substance,
- small (nano) size is designed intentionally; it does not appear like that naturally, and its production process mainly determines its physicochemical properties,
- it exerts specific properties which are not achievable in individual components of the nanostructure nor with the macro counterparts.

At the moment, there is no specific legislation related precisely to the approval of nanomedicines. However, there have been continuous efforts devoted to this area. In

2009, the International Regulators Working Group on Nanotechnology was established, aiming to discuss issues in the regulated products containing nanoscale materials (42). Further, the EMA has published 5 nanomedicine-related reflection papers (for specific types of nanomedicines):

- Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (24);
- Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (25);
- Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (26);
- Development of block-copolymer-micelle medicinal products – Joint EMA and Ministry of Health, Labour and Welfare – Japan (27);
- Non-clinical studies of generic nanoparticle iron medicinal product applications (28).

Further collaboration of the expert bodies led to the establishment of a Nanomedicines Working Party (in March 2023, following the steps of the Non-Biological Complex Drugs Working Party) and another one, also related to this topic - mRNA Vaccines Working Party (in June 2022) (40) at the European Directorate for the Quality of Medicines (EDQM), elaborating on the quality standards supporting these emerging fields that will be included in the European Pharmacopeia. Taking into account the accumulated knowledge and experience, experts from different fields are joining forces to develop harmonized standards for assessing nano-enabled medicinal products.

Conclusion

In recent years, pharmaceutical research has prominently focused on advanced formulations incorporating nanoparticle systems. Consequently, there has been a growing focus on addressing the establishment and application of standards for nano-enabled medicinal products. On the whole, certain knowledge on quality, safety, and efficacy of nanomedicines has been gained so far, while methods for their critical quality attributes evaluation and toxicological assessment should be standardized and upgraded, applying new approach methodologies. Regulators should capitalize on these findings to support the decision-making process, facilitating the translation of these products towards clinical applications, and reducing the ambiguities in interpretations concerning their quality, safety, and efficacy, and therefore potentially different approaches among referent authorities (e.g., between the EMA and FDA).

Appendix

Table I The most important regulatory information requirements associated with all nanotechnology-enabled medicinal products (24-28)

Tabela I Najznačajnije informacije o nanolekovima koje zahtevaju regulatorna tela (24-28)

Information related to nanomemedicines required by the regulatory authorities	
Physicochemical	**Biological**
• Chemical composition/structure • Crystallinity • Impurities • Size and size distribution • Morphological properties • Surface properties (area, charge, ligands, hydrophobicity, roughness…) • Particle concentration • Stability – physical and chemical (under relevant conditions) • Degradation pathway • Drug loading • Physical state of the active ingredient, distribution within the formulation	• Bioburden (sterility, endotoxin levels) • Stability in the biologically relevant environment (blood, serum) • Plasma protein binding • Biocompatibility with blood and serum • In vitro cellular uptake and cytotoxicity • Immunogenicity • In vivo fate • Risk assessment associated with the administration route

Table II The most important methodological gaps recognized through a survey among regulatory and scientific bodies (Adapted from: 29)

Tabela II Najznačajnije metodološke praznine u karakterizaciji nanolekova prepoznate od strane regulatornih tela i relevantnih naučnoistraživačkih ustanova (prilagođeno prema referenci 29)

Methodological need/gap	**Category**	**Observation**
Size Size distribution Stability Surface properties	**Physicochemical**	• Optimization to a specific type/class of nanosystem • Methodological problems for soft matter nanoparticles
Drug loading and release		• Specific gaps for large APIs
Investigation of protein corona	**Biological**	• Challenges in separation of nanoparticle-protein complexes from excess of plasma • Difficulties with soft matter organic nanoparticles • High variability/low predictive potential
Complement activation		• Lack of advanced in vitro models
Cytotoxicity		• Interference of nanomaterial with commonly used readouts
Inflammation		• Assay variability • Relevance of *in vitro* assays
Endotoxin presence		• Alternative methods to the existing ones (LAL test) are needed (due to interaction of the nanoparticles with the nanoparticles)

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„Pejzažni" prikaz nanolekova: ekspertska perspektiva

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Kratak sadržaj

Polje nanotehnologije se nalazi na čelu naučne revolucije, gde se termin „nano" izdiže iznad pukog označavanja veličine, otvarajući vrata novim mogućnostima. U kontekstu razvoja lekova, izbor odgovarajućeg sistema za isporuku / nosača (koji odgovara određenoj aktivnoj supstanci) predstavlja ključnu odluku. U tom kontekstu, nanosistemi već određeno vreme predstavljaju inovativna rešenja.

Iako farmaceutski nanosistemi nose ogroman potencijal, suočavaju se sa određenim izazovima u pogledu translacije sa prekliničkog na klinički nivo, što se ogleda u nedostatku odgovarajućih protokola za ispitivanje kvaliteta i bezbednosti i, shodno tome, nedefinisanom regulatornom okruženju. Od revolucionarnog odobrenja liposomalnog doksorubicina od strane Američke agencije za hranu i lekove 1995. godine, pa sve do danas, oko 80 nano formulacija (nanolekova) odobreno je za kliničku primenu. Odnedavno je intenzivnija pažnja usmerena ka nanoformulacijama baziranim na lipidima, što je delom posledica razvoja mRNK vakcina tokom pandemije COVID-19. Međutim, relativno skroman nastup nanolekova na tržištu (u poređenju sa obimnim istraživačkim naporima i finansijskim ulaganjima u ovu oblast) otvara važna pitanja.

Ovaj rad pruža pregled izazova u definisanju nanolekova, njihovih svojstava, kompleksnosti regulatornih okvira i imperativa za stvaranje standardizovanih protokola karakterizacije.

Ključne reči: nanolekovi, nanočestice, protokoli za karakterizaciju, regulatorni aspekti nanolekova