REVIEW PAPER

Regulatory intelligence-driven oversight of nanomedicines: gaps in US, EU, and India

Harish Murthyappa[1*], Prakash Goudanavar[1], Ravi Kumar Reddy Juturi[1], Hemanth Prasad Konasuru Puttaraju[1], Hemanth Boregowda[1], Mallamma Thippeswamy[1]

[1]*Department of Pharmaceutical Regulatory Affairs, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G. Nagara, Mandya, Karnataka, India*

ABSTRACT

A regulatory framework is required for the safe and successful clinical translation of nanomedicines. Accelerated global development: the nanomedicine market had a valuation of about USD 241 billion in 2024, with projections suggesting it will grow at double-digit rates, driven by more than 1,000 active clinical trials across the globe. Several of these complex products include RNAi-based therapies and advanced liposomal formulations, all of which have received the green light from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the years past. However, there are notable geographical differences in the definitions, standards, and methods of testing for nanosimilarity. India's 2019 Guidelines for Evaluation of Nanopharmaceuticals marked the initial step, but Implementation and capacity are still limited. Significant regulatory gaps in immunogenicity testing, bioequivalence studies, uniform characterisation, and nano-specific pharmacovigilance leave producers and regulators in the dark. This review compares methods in the US, EU, and India using recently published clearance data, clinical trial findings, and policy papers. The role of regulatory intelligence (RI) is one of the primary concerns raised.RI a strategic tool to overcome fragmentation and enable foresight in the development of nanomedicine is the systematic monitoring of evolving regulations, authorizations, and safety reports.

We conclude our offering by proposing recommendations to India on how to enhance post-market surveillance, develop capacity, set up specialized reference labs, and improve regulations. These recommendations for harmonized and evidence-driven oversight of nanomedicines make significant strides in articulating global lessons to national priorities.

Keywords: *Nanomedicines; Regulatory affairs; FDA; EMA; CDSCO; Regulatory intelligence.*

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INTRODUCTION

Nanomedicine is a term that applies to nanoscale structures, more than 1 and less than 100 nm in size, which are applied for therapeutic purposes and delivery of drugs. These systems, unlike the traditional formulation, provide the opportunity for better solubility and targeted delivery, with reduced toxicity [1]. Doxil, Abraxane, and Onivyde are nanoformulations that have received clinical approval, primarily in oncology, demonstrating better safety and therapeutic benefits than traditional chemotherapy [2]. The global research in nanomedicine has broadened with a sudden increase of studies into cancers in the last decade. The US and nations such as China and India are active contributors through publications and clinical trials [3]. Year-wise growth in nanomedicine publications and approvals from 2000 to 2024 is illustrated in Figure 1.

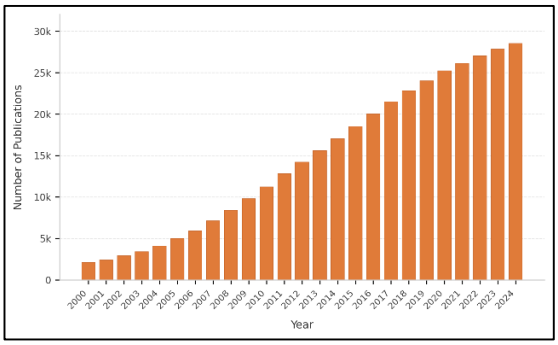

Fig. 1. Illustrates the Annual growth in nanomedicine-related publications over time [4].

* *Corresponding author(s):* Harish Murthyappa, M Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G. Nagara, Mandya, Karnataka571448, India. Phone: +91 9019843341, Email: *hmdvlr2015@gmail.com*.

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There has been significant growth in research and regulation of nanomedicine globally over the years. By 2024, there will be more than a thousand international clinical trials related to nanomedicine, of which oncology nearly embodies 60 %, with India contributing about 8 % to this [5–7]. The global market for nanomedicine is expected to grow to the tune of ≈USD 241 billion by 2024, and is likely to reach about USD 430 billion by 2030, developing at a compounding annual rate of approximately 11 % [8,9]. The same trend was reflected by other regulatory agencies in the following way: the U.S. FDA (2022) published its Guidance for Industry: Drug Products Containing Nanomaterials; EMA issued in 2020 an updated Reflection Paper on Nanotechnology-Based Medicinal Products; and in 2019 India came up with Guidelines for Evaluation of Nanopharmaceuticals [7,9,10]. Despite such progress, the language used for nanomedicine, criteria for nanosimilarity, and data basis remain different, resulting in continued regulatory fragmentation [11,12]. The FDA has also reviewed and approved over 60 nanocarrier-based dossiers, while much of the approvals from India are essentially reformulated generics [13]. In the changing landscape on nanomedicine regulatory scenarios, RI holds the edge for tracking changing guidance, analyzing trends in approvals, and projecting global requirements-the latter of which is crucial for India's compliance with international best practices [14,15].

Although for nanomedicine regulatory agencies like FDA or EMA have applied a case-by-case approach, in 2019, India’s CDSCO has launched a draft guidance [16]. Regarding safety assessment pertaining to nanomedicines, challenges still exist, such as lack of standardization in definitions, gaps within safety assessments, and absence of global harmonization [17].

Artificial intelligence (AI) is shifting paradigms across industries-aided in large measure by automation and insight you get from data. In nanomedicine regulation, AI-based tools are increasingly utilized for automated regulatory monitoring, large-scale analyses of guidance documents and data-driven decision-making across jurisdictions [18]. Clinical trial assessments have manifested frequent quality-related issues. More than 80 percent of the evaluated nanocrystalline formulations fail across concerns such as stability, batch characterization, and GMP compliance [19]. Nanomedicines create toxicological uncertainties over and above the challenges related to manufacture. Size, shape, and surface charge determine biological interactions, but there are insufficient sensitivity and standardization currently in characterization tools to assess such effects [20]. The regulatory frameworks of international jurisdictions are still fragmented. Ventola claims that the lack of common definitions, review procedures, and evaluation standards causes delays and inefficiencies for developers trying to reach different markets [21]. To fill these gaps, risk-based regulatory approaches have been put forth, such as immunotoxicity evaluation, early safety profiling, and key quality attribute (CQA) alignment with regulatory expectations [22].

The lack of globally recognized standards and assessment techniques is one element causing the regulatory difficulties pertaining to nanomedicines. Regarding categorization standards, data requirements, and approval processes, the regulatory frameworks of various agencies, including the FDA, EMA, and CDSCO, vary substantially. Developers looking to enter several jurisdictions face a fragmented compliance environment as a result of these variances [23]. This discrepancy typically results in little differences in terminology, testing standards, and docket forms for global operating companies, which can contribute to delays, effort duplication, and substantial expenses [24].

Navigating the quickly changing and dispersed regulatory environment of nanomedicine is becoming increasingly dependent on RI. Regulatory bodies such as the FDA and EMA are releasing ever-more-complex guidelines that call for accurate and comprehensive evaluation and characterization of nanomaterials and their unique properties. This makes it very challenging for developers to understand and meet these location-specific needs [25]. Therefore, in a regulatory framework that has not yet been harmonized for nanomedicine and its derivatives, such as nanosimilars, the FDA and EMA continuously rely on different scientific or clinical assessment methods; as a result, RI that can interpret and track the regulatory trends and updated in real-time is required [26]. By systematically collecting, evaluating, and implementing regulatory updates and guidance, RI assists sponsors in better preparing for new requirements while avoiding typical mistakes in technical submissions for nanomedicines [27]. Additionally, agencies like EMA explicitly encourage early communication and scientific advice between applicants and regulators, a process made possible by robust RI and ensuring better quality and success in the creation of nanomedicine products [28].

The article focuses on the evolving situation and gaps in policy, scientific rigor, and evaluation criteria to allow comparisons of regulatory regimes related to nanomedicines in the USA, EU, and India

[29]. Among the obstacles to clinical translation and adoption are discussions of specific scientific concerns that the FDA, EMA, and CDSCO have with regard to health products that use nanotechnology, including characterization, risk assessment, and post-market surveillance [30]. Interventions that can dramatically increase patient safety and therapeutic efficacy across locations include harmonized processes, stakeholder participation, and inconsistent regulatory science [31]. The assessment goes on to address how regulatory information assists in the preparation of dossiers, predicts changes in guidance, and provides sponsors with assurance when negotiating the rapidly evolving policy landscape [32]. The paper concludes with good recommendations for improving India's regulatory environment to support ethical innovation in nanomedicine and align with global best practices [33].

Notifying the primary nanomedicine platforms that constitute the basis of the field is essential before performing regulatory comparisons, as illustrated in Figure 2.

Overview of Nanomedicine

Since nanomedicines are a rapidly expanding field in pharmaceutical development, different global regions have different regulatory requirements. The FDA and EMA appear to have their own oversight frameworks that are still in their infancy, with significant differences between the regulations that were established regarding the standardization criteria for clinical evaluation, toxicity assessment, and nanoparticle characterization. These deviations add a growing need for a harmonized regulatory framework and definition for all well accepted globally to aid safe and efficacious translation of nano-therapies from lab to clinic [34].

Nanomedicines encompass an extensive range of nano-scale platforms. These platforms are designed either for therapeutic or diagnostic purposes. The major classes comprise liposomes, polymeric nanoparticles, dendrimers, micelles, nanocrystals, and metallic nanoparticles. Each class exhibits a distinct profile in their structural and functional attributes, which are aimed at enhancing drug solubility, bioavailability, and targeted tissue distribution [15].

Nanocarriers receive their regulatory definition from physicochemical properties and biological characteristics that exist at nanoscale dimensions because these properties can affect product quality and safety and efficacy. The U.S. FDA and EMA use a case-by-case risk-based assessment method to define their regulatory framework because materials that exceed the standard 1–100 nm size limit can still qualify as nanocarrier products when they show changes in biodistribution or stability or immunogenicity or pharmacokinetic performance in relation to non-nanoscale materials [35,36].

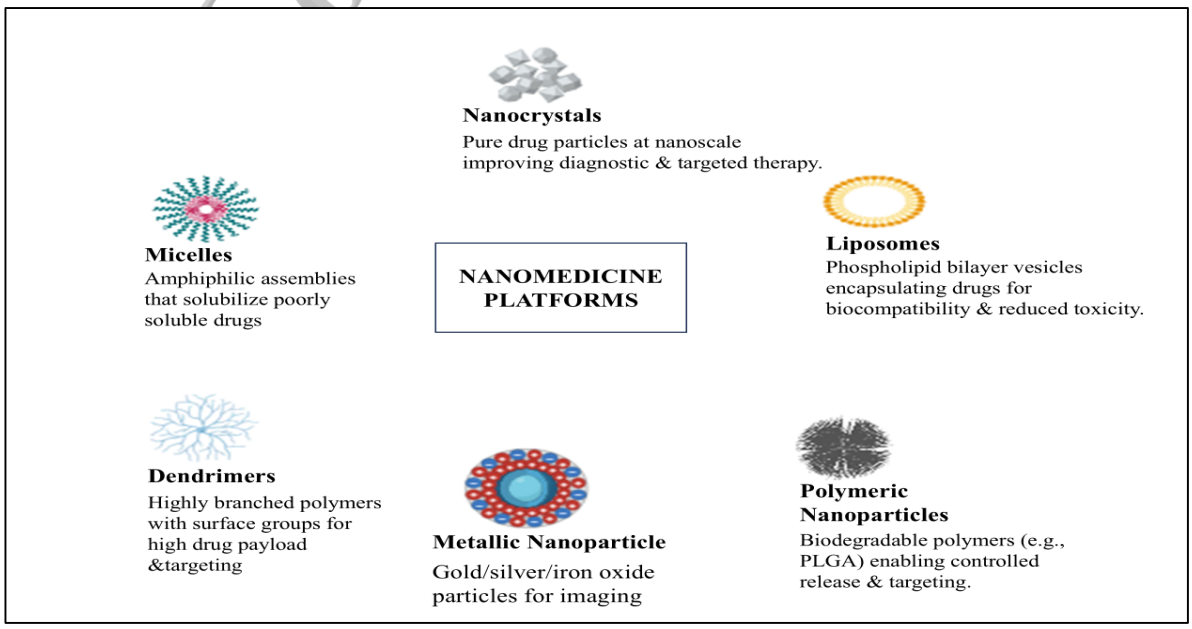

Fig. 2. Key nanomedicine platforms that offer distinct benefits in drug solubility, targeting, imaging, and controlled release include liposomes, dendrimers, metallic nanoparticles, polymeric nanoparticles, nanocrystals, and micelles [4,12].

Table 1. Examples of FDA/EMA-Approved Nanomedicines and Their Applications [40,41].

Nanomedicine (Brand Name)	Active Ingredient	Carrier Type/Platform	Indication	Regulatory Region (First Approval Year)*
Doxil / caelyx	Doxorubicin	PEGylated liposome	Ovarian cancer, multiple myeloma	FDA (1995), EMA (1996)
Abraxane	Paclitaxel	Albumin-bound nanoparticle	Breast cancer, NSCLC	FDA (2005), EMA (2008)
Onivyde	lrinotecan	Liposomal formulation	Metastatic pancreatic cancer	FDA (2017), EMA (2018)
AmBisome	Amphotericin B	Liposomal formulation	Fungal infections	FDA (1997), EMA (1998)
Nano Therm	Iron Oxide nanoparticle	Magnetic nanoparticle suspension	Glioblastoma hyperthermia therapy	EMA (2010, conditional)

*The first approval year marks the date when the product obtained its first marketing rights from the relevant regulatory body; conditional approvals are indicated where applicable.

The carbon nanotubes which scientists studied for drug and gene delivery possibilities because of their high aspect ratio and their ability to develop surface functionalizations, face clinical application challenges because their medical usage is restricted by their biopersistence, their ability to cause inflammatory responses, and their unknown safety for extended periods [30,32]. The gas-filled nanoscale vesicles known as nanobubbles have three main applications in diagnostic imaging and ultrasound-driven drug delivery and oxygen transport, but regulatory bodies find it difficult to assess their safety because the technology struggles with both stability and characterization challenges [18,37].

The regulatory authorities currently evaluate emerging nanocarrier platforms which include exosomes and solid lipid nanoparticles or nanostructured lipid carriers (SLNs/NLCs). The classification and control of exosomes face difficulties because of their biological origin while SLNs/NLCs require formulation-specific evaluation because of their lipid polymorphism and scalability and batch-to-batch reproducibility requirements which demonstrate the need for platform-aware regulatory assessment [25,38].

Incorporating nanoscale delivery systems into pharmaceutical design bears important therapeutic advantages: these include site-specific delivery, reduction in off-target toxicity, improved pharmacokinetic properties, and enhanced stability of encapsulated agents, and can be used mainly for conditions needing localized treatment, such as tumours, neurological conditions, or inflammatory disorders [39].

Numerous nanomedicine formulations are now approved by leading regulatory agencies, exemplifying the clinical translation of nanoscale platforms into successful therapies. Representative examples are indicated in Table 1 [40].

As shown in Table 1, Doxil and AmBisome liposomal formulations were among the first nanomedicines approved, predominantly in oncology and infectious diseases. Newer formulations, such as Vyxeos and Onivyde, pave the way toward more complex co-formulations and targeting. This marks the global approval landscape for an analysis of the various regions' regulatory approaches in the following sections [41,42].

In the last few years, there has been an escalating global momentum in the area of nanomedicine development and commercialization, and now over 60 nanomedicines have been approved for clinical use while more than 500 products are in various stages of clinical investigation. Landmark approvals such as Onpattro (patisiran, 2018), Givlaari (givosiran, 2019), Leqvio (inclisiran, 2021), and Comirnaty (BNT162b2, 2020) illustrate how nanoscale platforms have traversed beyond oncology into genetic and infectious diseases. With an estimated value of about USD 241 billion in the year 2024, the global nanomedicine market is anticipated to proceed to expand at a rate of 11 % every year until 2030 [15].

Nanomedicine development remains shrouded in some potential but complex challenges: difficulties in reproducible synthesis of nanoparticles, along with incomplete toxicological profiling and the absence of universally accepted quality standards, serve as major hindrances. Nanomedicines are difficult to regulate since they frequently contain elements of medications, biologics, and devices [38].

Regulatory Frameworks

Nanomedicines are difficult to regulate since they frequently contain elements of medications, biologics, and devices. The US FDA the EMA, and India's Central Drugs Standard Control Organization (CDSCO) have come up with different approaches to tackle the diversities related to this new area, but several gaps remain for harmonization and implementation [43].

In the last few years from 2022 to 2025, global actions have added strength to the nanomedicine governance system. In 2022, the U.S. FDA finalized Guidance for Industry: Drug Products Containing

Nanomaterials, wherein a risk-based case-by-case approach has been highlighted for the characterization of all critical quality attributes (CQAs) needed to support regulatory decisions. Afterward, the EMA has come up with its revised Reflection Paper (2020) and Horizon Scanning Report (2024) to address the issues of emerging nanotechnology-based medicinal products and borderline medical devices. The CDSCO Guidelines for Evaluation of Nanopharmaceuticals continued to hold ground in India (2019); however, the Indian Pharmacopoeia added draft monographs on nanomaterials, which would set more standards in current consideration. Collectively, these changes are pointers toward improved structured regulation; however, definitions, dossier requirements, and nanosimilarity criteria continue to vary with different jurisdictions [10,13,36].

United States (FDA)

The U.S. FDA controls nanomedicines through its case-by-case assessment process which uses scientific evidence and risk evaluation to determine the appropriate regulation for each specific nanoscale drug product. The flexible regulatory system enables assessment of product-specific quality and safety and efficacy standards which supports innovation and creates new nanotechnology-based treatment options [23,33].

Developers and regulatory planners view this flexible system as a development and regulatory planning tool which helps them develop advanced product approval pathways for obtaining platform-specific approval. The lack of standardized approval pathways results in unpredictable regulatory outcomes which particularly affects the approval process for follow-on nanomedicines and nanosimilars [26,44]. The FDA has built regulatory consistency through its review work because it developed guidance documents that describe nanotechnology-based products which resolve past scientific uncertainties through established scientific standards [34,36].

European Union (EMA)

In Europe, the centralized marketing authorization procedure managed by EMA applies to nanomedicines especially complex therapies and innovative ones. Rather than separated bunch of legislation, EMA applies the "reflection papers" and product-specific scientific advice to applicants [35]. In addition to precautionary principles that EMA applies to iron oxide colloids, liposomal injections, and polymer therapeutics, implementation of Medical Device Regulation (MDR) Rule 19 increasingly affects borderline products while expanding supervision of devices that contain nanomaterials. Yet, even as things progress, it is also clear from the EMA viewpoint that platform-level regulation would be more efficient and that harmonization of guidance across combination nanomedicine products would be desirable [45].

India (CDSCO)

With the release of draft guidance on nano pharmaceuticals in 2019, the CDSCO of India has made some very important initial steps in incorporating features of ICH and WHO guidelines while contextualizing them for Indian healthcare needs. These drafts laid emphasis on the comparability with conventional formulations, rigorous in vitro/in vivo characterization, and generation of clinical data at a local level. However, India still does not have an official definition or classification for nanomedicines as per product types, thus creating ambiguities in classification and evaluations [46]. Meanwhile, activities by the Indian Pharmacopoeia Commission (IPC) and research agencies are giving impetus to the setting of standards and regulatory capacity-building [47].

Global divergence and need for harmonization

The worldwide understanding of nanomedicines has grown, yet countries still struggle to create unified rules for their regulatory assessment because different regions use distinct methods to classify and assess these products, which results in varying data requirements for product developers [22,30]. Pharmaceutical regulation depends on existing international frameworks which include ICH quality guidelines and Good Manufacturing Practice (GMP) standards as their core requirements; however, these frameworks lack specific provisions for nanomedicine and they fail to address essential nanoscale properties which include particle size distribution and surface characteristics and process sensitivity. The ICH and GMP frameworks establish a fundamental regulatory framework which needs additional nano-specific regulations to achieve worldwide standardization for nanomedicine product evaluation [18,22,48]. A trio region comparison of key regulatory parameter is described in Table 2.

Table 2. Comparison of Key Regulatory Parameters in US, EU and India [46,48,49].

Parameter	USFDA	EMA	CDSCO (India)
Pathway	Case-by-case (no unique path)	Product-type focus, reflection papers	Draft guidance, general frameworks
Definitions	1-100nm, new properties	Contextual, up to 100nm	1-100nm, site-specific or efficacy
Dossier Req.	Standard plus supplemental data	Detailed CMC, safety, post-market	Quality, safety, efficacy emphasis
Experience	Numerous approvals	Moderate	Few (emerging field)

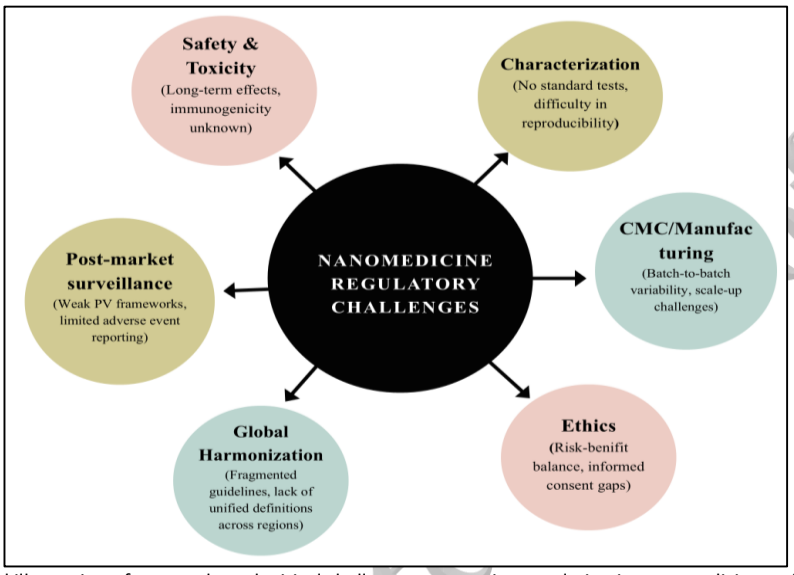

Fig. 3. Conceptual illustration of some selected critical challenges concerning regulation in nanomedicine: safety and toxicity; characterization; manufacturing; ethical concerns; post-market surveillance; and global harmonization [50–54].

Regulatory challenges in nanomedicine approval

Conceptually demonstrating the intricate knots tied in the regulatory hurdles is creation of a conceptual illustration (Figure 3), which summarizes the various and multi-faceted challenges sweeping through the countries in addressing nanomedicine regulation.

Nanomedicine is brought into existence, evaluated, and approved with a wholly new variety of scientific and regulatory challenges, owing to the complexity of nanoparticles whose dynamic and multicomponent nature renders difficult their interaction with biological systems. The challenges include safety assessment, analytical standardization, manufacturing quality and reproducibility, ethical and long-term safety monitoring, among others. While emerging guidance from major regulatory agencies is forthcoming, clear global alignment and status of universally accepted standards are absent [55].

Regulatory science has focused, in more recent years following 2020, to address real-life reproducibility issues in different fields along with nano safety challenges with data-oriented solutions. The FDA Nanotechnology Task Force (2022) described predictive modelling, micro physiological systems, and AI-facilitated toxicity screening to supplement in vivo methodologies. The EMA (2023), by the means of its Innovation Task Force, has begun horizon scanning for nanosimilars and hybrid nanoformulations as part of a cross-comparison improvement. The OECD has now updated its Test Guidelines for Manufactured Nanomaterials in 2024 and encourages harmonized analytical validation. However, the reality is that inter-laboratory variability continues to beset the field, coupled with the very few datasets that would generally cross- or between organisations acceptance, as well as highly inconsistent post-market safety monitoring with respect to the major global hurdle to general confidence in nanomedicine approval [13,56–58].

Safety and toxicity assessment

Behaviours that differ concerning the size of nanoparticles influence their absorption, distribution, metabolism, and excretion; the ways can usually be unpredictable. Many will increase cellular uptake and the capacity to breach physiological barriers, resulting in off-target effects or bioaccumulation. Existing preclinical assessment models probably do not cover all adverse long-term or systemic toxicity, and hence those uncertainties are regulatory [37]. Self-propelled nanomotors and biohybrid systems raise, however, entirely new risks resulting from dynamic interactions of

surfaces attributable to by-products from propulsion systems and modifications by biological fluids, difficult to model in vitro or in animals [59].

Characterization and analytical standardization

Standardization of test methodologies directed to evaluating nanomaterials' critical quality attributes such as particle size, zeta potential, surface chemistry, purity, and protein corona formation is a felt need. Many of these characteristics change dynamically in the presence of biological fluids, leading to lack of reproducibility of results and comparability in terms of regulation [58] The regulatory guidance does not seem to have a consensus on acceptable characterization protocols, especially with respect to nanoparticles evaluated in complex matrices or in vivo settings. Although advanced analytical tools exist, they are poorly accepted due to lack of inter-laboratory reproducibility and insufficient regulatory validation [60].

Chemistry, Manufacturing, and Controls (CMC), batch reproducibility

The process of making nanomedicine shows significant fluctuations because even small changes in production methods disrupt the process, which creates problems for maintaining consistent product quality between different production runs. The attributes of final formulations depend on three factors which include the raw material quality and environmental conditions and the intricate steps of the processing operation, so CMC documentation needs to provide detailed information while control strategy development requires particular control mechanisms to track those three factors [61]. The nanomedicine manufacturing sector has not yet adopted Quality by Design (QbD) and Process Analytical Technology (PAT) principles, which emerging economies do not make mandatory for their operations [62].

Ethical considerations and long-term surveillance

The use of nanomedicines which constantly develop together with their missing long-term clinical safety evidence raises ethical issues because researchers cannot obtain full informed consent during early human trials. The uncertain pharmacokinetics together with potential chronic toxicity require implementation of stringent post-marketing surveillance systems [63]. Ethical review boards need better nanoparticle guidelines because they currently operate without existing safety labelling standards and nanotoxicity warning requirements and environmental impact disclosure rules [64]. The primary regulatory obstacles which hinder nanomedicine evaluation appear in Table 3.

Table 3. Major Regulatory Challenges Affecting Nanomedicine Evaluation [4,65,66]

Challenge	Description
Safety & Toxicity Assessment	Unpredictable toxicity, Bioaccumulation, lack of standard tests
Characterization & Standardization	Complex attributes, analytical gaps, harmonization needs
Quality & Batch Reproducibility	Sensitive to manufacturing changes, batch variability, demanding documentation
Ethical Considerations	Informed consent, long-term risk, transparent stakeholder communication

Role of regulatory intelligence in nanomedicine

What is regulatory intelligence?

RI involves the systematic collection, analysis, and application of regulatory information to guide the development and approval of pharmaceutical products which include nanomedicine products [67]. The regulatory process for liposomes dendrimers and polymeric nanoparticles requires RI because these nanomedicines possess unique physicochemical properties that disrupt existing regulatory systems [68,69]. RI monitoring of guidance documents and approval trends and policy changes from agencies such as the U.S. FDA, EMA and CDSCO [23,45].

Regulatory authorities used to handle their decision-making process together with their compliance procedures through manual systems, which monitored regulatory requirements and reviewed agency communications at specific times while using historical regulatory precedents and expert knowledge to make their decisions. The existing methods provide multiple benefits because they achieve regulatory acceptance through established practices and use verified historical data and they apply to products with established regulatory paths that maintain consistent performance [53,56].

The methodologies demonstrate significant challenges which become especially evident in fields that undergo rapid development and possess complex challenges. Current regulatory frameworks function as reactive systems which handle regulatory matters based on certain territorial boundaries while their effectiveness depends on the specialized knowledge of their personnel who work to predict upcoming regulatory changes and new safety standards and variations between different regions of regulatory

practices. The limitations of these regulations lead to two main problems which include delayed international regulatory response and increased uncertainty in global regulatory framework development [59,62].

RI has developed into a methodical technique that combines regulatory data with policy developments and future trend analysis to help firms make educated decisions about the lifetime of their products. [63].

RI professionals use AI tools like Cortellis and regulatory databases to monitor changing standards, such FDA nanotechnology guidelines and EMA reflection documents, to ensure compliance in complex regulatory contexts [6,70]. A paradigm shift has occurred in the field of RI in recent years, from a state of passive monitoring to a proactive framework enabled by AI that is creating a system that supports evidence-based decision-making in nanomedicine regulation. The issues with expos without validation for AI models in submissions were highlighted in the FDA's Draft Guidance, "Considerations for the Use of AI to Support Regulatory Decision-Making" (2025). However, EMA (2025) adopted its Workplan on Data and AI integration in regulatory assessment for real-world evidence, and Japan's PMDA (2024) initiated some pilot projects for AI-based horizon scanning in advanced medicines. Collectively, these initiatives show how RI is shifting toward digital automation and predictive analytics to assist developers in anticipating regulatory requirements, coordinating global submissions, and guaranteeing compliance in the world of nanomedicine, which is becoming an increasingly complicated subject [71–74]. Figure 4 shows the overall workflow.

The development of a fully harmonized regulatory framework applicable to all nanomedicines remains challenging because the diverse properties of nanostructures which include their composition and physicochemical characteristics and their risk assessment methods present significant obstacles. The existing liposome platforms which have reached advanced development status show improved regulatory alignment among major regulatory agencies because they possess documented clinical data and established quality standards yet the scientific and regulatory challenges of applying one unified regulatory system to multiple distinct and upcoming nanocarrier types remain difficult to resolve [14,75]. The current regulatory framework for nanomedicines should pursue platform-specific or principle-based regulatory alignment instead of universal standardization as its primary objective according to current industry perspectives [77]. RI pathways in this context enable organizations to identify specific jurisdiction requirements through early detection while they support strategic program development alignment and decision-making during times of incomplete global harmonization [64,78].

Benefits of regulatory intelligence in nanomedicine

The onset of digital tools and AI has significantly supplemented the domain of RI and its applications in the field of nanomedicine. The modern RI platforms provide predictive analytics RWD and automated regulatory tracking through all developmental steps to assist decisions.

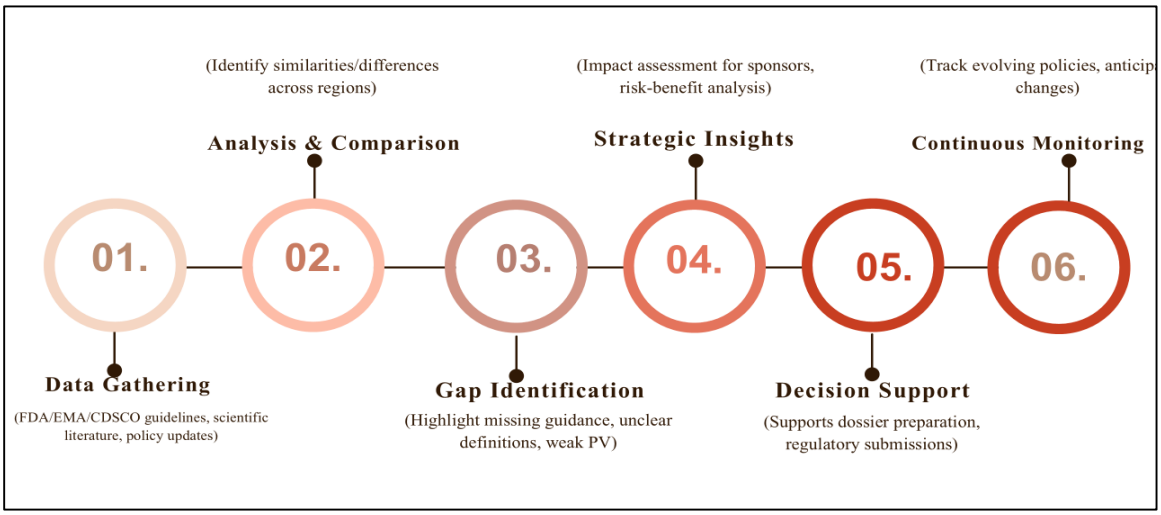

Fig. 4. RI workflow demonstrated through data collection, analysis, gaps identification, strategic insights, decision support, and ongoing monitoring [75,76].

For instance, through improved data accessibility and interagency learning, the FDA's Regulatory Science Data Commons (2024) and the EMA's Big Data Workplan (2023) further offer evidence-based reviews. These programs enable RI professionals to stay up to date with changing regional standards while also anticipating changes in regulatory requirements and potential submission gaps. Consequently, AI-based RI greatly promotes worldwide harmonization and speeds up approval processes for nanomedicine products, while also assisting with dossier design and risk mitigation [77–80].

Dossier planning

RI facilitates the development of Marketing Authorization Applications (MAAs), Clinical Trial Applications (CTAs), and Investigational New Drug (IND) applications by streamlining the regulatory submission procedure. By investigating the particular needs of different agencies, such as drug release kinetics and particle size and stability, RI verifies that dossiers satisfy the standards of nanomedicine [81,82]. The RI system lowers an organization's risk of receiving regulatory inquiries while assisting it in adhering to FDA chemistry manufacturing and controls CMC standards and EMA Quality Review of Documents QRD requirements [23,83]. Faster approval times result from the process's strategic approach, which also makes submission operations more seamless [67,84].

Risk mitigation

The nanoscale characteristics of nanomedicines raise some safety issues that need to be addressed. The particles' tiny size causes them to travel randomly throughout the body, which may be dangerous [85]. The RI strategy assists researchers in designing targeted research studies throughout their early development stage, thereby recognizing agency difficulties, as the FDA demands long-term safety data for nanomaterials [86]. To create thorough safety assessments for nanoparticles and avoid regulatory delays, RI keeps an eye on pharmacovigilance regulations [87]. The proactive approach not only speeds up the medical approval process but also improves patient safety [88].

Multi-region alignment

Different governments have set up different regulatory systems to monitor products pertaining to nanomedicine. The FDA conducts independent product evaluations, concentrating on the distinct risks associated with each product [83]. Through reflection papers, the EMA provides direction on the advancement of nanomedicine [89]. The CDSCO of India has released tentative suggestions to help regulate nanomedicine items in compliance with the Drugs and Cosmetics Act [90]. RI promotes alignment by comparing labeling and clinical trial standards, which leads to consistent submissions that make it easier to reach global markets [91].

Additional benefits

RI looks for options for faster paths, such as the FDA's Fast Track designation for nanomedicines that fulfill urgent medical needs [84]. Advanced AI-driven tools enhance RI by automating the analysis of regulatory guidelines, enabling real-time adaptation to evolving standards [92]. These tools support strategic planning by forecasting regulatory trends, ensuring developers stay ahead of compliance requirements [93].

Case examples

RI has played a pivotal role in guiding nanomedicine developers through complex and evolving regulatory landscapes. From 2023 to 2025, RI has facilitated the real-life conduct of many implementations still considered in the interest of faster regulation for nanomedicine developers. The FDA thus has incorporated digital intelligence into the NextGen Portal for a tracer study of complex drug submissions by allowing the sponsors to benchmark nanomedicine dossiers against the background of comparative approvals. The EMA's Data Analysis and Methods Task Force (2024) has begun accordingly to intertwine real-world data and AI-assisted horizon scanning for identifying the regulatory cracks for nanoparticle-based therapies. The development in Nanopharmaceutical evaluation via data-mapping tools within the framework of their National Regulatory Science Platform has been made by India's CDSCO-DBT (2024). All of this is a testament to RI, working on the essence of digital analytics, to act as a proactive dossier alignment and diminished review ambiguity through the enhanced harmonization of global oversight on nanomedicines [10,23,94,95]. The following case examples illustrate how RI has enabled strategic decision-making, dossier optimization, and multi-region alignment.

Liposome doxorubicin – FDA guidance alignment

In its Guidance for Industry: Liposome Drug Products, the FDA specified particular standards for CMC data, bioequivalence, and characterisation techniques. Generic liposomal doxorubicin developers were able to improve dossier quality

and reduce regulatory turnaround times by using RI to match their submissions with prior approvals and the FDA's pharmacokinetic requirements [96].

EU-NCL survey – horizon scanning for regulatory gaps

Through a cross-agency survey, the European Nanomedicine Characterization Laboratory (EU-NCL) identified regulatory shortcomings in the evaluation of nanomedicine in nine jurisdictions. The study of these gaps and the proposal of harmonized testing methodologies and critical quality characteristics (CQAs) enabled by RI technologies subsequently guided EMA's reflection papers and the creation of standardized characterisation protocols [97].

siRNA nanomedicine – EMA-PMDA reflection paper

The Japanese EMA and PMDA jointly published a reflection paper on siRNA-loaded nanocarriers. Developers used RI to anticipate regulatory expectations, synchronize safety and quality data across locations, and eliminate ambiguity in dossier preparation. This improved regulatory readiness and made it easier for submissions from different locations [30].

Nanocrystal-based products – EMA horizon scanning

The European Medicines Agency's Horizon Scanning Report on nanotechnology-based pharmaceuticals highlighted classification problems and CMC concerns for nanocrystals and polymeric nanoparticles. Developers were able to adapt their submission strategies, stay abreast of current regulatory discussions, and meet evolving FDA and EMA requirements by using RI [98].

Indian nanopharmaceutical guidelines – CDSCO & DBT

The Guidelines for Evaluation of Nanopharmaceuticals in India, published by the CDSCO and DBT, created a basic foundation for the regulation of nanomedicine. Indian developers employed RI to establish product classification, evaluate the evolving regulatory position, and unify safety testing techniques with foreign standards in order to increase submission quality and regulatory compliance [10].

Table 4 lists real-world company case studies that illustrate how RI affects nanomedicine approvals. Because of the great diversity of nanostructures, including differences in liposomal content and production methods, it is currently challenging to create a single, fully unified regulatory framework for all nanomedicines. Although established platforms such as liposomes have partially achieved regulatory convergence due to accumulated clinical and regulatory experience, principle-based or platform-specific alignment is a more feasible approach to addressing broader harmonization across varied nanocarriers [77,78]. Informed decision-making is aided in this situation by regulatory information channels, which make it easier to identify jurisdiction-specific expectations early on and align development initiatives strategically. Their effectiveness is still dependent on the data's quality, experts' interpretations, and resource availability, though [65,79].

Table 4. Real world company case examples showing the impact of RI in approval of nanomedicines (2018-2023).

Company / Developer	Nanomedicine product	Regulatory Agency Involved	RI Strategy Applied	Outcome / Quantifiable Impact	Ref.
Alnylam Pharmaceuticals (USA)	Onpattro (patisiran) - siRNA lipid nanoparticle	FDA & EMA	Continuous horizon scanning on lipid nanoparticle guidance; early management through parallel scientific advice	Achieved parallel approvals (FDA 2018, EMA 2018) with minimal CMC queries	[99]
Alnylam Pharmaceuticals (USA)	Givlaari (givosiran) – RNAi nanomedicine	FDA &EMA	Used RI to anticipate toxicology and comparability expectations for siRNA therapies	Accelerated approval in both regions within 4 months of NDA submissions	[100]
Pfizer-BioNTech (Germany / Usa)	Comirnaty (BNT 162b2) – mRNA vaccine (lipid nanoparticle)	EMA & FDA	Global RI coordination to align with evolving mRNA nanoliposomes guidance; real-time rolling review	Review completed in <25 days (EMA), leading to simulations global authorization	[101]
Intas Pharmaceuticals	Peglyated liposomal doxorubicin (nanosimilar)	CDSCO & EMA	Mapped regulatory trends using Ri; pre-submission queries guided dossier comparability with EMA refection papers	Clarified classification early and avoided repeat studies, expediting CDSCO review	[102]
Moderna Therapeutics (USA)	mRNA-1273 vaccine (lipid nanoparticle)	FDA, EMA, MHRA	Used RI to track evolving mRNA quality guidance and global harmonization of emergency use pathways	Parallel authorization across US, EU, UK within 3 months; reduced regulatory cycles	[103]

Gaps and recommendations (with Indian focus)

India's regulatory framework for nanomedicines, particularly the Central Drugs Standard Control Organization's (CDSCO) 2019 recommendations, is a significant step in integrating nanotechnology into the pharmaceutical sector [104], However, there are several areas where further development and harmonization could significantly improve India's standing in this rapidly evolving field when compared to the well-established regulatory frameworks of the US.FDA and the EMA [58,105,106]. With an emphasis on the regulatory space, policy regimes, governance locations, and the durability of nanomedicine, a multilayer governance structure has been proposed for India [107].

Identified gaps in India vs US/EU

How the Indian regulatory approach varies from the more established US and EU frameworks is seen in the following areas:

Guidance specificity and scope*:* The CDSCO's guidelines are important, but they need more specific details about the kinds of nanomedicine, their uses, and how to give them [108]. A multilayer governance system has been proposed for India, with an emphasis on the regulatory space, policy regimes, governance locations, and the lifespan of nanomedicine [107].

Safety and toxicity assessment: Standardized techniques for evaluating the many toxicological profiles of nanomaterials, such as immunogenicity, long-term effects, and biodistribution, are being actively developed by international norms and frameworks [110]. To facilitate the safe development of nanomedicine systems, India must enhance its specialized evaluation techniques and assessment infrastructure [106,111]. Studies reveal that nanoparticles can have unidentified harmful consequences that affect human health and the sustainability of the environment [112].

Characterization and analytical standardization: The European Union has established testing standards for nanomaterials that must be in line with the state of testing in this area, even though testing organizations have determined what needs to be improved in their testing procedures [113]. Undefined testing procedures, unmeasured material qualities, and a lack of standardized nomenclature are major obstacles to the advancement and regulatory assessment of nanomedicine in India and globally [112,114].

Quality Control (CMC) and batch reproducibility: Batch Reproducibility and Quality Control (CMC): Batch-to-batch reproducibility and consistent manufacturing processes may be challenging to ensure due to the structural complexity of nanomedicines [108]. India needs robust quality control protocols and standards to guarantee the safety, stability, effectiveness, and quality of produced nanomedicines [115]. Nanomedical production processes need to be strict before they are approved [108].

Ethical considerations*:* Although ethical concerns are acknowledged [116], India's framework requires specific guidelines and processes to address moral dilemmas concerning informed consent, public involvement, and long-term safety [116]. Ethical dilemmas arise from risks that may have long-term effects on human health and the environment [116]. Transparency and open communication are essential for establishing public trust [117]. Concerns regarding informed consent are growing as nanomedical devices incorporate AI and machine learning [52].

Infrastructure and expertise: By leveraging their reference laboratories, specialized regulatory scientific committees, and nanomedicine expertise, advanced nations could be formed [47]. Delays in the development and implementation of accurate and practical regulations may result from India's lack of scientific infrastructure and experience [47].

Harmonization efforts: While international papers are taken into consideration in India's current guidelines, it is imperative that more active participation in international harmonization efforts be made [115,118]. Because of agencies like the WHO and ICH, international regulatory standards for nanomedicines are largely in line [115]. Regarding approval delays, review procedures, and product classification, the regulatory approaches taken by various jurisdictions with regard to nanomedicines differ greatly [118].

Post-market surveillance: While India's Pharmacovigilance Programme of India (PvPI) is improving, it could be beneficial to strengthen its nanomedicine-specific risk management plans, similar to the USFDA's Risk Evaluation and Mitigation Strategies (REMS) or the EMA's Risk Management Plans (RMP) [119,120]. Post-market surveillance is crucial for monitoring and mitigating risks effectively post-approval [119].

According to these gaps mentioned on specificity of guidance, safety assessment, characterization, quality control, ethics, infrastructure, harmonization, and surveillance, it indicates that the regulatory framework of this

country is still in an evolving condition when compared to the US and the EU. The gaps have been summarized comparatively along with their possible recommendations in Table 5 for a quick subtle understanding of the regulatory landscape [121].

Recent initiatives like the OECD Nano safety Programme (2024) and the FDA-EMA Nanomedicine Cluster (2023) have made the universal fact clear with respect to harmonizing data sharing and risk assessment frameworks for nanomedicines [48,122]. The need for consistent international engagement and policy convergence is highlighted by India's limited participation in these international cooperative initiatives. The Indian Pharmacopoeia Commission (2023 Addendum) has also taken the initial steps toward standardizing tests by establishing consistent standards for the characterization of nanoparticles [123]. The effective creation of such a national digital RI network, supported by CDSCO and DBT, will enable real-time monitoring of all such safety alerts and guidance changes across major agencies, guaranteeing a consistent decision-making process and increasing India's competitiveness internationally [124,125].

Suggested improvements (with Indian focus)

Indian lawmakers, regulators, corporate executives, and academic institutions must deliberately collaborate in order to close the gaps.

Policy updates and refinement: In accordance with the EMA reflection papers technique and the USFDA product-specific procedure, the CDSCO is required to develop unique guidance documents for every category of nanomedicine [108,126]. To demonstrate their distinct position in relation to conventional drugs, nanomedicines must have well-defined regulatory frameworks [126]. It will be simpler to create new products and open up foreign markets if Indian laws adhere to international standards [114,118].

Strengthening RI practice: Pharmaceutical companies in India, together with researchers, need to implement responsible innovation practices during all stages of their nanomedicine development process [119,127]. The Indian industry requires dedicated research integrity teams which should receive training and access to worldwide regulatory databases and analytics tools [115]. The establishment of platforms which enable stakeholders to exchange research integrity best practices will improve their shared understanding while supporting a unified research integrity implementation process [114,119].

Capacity building and training: The development and execution of specialized training programs for regulatory personnel scientists and reviewers at CDSCO and industry needs to focus on the particular features of nanomedicine [47]. Interdisciplinary teamwork between material scientists and toxicologists and clinicians and regulatory experts needs to occur for developing a complete scientific understanding of the subject matter [126,128]. The establishment of centres of excellence for nanomedicine research and characterization and regulatory science will create centres of academic and professional development to support research and regulatory education [47,129].

Table 5. Comparative Gaps in Nanomedicine Regulation and Suggested Recommendations.[10,36,104,109,110]

Aspect	US/EU Status	India Status	Gap Identified	Recommendations
Regulatory Guidelines	Dedicated nanomedicine guidelines (FDA guidance, EMA reflection papers, MDR for nanomaterials)	No dedicated nanomedicine guidelines; regulated under general drug rules	Lack of nanomedicine-specific framework	Develop India-specific nanomedicine regulatory guidance aligned with international standards
Characterization Standards	Well-defined test methods for nanoparticle size, surface charge, stability	Limited standardized test protocols	Absence of validated characterization methods	Established national reference labs and adopt OECD/ISO standards
Clinical Evaluation	Clear guidance on PK/PD, immunogenicity, biosimilar nano-drugs	No specific requirements beyond conventional drug studies	Insufficient clinical evaluation parameters for nanoformulations	Introduce special requirements for toxicity, immunogenicity, and bioequivalence studies
Post-market Surveillance	Strong PV frameworks (EudraVigilance, FAERS) with nano specific case reports	Weak PV framework; limited reporting for nanomedicines	Under-reporting of nano-drug adverse events	Strengthen PV system with nano-specific adverse event coding and active surveillance
RI Integration	Active horizon scanning, stakeholder engagement, structured RI system	Minimal RI practices	Limited foresight in adapting to global nanomedicine trends	Build national RI platforms for nanomedicine policy tracking and industry guidance

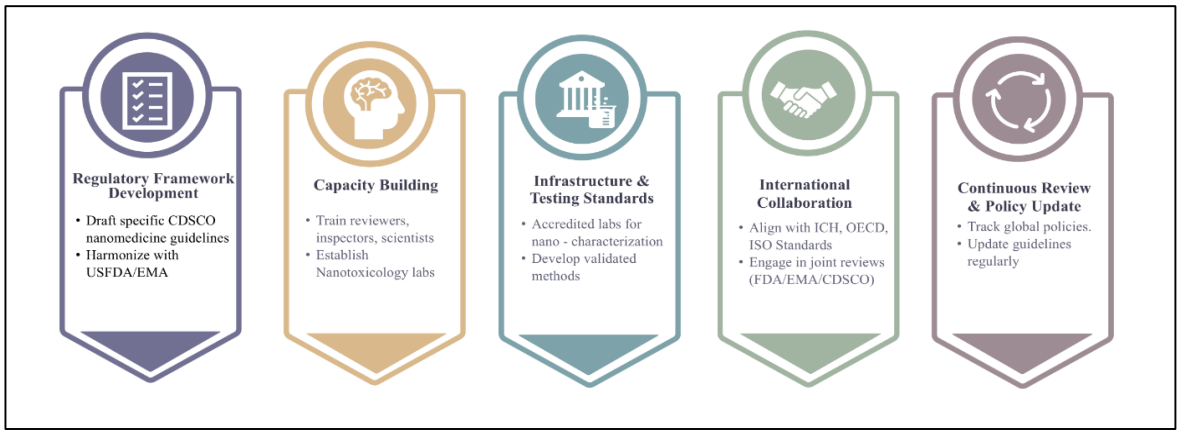

Fig. 5. Proposed roadmap for strengthening nanomedicine regulation in India [7,10,36,131]

Promoting research and development: The research budget needs to increase because scientists need funding to study nanomedicine regulatory science through their work on developing standard methods to characterize nanomedicines and test their toxicity and create analytical tools that suit Indian requirements [47]. Collaborative projects should be developed between industry and academic institutions and regulatory bodies to help organizations solve their particular problems while they develop new products [58,126]. Collaborative missions between industry and academic institutions work to speed up research which leads to scientific discoveries [126].

Public engagement and education: The field of public engagement and education requires initial dialogue sessions which healthcare providers and the general public and patients should conduct to build trustful relationships with the community while maintaining ethical standards and their duty to address patient concerns [117,130]. The regulatory process needs improved transparency which will help the public build confidence and better understand the process [117].

India can enhance its regulatory framework for nanomedicines by addressing existing gaps and executing recommended improvements which will promote innovation while maintaining safety and effectiveness for these life-changing products that benefit Indian citizens [47]. The proposed roadmap for strengthening nanomedicine regulations in India shows the identified challenges and gaps which Figure 5 illustrates.

CONCLUSION

Nanomedicine stands at the forefront of pharmaceutical innovation because it uses nanoscale delivery systems to provide new treatment options. Regulatory oversight throughout the world remains fragmented and inconsistent because major agencies like the FDA and EMA face challenges with regulatory progress in India through its CDSCO system. The global development process faces major difficulties because international standards lack defined terms and established methods of measurement and assessment procedures. India needs specific regulations that require international toxicological evaluation and quality control standards more than its existing basic guidelines because both functions as vital components of pharmaceutical development. RI serves as the main instrument which organizations need to handle their complex operational environment through its capacity to execute global strategies and protect against regional threats. The process of accelerating nanomedicine innovation will require 3 essential activities which include building capacities and implementing new policies and creating international partnerships. The implementation of a transparent and scientifically based regulatory system will establish the systems which enable nanomedicine to reach its full potential while ensuring patient security and making this life-changing treatment accessible throughout the world.

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The Authors declare no conflict of interest

AUTHORS CONTRIBUTION

HM contributed substantially to the conception and design of the work, performed synthesis, acquired, analyzed, and interpreted the data, drafted the manuscript, and revised it critically for important intellectual content; HP and HB contributed to the preparation of figures and tables. TM contributed to improving the scientific content of the manuscript. RJ and PG critically reviewed the manuscript for important intellectual content and gave final approval of the version to be published.

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