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REVIEW

Bridging the Gap: The Role of Advanced Formulation Strategies in the Clinical Translation of Nanoparticle-Based Drug Delivery Systems

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Abstract: Although nanoparticles (NPs) show tremendous potential in the laboratory, most of them fail to reach clinical applications, highlighting a significant "translational gap" in nanomedicine. This gap is often due to a lack of focus on advanced formulation strategies required to transform NPs into functional drug products. Therefore, this review systematically addresses the crucial role of secondary delivery systems in bridging this gap. We analyze and compare various advanced formulation platforms, such as sterile injectables for the intravenous route, hydrogels for topical delivery, microspheres for the oral route, dry powder formulations for inhalation, and polymer implants for controlled release, and discuss how each system addresses specific clinical challenges related to route of administration, stability, and bioavailability. We conclude that shifting the focus from nanoparticle design alone to integrated formulation strategies is a fundamental step towards accelerating the translation of nanomedicines from the laboratory to the patient.
Keywords: nanomedicine, translational gap, advanced formulation platforms, drug delivery, targeted therapy, biomedical nanotechnology

Introduction

Nanomedicine is positioned as a driver of a therapeutic revolution through more precise drug delivery, increased efficacy, and reduced toxicity,[1–3] This success is evidenced by a small number of clinical approvals, for examples include Doxil®/Caelyx® (liposomal doxorubicin) and Abraxane® (albumin-bound paclitaxel). These products serve as proof of concept for successful nanoplatforms in patients.[4,5] However, this optimism is at odds with reality. There is a wide translational gap, with thousands of published nanomedicines and candidates in preclinical trials. However, only an estimated 50–80 nanomedicines have achieved global approval for clinical use by 2025. This indicates a low conversion rate from the laboratory to the clinic.[6,7] Thus, despite the presence of iconic products, the aggregate evidence suggests a gap between the abundance of publications and products actually reaching patients.

This gap is rooted in fundamental scientific and preclinical barriers. Many findings in animal models do not translate well to humans, particularly regarding the phenomenon of Enhanced Permeability and Retention (EPR), which is often robust in mice but heterogeneous and limited in human tumors. Recent literature also highlights that vascular heterogeneity, interstitial pressure, and non-EPR entry routes complicate in vivo distribution predictions and require strategies beyond the EPR to achieve consistent targeting.[4] Furthermore, complex interactions with biological barriers impact pharmacokinetics/pharmacodynamics,[8,9] so that efficacy signals in animals often do not persist in clinical trials.

On the practical side, industrial and regulatory barriers further widen the translational gap.[10] Translational success is also critically dependent on the ability to overcome practical hurdles in Chemistry, Manufacturing, and Controls (CMC), GMP-scale production of nanomedicines requires thorough characterization and stringent process control to ensure inter-batch consistency. In the safety assessment pillar, the lack of uniformity in toxicity and immune response testing standards is a major focus for regulators. In the regulatory landscape pillar, developers must navigate the ever-evolving guidelines from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for complex non-biological products.[11,12] Challenges in biocompatibility, nanotoxicology, and regulatory oversight limit the clinical translation of nanomedicines.[11]

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Addressing these scientific and practical challenges requires an integrated approach that integrates clinical evidence evaluation, mechanism-based formulation strategy selection, and harmonized CMC, safety, and regulatory pathways. This review aims to map the clinical landscape and approved products, assess design and manufacturing strategies, and identify priority research gaps. This manuscript is structured as a roadmap: a summary of clinical status, an analysis of scalable formulation strategies, followed by relevant safety and regulatory aspects for next-generation development.

Clinical Landscape and Translational Gaps

Over the past decade, more than 100,000 scientific articles on nanomedicines have been published, but as of 2023, only about 90 products have actually obtained global marketing approval, with the portfolio dominated by liposomes, nanocrystals, and lipid nanoparticles (LNPs) as the most widely approved types of nanomedicines, accounting for more than 60% of the market share; approximately 500 additional candidates remain in clinical trials, resulting in <0.1% of research output reaching the clinic—a gap that reflects regulatory hurdles, manufacturing scale, and safety issues. Public-private investment continues to increase, for example, the European Union (EU) has allocated approximately US$3 billion since 2004, and the global market value is projected to exceed US$570 billion by 2032, underscoring the urgency of regulatory harmonization and more efficient development strategies.[2,6,13,14]

The nanomedicine ecosystem presents a fundamental paradox, while the volume of publications and preclinical candidates continues to skyrocket, the number of products successfully achieving clinical approval remains extremely limited.[15] Early successes in nanomedicine have historically been dominated by first-generation platforms such as liposomes. Iconic examples include Doxil® (pegylated liposomal doxorubicin (PLD)) and Abraxane®. These products provided strong proof of concept for clinical applications. However, broad replication remains challenging across platforms and disease indications.[16,17] Analysis confirms that most clinical approvals are concentrated in specific classes, highlighting a significant translational "bottleneck" from knowledge to product. This gap is exacerbated by the inherent challenges of drug development, such as costs that can exceed $2.5 billion and low clinical trial success rates, which are further complicated in the nanomedicine context by unique quality, manufacturing, and regulatory issues.[18,19]

As a pioneer, PLD demonstrated dramatic improvements in pharmacokinetic profiles compared to free doxorubicin, particularly significantly prolonged circulation time, which contributed to reduced cardiotoxicity.[17] Its clinical benefits have been demonstrated in ovarian and breast cancer. However, this success also provided an important lesson: the magnitude of efficacy in humans was not as high as projected from animal models, highlighting the variability of the EPR effect in patients as a major limiting factor.[20] Real-world data also confirmed the consistency of this product class and the limitations of its usefulness in specific clinical scenarios.

In contrast, BIND-014 (targeted docetaxel nanoparticles) exemplifies a clear translational challenge. Despite demonstrating a favorable safety profile and promising early activity signals, this more advanced platform failed to demonstrate convincing clinical improvement in several Phase II trials. The primary efficacy endpoint was not met, leading to the termination of the development program.[21] This case vividly illustrates the gap between robust preclinical evidence of molecular targeting and its actual impact on patient clinical outcomes, particularly when the complexities of intratumor distribution and biomarker-based patient selection are not adequately addressed.

Failures such as BIND-014 and the limited efficacy of Doxil are rooted in an over-reliance on the EPR effect. This concept, while valid, has proven to be highly heterogeneous, often low, and unpredictable in human patients. Factors such as vascular heterogeneity, interstitial pressure, and the tumor microenvironment limit the transferability of findings from animal models.[22] This suggests a critical conclusion, for the next generation of nanomedicines, passive reliance on EPR is no longer sufficient. Therefore, active targeting strategies, stimulus-responsive systems, and personalized approaches based on transport biomarkers need to be prioritized to rationally increase the probability of clinical success.

Critical Analysis of Advanced Formulation Strategies

Nanomedicine formulation strategies are evolving to simultaneously address biological barriers and manufacturing challenges. This approach is multi-scale, encompassing fundamental decisions in core particle design, such as material selection and synthesis method, surface engineering through functional coatings such as PEGylation and targeting ligands to regulate stability and biodistribution, and integration into a final dosage form suitable for clinical administration.[23,24]

The focus of this overall strategy is balancing enhanced efficacy and safety with measurability of critical quality attributes (CQAs) and scalability below quality standards, given their direct impact on reproducibility and translational opportunities. Some important notes about nanoparticles are shown in Figure 1.

With this framework in mind, the following discussion will review four platform families: lipid, polymer, hybrid/inorganic, and biocarrier, that represent solutions at the core design and surface engineering levels. Lessons learned from one platform can inform optimization in others.

Lipid-Based Platforms

Lipid-based platforms, particularly liposomes and lipid nanoparticles (LNPs), can be considered the backbone of translational nanomedicine. As pioneers, liposomes provide a versatile framework for encapsulating both hydrophilic and hydrophobic payloads. The ability to modify their surfaces with polymers such as PEG has proven crucial for suppressing clearance by the reticuloendothelial system (RES) and extending circulation time.[25,26] Their initial success was demonstrated by iconic products such as PLD (Doxil®) in oncology. Their most recent evolution, LNPs, has come into the global spotlight through the phenomenal success of COVID-19 mRNA vaccines, where a tailored lipid composition (including ionizable lipids) is key to protecting and efficiently delivering nucleic acids.[27–29]

This proven clinical success is rooted in several fundamental advantages, but also accompanied by significant challenges. On the one hand, lipid platforms offer superior pharmacokinetic control and have the most mature regulatory

Figure 1 Limitations in Nanoparticle Drug Delivery Development.

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track record, accelerating the development pipeline. On the other hand, their efficacy often relies on heterogeneous EPR effects in humans and can lead to specific side effects such as hand-foot syndrome in PLD. Furthermore, the risk of immunogenicity due to anti-PEG antibodies is a serious clinical concern, as it can trigger hypersensitivity reactions or accelerate drug clearance upon repeated administration.[30–32] Formulation stability during storage, which is susceptible to drug leakage or aggregation, also demands stringent quality control.[33]

This balance between benefits and risks directly highlights several crucial research gaps that must be addressed. Current priorities include the development of effective non-PEG stealth alternatives (such as zwitterionic polymers or poly(2-oxazoline),[34,35] the design of targeting ligands that do not enhance opsonization, and the establishment of standardized CQA metrics to reliably link physicochemical parameters to clinical outcomes.

Polymer-Based Platforms

If lipid platforms are the clinical pioneers, then polymer-based platforms are the "laboratories" for nanomedicine design, offering unparalleled chemical flexibility. Polymeric micelle-like architectures effectively enhance the solubility of hydrophobic drugs, as demonstrated in various experimental paclitaxel formulations. On the other hand, established polymers such as Poly(lactic-co-glycolic acid) (PLGA) provide controlled release profiles and reliable biodegradation, making them a leading choice for sustained therapy.[36–38] Meanwhile, natural biopolymers such as chitosan leverage their unique properties, such as positive charge and mucoadhesive properties, for mucosal surface delivery applications.[39–41] All of these platforms can be further modified with PEGylation or targeting ligands to enhance in vivo performance.

Despite offering exceptional design flexibility, polymer-based platforms face significant translational challenges, particularly in manufacturing and biological predictability. The primary advantage of this platform lies in its engineering capability to precisely control drug release profiles. However, this strength also presents a real-world weakness. This chemical diversity often leads to significant challenges in batch-to-batch variability and production scaling under GMP standards. Furthermore, there is often a weak correlation between physicochemical attributes measured in vitro and particle performance in vivo. For example, cationic polymers designed for gene delivery can interact strongly with cell membranes but also carry risks of biopersistence and toxicity if their degradation is inefficient.[42]

Overcoming these limitations requires progress in several key research areas. A crucial research gap centers on the standardization of advanced analytical methods for better characterization, including particle interactions with protein coronas and their true size distribution in biological environments. Furthermore, there is an urgent need for the development of a new generation of biodegradable polymers with higher biocompatibility and improved gene delivery efficiency, to address the safety concerns inherent in conventional cationic polymers.[43]

Hybrid and Inorganic Platforms

Hybrid and inorganic platforms differ from organic platforms, which rely on polymer chemistry. They offer functionality derived from the intrinsic physical properties of their core materials. Hybrid platforms combine different materials, such as lipid-polymer or organic-inorganic. This combination synergizes stability, payload capacity, and targeting capabilities in a single system.[44,45] At the heart of many of these systems are inorganic nanoparticles such as gold (AuNPs) and iron oxide (IONPs), which contribute distinctive physical properties such as plasmonic response (ideal for photothermal therapy) and superparamagnetism (for MRI contrast).[46,47] To function safely in biological environments, these inorganic cores almost always require functional coatings, such as silica, PEG, or targeting ligands, to enhance stability and biocompatibility. Their primary applications are often in the theranostics realm, where IONPs are used as contrast agents and AuNPs are explored for imaging-guided therapy, although these are largely still limited to the clinical exploration phase.[16,48,49]

This unique ability to combine diagnostics and therapy opens the door to precision-guided medicine, but also presents a fundamental set of long-term safety challenges. A key advantage of this platform is its multimodality, which allows for real-time visualization of particle distribution while simultaneously delivering therapy. However, this advantage introduces the fundamental challenge of biopersistence in non-biodegradable materials. Unlike biodegradable polymers or lipids, inorganic materials can accumulate in organs such as the liver and spleen, raising questions about chronic toxicology. Their clearance routes are often not fully understood, and some materials, such as quantum dots containing heavy metals, risk releasing toxic ions if they partially decompose in the body.[30]

Addressing this safety dilemma is a top priority, reflected in current research gaps. The most pressing need is the development of standardized protocols for clinically relevant long-term toxicology and biodistribution evaluations. Furthermore, a deeper understanding of clearance mechanisms and mapping of dose–exposure–response relationships for non-biodegradable materials is needed to establish acceptable safety thresholds for regulatory agencies for broader clinical use.

Biocarriers

As an alternative to synthetic materials, biocarriers such as exosomes and virus-like particles (VLPs) offer delivery strategies that borrow from natural biological mechanisms. Exosomes, as natural intercellular communication vesicles, possess inherent advantages in biocompatibility, low immunogenicity, and the ability to cross difficult biological barriers such as the blood-brain barrier.[50] Furthermore, VLPs mimic the precise architecture of viruses without an infectious genome, making them highly efficient platforms for antigen presentation in vaccines (such as the HPV vaccine) or as functionalizable carriers.[51] Both can be engineered to carry therapeutic payloads, ranging from small molecules to nucleic acids, with potentially superior tissue tropism compared to synthetic nanoparticles.

This potential to mimic endogenous pathways makes biocarriers highly attractive, but they present unique challenges rooted in their biological origins. The primary advantages of these platforms are undoubtedly their superior biocompatibility and the potential to evade immune responses, which are often problematic with synthetic materials. However, the greatest challenges lie in the realm of Manufacturing and Quality Control. Their biological origins naturally produce heterogeneity, making it difficult to achieve inter-batch consistency. Purification processes to separate biocarriers from other cellular contaminants are also highly complex and difficult to scale. Furthermore, methods for loading therapeutic payloads into them are often inefficient and difficult to control.[50,52] Translational analysis, as shown in Table 1, is important to obtain the right approach in designing further dosage forms.

These fundamental limitations in standardization and production define the most pressing research gap. Clearer regulatory guidelines from agencies like the FDA/EMA specifically addressing these nano-like biologics are needed. In

Table 1 Translational Analysis of Nanoparticle Platforms

Nanoparticle Platform	Main Applications	Translational Analysis	Refs
Metal NPs (Gold/Silver)	Photothermal therapy; biomedical imaging	• Advantages: unique optical/physical properties enabling photothermal conversion and sensitive detection. • Challenges: colloidal stability, protein corona formation, biocompatibility, and biopersistence with potential tissue accumulation. • Strategies: polymer stealth coatings (PEGylation) to enhance stability, reduce RES clearance, and prolong circulation; consider non-PEG stealth alternatives where immunological risk must be minimized.	[53,54]
Quantum dots	High-resolution cellular imaging	• Advantages: superior fluorescence intensity and photostability for precision imaging. • Challenges: heavy-metal-related cytotoxicity, ion release, and in vivo biodegradation issues. • Strategies: encapsulation in silica or polymer matrices to reduce toxicity and improve biocompatibility; consider heavy-metal-free QDs as a complementary design path.	[55–57]
Magnetic nanoparticles (iron oxide)	Targeted drug delivery; MRI contrast agents	• Advantages: MRI compatibility and magnetic targeting capability. • Challenges: achieving high target specificity, controlling protein corona interactions, and ensuring safe degradation/clearance to avoid biopersistence. • Strategies: polymer coatings or liposomal encapsulation to improve biocompatibility and modulate biodistribution; optimize size/loading to meet dual imaging–therapy requirements.	[58,59]

(*Continued*)

Table 1 (Continued).

Nanoparticle Platform	Main Applications	Translational Analysis	Refs
Nanostructured lipid carriers (NLC)	Topical/transdermal administration	• Advantages: effective interaction with the skin barrier, improved local retention, and potential for controlled release. • Challenges: maintaining physical stability and preventing aggregation during storage/use. • Strategies: incorporation into hydrogels to enhance stability, smooth release profiles, and practical topical application; optimize lipid composition to minimize unfavorable crystallization.	[60,61]
DNA-based nanomaterials	Cancer therapy; diagnostics	• Advantages: high modularity, programmability, and dual function integration (theranostics). • Challenges: in vivo stability against nucleases, production scalability, and manufacturing cost. • Strategies: encapsulation within lipid or polymer carriers for protection and improved circulation stability; combine with stabilization techniques to resist degradation and preserve function.	[62,63]

addition, innovations in scalable production and purification methods and precise and controlled payload loading techniques are crucial to unlocking the full potential of biocarriers in broader clinical applications beyond vaccination.

Formulation Strategy Based on Route of Administration

The choice of route of administration is not simply a logistical decision, but rather an integral part of nanomedicine design, determining the coating type, particle architecture, and CQAs required to penetrate specific biological barriers while minimizing side effects. For the oral route, the design must withstand pH extremes and enzymes; for intravenous, the formulation needs to manage interactions with the protein corona and opsonization; for inhalation, aerodynamic size is a determinant of deposition; and for topical, the ability to penetrate the stratum corneum is key. Within this framework, formulation strategy is mapped as a spectrum of complementary solutions, where lessons from one route can often inform optimization of another.

Oral Route

The oral route, while preferred due to convenience and patient compliance,[64] faces a harsh gastrointestinal (GI) environment. Key challenges include stability against extreme pH fluctuations from the stomach to the intestine, degradation by proteolytic enzymes, and penetration through the thick mucus barrier that limits diffusion and interaction with the intestinal epithelium.[40,65,66]

Effective designs often combine protection against degradation in the stomach through enteric coatings, while mucoadhesive polymers are utilized to extend residence time and enhance contact with the absorption surface. Various modifications of chitosan, for example, have demonstrated improved acid stability and permeation in preclinical studies. Chitosan succinate combined with hydroxypropyl methylcellulose phthalate (HPMCP) has shown improved resistance to acidic conditions, holding drug release under 10% in acid medium. Another modification, chitosan-laurate (CS-LA), demonstrated significant acid stability, maintaining its structure in acidic conditions for over 22 hours.[67,68] An ideal oral formulation must overcome the harsh GI environment to deliver drugs effectively. Small molecule ligands, such as fatty acids, glucose, bile acids, are more suitable than peptides or proteins, as they resist pH and enzymatic degradation, are cost-effective, and align with natural nutrient absorption pathways, enhancing transepithelial transport and in vivo safety. Surface engineering with ligands to utilize intestinal transporters is also a central strategy for increasing bioavailability.[69,70]

Despite promising preclinical signals, clinical translation of nano-oral formulations remains limited. The main limitations are high interpatient bioavailability variability and the difficulty of predicting drug release in the dynamic GI environment.[71] Therefore, current research priorities are shifting to the development of more relevant in vitro–in vivo

correlation (IVIVC) models, the determination of biomarkers for mucosal transport, and the development of in vitro assays that better capture particle–mucus interactions representatively.

Intravenous (IV) Route

The IV route places the formulation directly into the complex blood circulation, shifting the primary challenge to interactions with blood components. The design focus is on preventing opsonization (coating by serum proteins) and rapid clearance by the reticuloendothelial system (RES) in the liver and spleen, including issues of biocompatibility, toxicity, drug loading and release, storage stability, biodistribution, organ/tissue selectivity, cell internalization, and biodegradability.[72]

The most common strategy is to create a "stealth coating", typically through PEGylation, to reduce recognition by the immune system.[39,73] Simultaneously, the use of targeting ligands, such as antibodies or peptides, aims to enhance tissue selectivity. Here, control of CQAs such as size, zeta potential, and surface composition is crucial because they directly influence protein corona formation, circulation time, and biodistribution patterns. In intravenous (IV) injections, NPs must avoid immune recognition and clearance, and possess optimal size and surface properties to reach the target tissue through the EPR effect.[16,74]

The strengths of the IV route are 100% systemic bioavailability and precise exposure control. However, challenges include EPR-based accumulation heterogeneity in humans and the risk of PEG-related immunogenicity. In some patients, anti-PEG antibodies have been associated with hypersensitivity reactions and accelerated blood clearance (ABC) phenomena. Future research agendas include exploring alternative non-PEG stealth coatings (such as poly(2-oxazoline) and polyglycerol[34,35] and cell membrane-based biomimetic coatings,[75–77] along with the development of a framework for immunological risk screening in patients.

Inhalation/Pulmonary Route

NPs carrying bronchodilators or anti-inflammatories enable targeted respiratory therapy, The main challenges are particle deposition at the appropriate site (distal airways) and interaction with the mucus barrier. Particles must be able to avoid rapid elimination by mucociliary clearance mechanisms.[78]

The success of this route requires careful control of aerodynamic particle size. Surface engineering is also crucial, where anti-mucus coatings can enhance penetration, while mucoadhesive strategies are used for longer local retention. Formulation as a dry powder inhaler offers the advantage of storage stability.[79] For nucleic acids, approaches such as charge stabilization of LNPs have demonstrated efficient delivery of mRNA to the lungs in animal models.[79]

The advantage of this route is the ability to achieve high local drug concentrations with minimal systemic toxicity. However, inter-individual deposition variability, potential local irritation, and dependence on patient inhalation technique present significant uncertainties. Crucial steps forward are the development of quality by design (QbD) aerosol testing methods, deposition metrics that correlate with clinical outcomes, and safety standards for chronic pulmonary exposure to nanoparticles. Strategies for rational formulation and optimization of nanomedicine manufacturing, aligned with the principles of QbD and quality risk management (QRM).[7]

Topical and Transdermal Routes

In dermal application, the greatest challenge is penetrating the highly hydrophobic stratum corneum, which serves as the primary barrier.[39,80] Formulation strategies focus on combining permeation enhancers with deformable nanocarriers such as transfersomes, which are able to "squeeze" themselves through lipid gaps in the skin. Another approach is the use of microneedles to temporarily open micropathways. Coatings are designed to enhance local retention in specific skin layers or facilitate permeation.[81,82]

The main advantages of this route are local exposure control and an excellent systemic safety profile. Transdermal drug delivery presents a promising noninvasive approach, bypassing first-pass metabolism and gastrointestinal degradation.[83] Limitations include low penetration rates in intact skin, interindividual variability, and formulation stability challenges in dosage forms such as creams or gels.[82] Urgent research agendas include standardizing methods for assessing penetration in human skin such as using ex vivo skin models, linking penetration metrics to clinically meaningful outcomes, and strengthening product stability under realistic storage conditions.

Mapping the specific challenges for each drug delivery route, from payload protection in the gastrointestinal tract to immune evasion in the IV route, is crucial (as shown in Table 2). Therefore, the next step in research should focus on developing modular and adaptable nanotechnology platforms. Such platforms can be specifically modified; for example, by adding gut-targeting ligands for oral formulations, or by inserting stealth polymers for intravenous applications, while maintaining the same nanocarrier core. This direction will accelerate the development of new drugs by enabling rapid adaptation to different routes of administration. Integrating these principles forms the foundation for CMC decisions, safety evaluation plans, and targeted regulatory navigation, ensuring designs are not only biologically robust but also ready for scale-up and clinical evaluation.

Practical Barriers on the Road to the Clinic

The successful translation of a nanomedicine depends not only on intelligent scientific design but also on its ability to navigate a complex set of practical obstacles. Ultimate success requires alignment between science, manufacturing and regulatory strategies. This section reviews three key practical obstacles that often determine the success or failure of a nanomedicine candidate in advanced development stages.

Manufacturing & Scalability

A fundamental challenge in CMC is translating successful laboratory-scale synthesis processes into robust, controlled, and scalable production processes under Good Manufacturing Practice (GMP) standards. Regulatory bodies require stringent characterization and control of CQAs, such as particle size, size distribution (PDI), surface charge, composition, and drug loading efficiency. Inter-batch variability, even differences as small as 10 nm in size, can significantly alter pharmacokinetic and biodistribution profiles. Conventional manufacturing techniques often face challenges in scalability and precise size control.[97,98] Meanwhile, effective and scalable purification methods, such as tangential flow filtration (TFF), are preferred over centrifugation to maintain colloidal stability.[99]

A key research gap in this area is the lack of a thorough understanding of the relationship between manufacturing process parameters, CQAs, and in vivo clinical performance. The development of more specific CMC guidelines for nano-intensity manufacturing processes such as microfluidics for LNP production and reliable in-process analytical methods remain priorities to ensure product consistency and quality.

Safety & Biocompatibility

Non-clinical safety assessments for nanomedicines present unique complexities. One of the most prominent challenges is immunogenicity, particularly related to polymer coatings such as PEG. The formation of anti-PEG antibodies in some patients has been shown to trigger hypersensitivity reactions, accelerate clearance (ABC phenomenon), and ultimately decrease drug exposure and efficacy. The prevalence of pre-existing anti-PEG antibodies in the general population further increases the urgency of this issue. Beyond immunogenicity, nanotoxicology is a major concern, where toxicity mechanisms can range from solubilization of toxic ions to induction of oxidative stress and inflammatory responses, which are highly dependent on the composition and surface properties of the particles.[100–103]

A pressing research gap is the lack of validated and sensitive standardized assays to predict and monitor immune responses to nanomaterials, including anti-PEG antibodies.[29] There is a significant need for the development of alternative, next-generation, non-immunogenic stealth materials. Furthermore, the integration of a proactive risk management plan for immunogenicity issues into clinical trial design is a crucial next step.

Challenges and Regulatory Landscape

Regulatory frameworks for nanomedicines often lag behind the pace of technological innovation, creating uncertainty for developers.[12] Regulatory agencies such as the FDA and EMA generally adopt a risk-based and case-by-case approach, given the heterogeneity of nanomedicine platforms. Existing guidelines, such as those from the FDA's Nanotechnology Task Force, emphasize the importance of comprehensive CMC documentation, in-depth physicochemical characterization, and relevant safety evaluations. However, the lack of a globally harmonized regulatory pathway can delay approval and limit patient access to innovation.[73]

Table 2 Implications and Critical Considerations of Nanoparticles Based on Routes of Administration

Route of Administration	Key Biological Challenges	Formulation Strategies	Clinical Advantages and Limitations	References
Intravenous (IV)	Rapid clearance by the immune system (RES), opsonization by blood proteins, endothelial barriers to reach target tissues	Stealth coatings (PEGylation) to evade RES; surface functionalization with ligands (antibodies, peptides) for active targeting	• Advantages: 100% bioavailability, precise dose control. • Limitations: invasive, risk of immunogenicity (anti-PEG reactions), reliance on heterogeneous EPR in humans	[64,84,85]
Oral	Extreme gastric pH, enzymatic degradation, thick intestinal mucus barrier	Enteric coatings (pH-sensitive polymers) to protect in the stomach; mucoadhesive polymers, such as chitosan, to prolong gastrointestinal residence	• Advantages: non-invasive, high patient adherence. • Limitations: low and highly variable bioavailability, limited clinical success to date	[64,70,86]
Inhalation (pulmonary)	Mucociliary clearance, alveolar macrophage uptake, viscous airway mucus	Control aerodynamic diameter (approximately 1–5 μm); dry powder formulations for storage stability; mucoadhesive or mucus-penetrating surface coatings	• Advantages: rapid local action, avoids first-pass metabolism. • Limitations: interpatient deposition variability, potential airway irritation, dose impacted by inhalation technique	[64,78]
Topical (skin)	Highly hydrophobic, tightly packed stratum corneum; risk of local irritation	Permeation enhancers; deformable nanocarriers, such as Transfersomes, incorporation into hydrogel vehicles	• Advantages: focused local delivery with minimal systemic effects. • Limitations: poor penetration for large molecules, variability across skin conditions	[64,87–89]
Intranasal	Small dosing volume, rapid mucociliary clearance, enzymatic degradation in nasal mucosa	Mucoadhesive formulations to extend contact time; exploitation of nose-to-brain delivery pathways	• Advantages: fast onset, bypasses first-pass metabolism, non-invasive route to CNS. • Limitations: small absorptive area, best suited for potent, low-dose drugs	[90,91]
Ocular	Rapid precorneal loss via tear turnover, tight corneal barrier	In-situ gelling systems that gel upon administration; mucoadhesive polymers to increase bioadhesion	• Advantages: reduced dosing frequency, improved adherence. • Limitations: typically very low topical ocular bioavailability (<5%)	[92–94]
Rectal	Relatively small absorptive surface, variable absorption	Suppositories or gels enabling local nanoparticle release	• Advantages: partial avoidance of first-pass metabolism; useful for local therapy or for patients unable to swallow. • Limitations: low patient acceptability, inconsistent absorption	[95,96]

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In Table 3, in developing nanomedicine products, key regulatory insights from EU, FDA, MHRA, and global frameworks (2024–2025) underscore the need for a case-by-case, risk-based approach, prioritizing detailed physicochemical characterization, stability, and biological interactions to address complexities in multi-component systems for

Table 3 Current Nanomedicine Regulatory Guidelines Table (2024–2025)

Regulator / Authority	Key Guidance	Key Points	Challenges & Recommendations	Refs
European Union (EU)	EU Innovation Network Horizon Scanning Report	• Product trends are shifting from simple nanoparticles to multi-component systems. • Applications are expanding into cancer, autoimmune, and infectious diseases. • Evaluation remains on a case-by-case basis.	• Challenge 50% of stakeholders find current guidance unclear. • Recommendation Early engagement with regulators, a clinical trial tracking system (CTIS), and international harmonization.	[12,104]
United States (FDA)	Risk-Based Approach (ongoing)	• No specific legal basis; case-by-case evaluation. • Common pathways: New Drug Application (NDA) 505(b)(1) for new products or 505(j) for generics. • Focus on characterization, physicochemical properties, and manufacturing stability.	• Challenge Complexity of new formulations. • Recommendation Robust control strategies to ensure product quality and biological effects.	[12,105]
United Kingdom (MHRA)	Decision Tree (February 2025)	• Medicinal product or medical device (focus medicinal) classification. • Use biosimilar guidelines with nano CQAs. • Determine type, apply ICH/MHRA guidelines. • Non-biological, Conduct bioequivalence; apply ICH quality guidelines. • Consider NAS status for DS/DP. • Key ICH: Q1A-Q13, M7, etc, plus QP declaration and British Pharmacopoeia/European Pharmacopoeia. • Prioritize legal basis before submission.	• Challenges Lack of specific nanomedicine guidelines; case-by-case evaluation; complex classification (medicine vs device); regulatory delays. • Recommendations Use decision tree as navigation tool; submit queries to MHRA; conduct bioequivalence studies and follow ICH for quality; involve MHRA Innovation Office for innovations.	[106]
Global/General	Interdisciplinary Platforms & Reviews	• Launch of the European Platform for Regulatory Science Research. • Emphasis on a combined approach of biotechnology and nanomaterials.	• Challenge Classification ambiguities and lack of standardized testing for follow-on nanomedicines, difficulties in physicochemical characterization, safety/toxicity assessment, and scalability/manufacturing. • Recommendation Foster dialogue between researchers and regulators to accelerate clinical translation, including international harmonization of guidelines and collaboration among academia, industry, and agencies.	[12,107]

applications like oncology and infectious diseases; tackle classification ambiguities and standardization gaps by leveraging tools like MHRA's Decision Tree and fostering international harmonization via platforms such as the European Platform for Regulatory Science Research; engage regulators early through systems like CTIS to mitigate delays and ensure robust quality controls; and emphasize interdisciplinary collaboration among researchers, developers, and agencies to accelerate clinical translation while balancing innovation with patient safety.

Research and development gaps in this area center on the development of reliable IVIVC models for nanoformulations, which currently remains a significant challenge due to the complexity of nanomaterial pharmacokinetics.[108] Furthermore, greater international harmonization efforts are needed to simplify data requirements and expedite regulatory review for these complex non-biological products. The development of validated modeling and simulation approaches is also key to predicting in vivo behavior and supporting safety and efficacy arguments to regulators.

Conclusions and Future Directions

The nanomedicine journey from laboratory concept to clinical approval faces a significant "translational gap", with most promising candidates failing to overcome development hurdles. This review has explored the roots of this gap, demonstrating that success is not solely determined by nanoparticle design at the nanoscale, but crucially relies on integrated, advanced formulation strategies. Analysis of multiple platforms, from clinically mature lipids to next-generation biocarriers, reveals a common thread: rational matching of particle architecture, route of administration, and specific biological challenges is key. Consistent translational success demands a holistic approach that balances scientific innovation with manufacturing realities, safety, and regulatory challenges.

Based on this analysis, several priority research gaps emerge as a collective agenda for the nanomedicine community. First, the development of alternative, non-PEG-based, non-immunogenic stealth materials to overcome the limitations of current PEGylation platforms. Second, standardization of protocols for long-term safety and toxicology assessments for non-biodegradable materials. Third, development of more predictive IVIVC models, especially for complex administration routes such as oral and inhalation. Finally, more robust and scalable manufacturing and characterization methods are needed, capable of ensuring inter-batch consistency, a prerequisite for regulatory approval.

Looking ahead, the future of nanomedicine will likely be driven by a paradigm shift from a "one-size-fits-all" approach to nano-based precision medicine. This will involve the integration of high-throughput screening platforms, computational modeling, and the use of companion biomarkers to select patients most likely to benefit from specific therapies. Realizing this vision will require unprecedented collaboration between materials scientists, biologists, process engineers, clinicians, and regulatory agencies. By addressing existing research gaps and working within an integrated translational framework, nanomedicine can begin to consistently deliver on its promise, transforming the way we treat the world's most challenging diseases.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

The author made a significant contribution to the work reported, including conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; has agreed on the journal to which the article has been submitted; and agrees to be accountable for all aspects of the work.

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Disclosure

The author declares no conflicts of interest in this work.

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