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REGULATORY FRAMEWORKS AND GLOBAL PERSPECTIVES ON NANOMEDICINE DEVELOPMENT: CHALLENGES AND OPPORTUNITIES IN DRUG DELIVERY

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ABSTRACT

Regulations for nanomedicines are crucial to ensure their safety, efficacy, and quality. Given the unique properties and potential risks associated with nanoparticles, a clear regulatory framework is essential to guide the development, testing, and commercialization of these innovative therapies. Robust regulations also provide clarity for manufacturers, healthcare professionals, and the public, fostering trust and facilitating the responsible advancement of nanotechnology in medicine. Without standardized regulations, the potential benefits of nanomedicines could be overshadowed by safety concerns and inconsistent product quality. Despite these advancements, the regulatory landscape for nanomedicines remains fragmented and underdeveloped. The lack of clear, global regulatory frameworks presents significant challenges for the continued development and commercialization of nanotechnology-based therapies. Variability in classification across jurisdictions, with some nanomedicines being treated as medical devices and others as pharmaceuticals, underscores the need for a unified approach. This regulatory ambiguity threatens to stall the momentum of nanomedicine development and potentially divert investment away from this promising field. Efforts are underway within academic and governmental organizations to address these challenges. The establishment of National Characterization Laboratories and the call for a global consortium dedicated to the regulation of nanomaterials reflect a growing recognition of the need for coordinated regulatory oversight. Moreover, emerging trends in regulatory science, such as enhanced collaboration between materials science and translational research, are expected to play a crucial role in bringing nanomedicines from the lab to the clinic. In conclusion,

nanotechnology represents a critical frontier in modern medicine, with the potential to revolutionize healthcare delivery through innovations in drug delivery systems, diagnostics, and regenerative medicine. However, the full realization of this potential will require a concerted effort to establish robust regulatory frameworks that can keep pace with the rapid advancements in nanotechnology. As the field continues to evolve, the integration of scientific disciplines within a cohesive regulatory structure will be essential to ensuring the safe and effective application of nanomedicine in addressing unmet medical needs.

KEYWORDS: Nanomedicine, Drug delivery.

INTRODUCTION

The phrase 'Nanotechnology' gained significant public attention following the publication of K. Eric Drexler's 1986 book, 'Engines of Creation: The Coming Era of Nanotechnology. This concept was originally inspired by an idea introduced by Nobel Prize winner Richard Feynman during a lecture he delivered in 1959, titled 'There's Plenty of Room at the Bottom.

Nanoparticles exhibit superior stability and carrier capacity compared to traditional drug delivery systems. They facilitate the incorporation of both hydrophilic and hydrophobic compounds and support multiple administration routes, such as oral and inhalation methods. As an advancing field, Nanotechnology is anticipated to have a significant global impact if its current momentum persists. The ongoing evolution of Nano products and their applications is crucial across various industry sectors, driving innovation in research, patent development, commercialization, and technology transfer.

Nanomedicines can surpass the limitations associated with traditional medicinal products manufactured and designed in various ways. This category encompasses a wide range of drugs characterized by varying degrees of complexity. The designation "Nanomedicine" refers to medicinal products incorporating Nanomaterials and/or utilizing Nanotechnology in their development and production. However, a universally accepted definition for Nanomedicines remains elusive, as these products exhibit significant diversity in type and structure, and they are employed across numerous indications for both acute and chronic conditions.

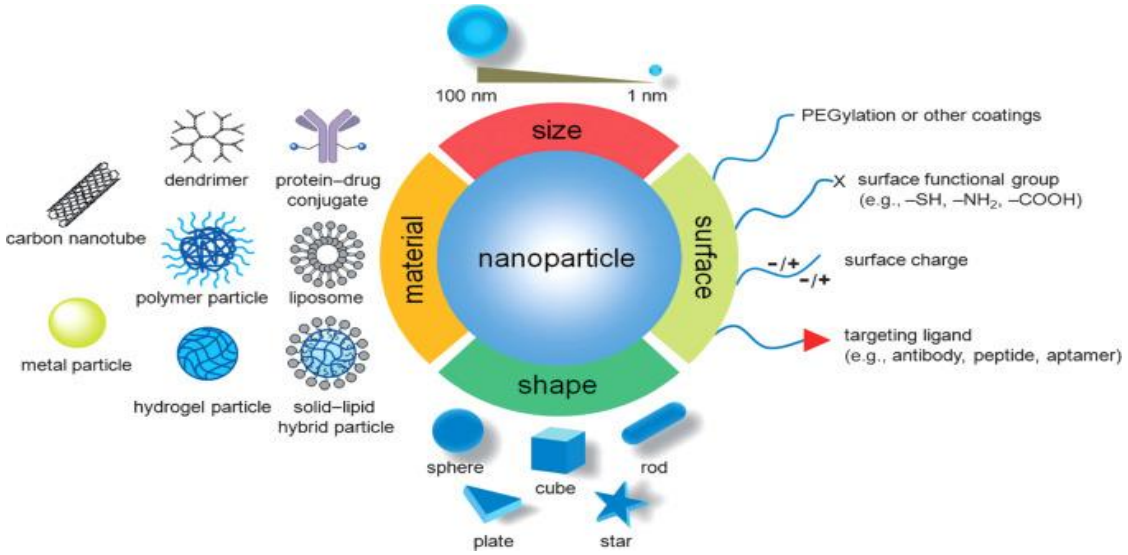

Figure 1: Nanoparticle properties.

The field of Nanomedicine, which integrates Nanotechnology into medical applications, has facilitated the creation of therapeutic carriers utilizing Nanoparticles. These drug delivery systems are designed to selectively and passively target tumors by leveraging the enhanced permeability and retention effect, making them exceptionally suitable for effective drug administration.

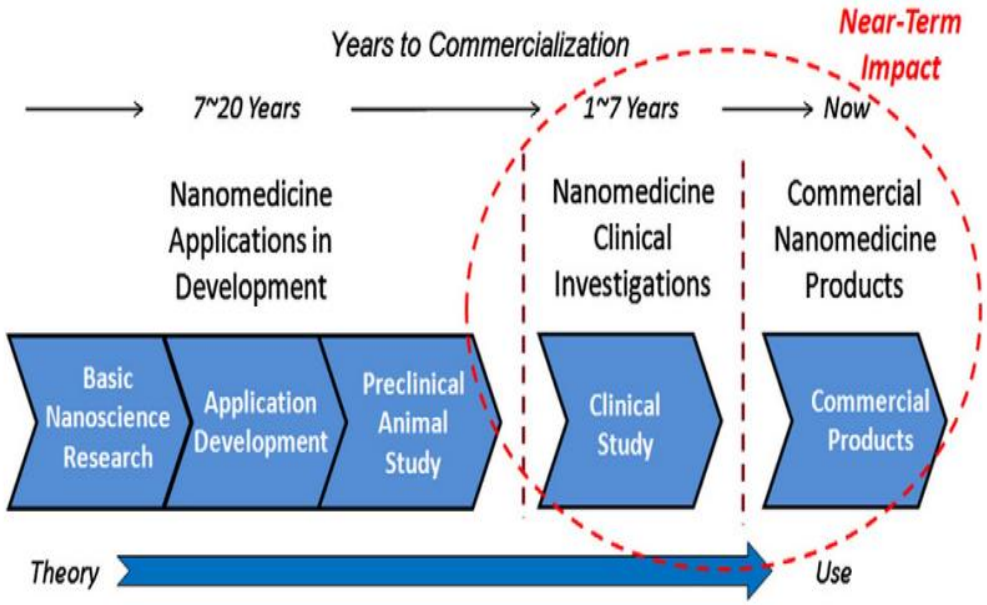

Figure 2: Nanomedicine Technology Development Pipeline.

1. Nanoparticles for drug delivery

Nanoparticle complexes can incorporate a variety of functionalities, such as surface chemistry that facilitates the binding of cell-specific ligands for precise targeting, surface

coatings designed to prolong circulation times and improve bioavailability, and specific materials located on the surface or within the Nanoparticle core that permit the storage of therapeutic agents until they arrive at the intended site. Additionally, these complexes can utilize materials that respond to local or remote activation signals, enabling the controlled release of therapeutics to the target cells. Various types of Nanoparticles are employed for drug delivery (Figure 3), depending on the characteristics of the drug involved. They may be,

- Nanotube
- Dendrimer
- Polymeric Nanoparticles
- Nanocrystal
- Inorganic Nanoparticles
- Metal-based Nanoparticles
- Liposomes

2. Regulatory background

The regulation of the Nanomedicine sector presents significant challenges due to the extensive variety of Nanomaterials involved, which include, but are not limited to, polymers, liposomes, dendrimers, Nanocrystals, Nano complexes, Nano-emulsions, Nanoparticles, metal colloids, micelles, quantum dots, fullerenes, carbon Nanotubes, liposomes, and virosomes. Each of these materials possesses distinct characteristics, such as differing compositions, sizes, shapes, and charges, leading to a wide spectrum of activities.

3. Government programs for Nanotechnology research: the US Perspective

The United States pioneered the establishment of a formal government-funded research program in Nanotechnology, initiating the National Nanotechnology Initiative (NNI) in 2000, which has allocated approximately USD 22 billion towards this field, including an estimated USD 1.5 billion requested in the President's budget for the fiscal year 2016. The leading federal agencies contributing to funding in the 2016 budget include the National Institutes of Health (NIH), the National Science Foundation, the Department of Energy, the Department of Defense, and the National Institute of Standards and Technology (NIST).

Table 1: launched Nanomedicine for treating multiple diseases by FDA.

Name	Year of Approval	Type of Formulation	Drug	Company	Therapeutic Applications
Ontak®	FDA-1999	Protein-based formulation	Denileukin diftitox	Eisai (Norcross, GA, USA)	Cutaneous T-cell lymphoma therapy
Oncaspar®	FDA-1994	Pegylated enzyme L-asparaginase	L-asparaginase	Enzon Pharmaceuticals (Cranford, NJ, USA); Baxter BioScience (Deerfield, IL, USA)	Acute lymphocytic leukemia
Restasis®	FDA-2002	Nanoemulsions	Cyclosporin	Allergan (Lansing, MI, USA)	Severe keratitis in dry eye patient Topical
Feraheme™ Intravenous	FDA-2009	Semi-synthetic iron oxide Nanoparticles	Iron oxide particles	AMAG Pharmaceuticals (Waltham, MA, USA)	Anemia related to chronic kidney disease (CKD)
Injectafer®	FDA-2013	Iron Nanoparticles	Polynuclear iron (III) oxyhydroxide iron particles	For Int. (Waltham, MA, USA)	Iron deficiency anemia
Monofer®	FDA-2010	Iron Nanoparticles	Iron molecules with unbranched carbohydrate iron particles	Pharmacosmos (Rorvangsvej, Holbæk, Denmark)	Iron deficiency anemia
Mircera®	FDA-2007	Polymer-protein conjugate	Methoxy polyethylene glycol-epoetin beta	Hoffman-LaRoche (Basel, Switzerland)	CKD associated anemia
Adynovate ®	FDA-2015	Polymer-protein conjugate	Recombinant anti-hemophilic factor VIII	Baxalta (Montgomery, AL, USA)	Hemophilia A
Neulasta®	FDA-2002	Polymer-protein conjugate	Recombinant human granulocyte colony-stimulating factor (G-CSF)	Amgen (Thousand Oaks, CA, USA)	Febrile neutropenia
Pegasys®	FDA-2002	Pegylated Nanoparticles	Interferon alfa-2a	Genentech biotechnology (San Francisco, AL, USA)	Hepatitis B and C therapy
Pegintron®	FDA-2001	Pegylated Nanoparticles	Interferon alfa-2b	Merck (Rahway, NJ, USA)	Hepatitis C
Copaxone®	FDA-1996	Polypeptide colloidal formulation	Glatiramer acetate	Teva Pharmaceuticals (Marietta, GA, USA)	Relapsing or remitting type of multiple sclerosis
Estrasorb®	FDA-2003	Emulsion	Estradiol	Novavax (Lutherville Timonium, MD, USA)	Estrogen therapy
Nanocoll®	FDA-1995	Albumin-based radiopharmaceutical Nano colloid	Albumin and stannous	GE Healthcare (Raleigh, NC, USA)	Breast cancer and also melanoma
Nanocis®	FDA-2000	Radiopharmaceutical colloid	Chloride dehydrates Radio pharmaceutical colloid	CIS Bio (Berlin, Germany)	As inflammation scintigraphy, bone marrow scintigraphy, and cutaneous route for lymphatic scintigraphy

4. The Regulatory Framework: The Europe perspective

During the approval process, Nanomedicines were incorporated within the conventional structure of benefit/risk assessment. An additional challenge associated with this is the necessity to establish a framework for evaluating follow-on Nanomedicines coinciding with the expiration of patents for reference medicines.

5. India Perspective

The document titled "Guidelines for Evaluation of Nanopharmaceuticals in India" has classified Nanopharmaceuticals based on several criteria, including the biodegradability of Nanomaterials, the characteristics of the Nanomaterials, the various Nanoforms of the active ingredients, and the approval status of both the drug and the Nanomaterial. Additionally, it outlines the necessary toxicological and clinical trial data, as well as the information essential for the assessment of Nanomaterials.

6. Australia perspective

It has been observed that no nation possesses a thorough and unified oversight framework to address the implications of Nanotechnology, including the United States, the European Union, and Australia. This situatsion is equally applicable to the field of Nanomedicine. Significant discrepancies exist among various organizations and legislative measures, not only across different countries but also within individual nations.

7. Current Regulatory Guidelines on Nanomedicines

To proactively address regulatory requirements, relevant authorities have begun to release preliminary reflection papers designed to offer initial guidance on the regulatory information that may be necessary throughout the various approval phases of innovative products (Committee for Medicinal Products for Human Use (EMA/CHMP, 2013a, b, c–2015; US FDA CDER, 2015). In the United States, the Nanotechnology Characterization Laboratory at the National Cancer Institute (NCI-NCL) (https://Nanolab.cancer.gov) has been conducting comprehensive assessments of the quality and safety of Nanomedicines for over a decade, thereby assisting product developers and facilitating the effective transition of these products into the market place.

8. Data supporting Approval of Nanomedicines

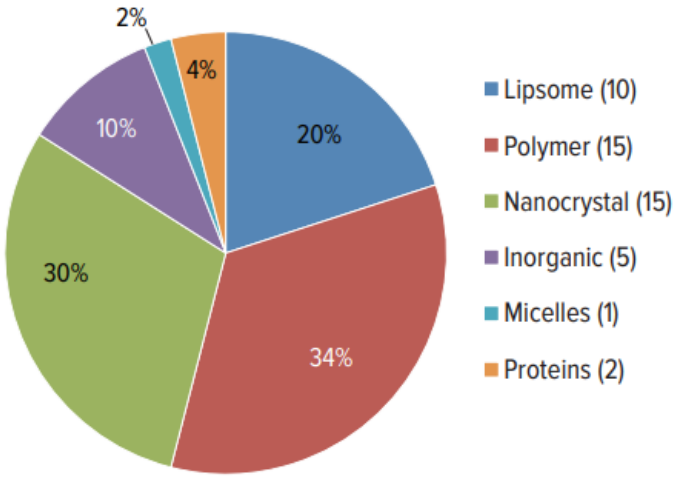

Figure 4: Types of NPs in Approved Drugs Available for Clinical Use (50).

At present, the nanoparticles employed in nanodrug formulations comprise a diverse range of materials, which include liposomes, polymers, micelles, nanocrystals, metals, and metal oxides, along with various inorganic compounds and proteins. Furthermore, current research is investigating the possibilities offered by alternative types of nanoparticles, including carbon nanotubes.

Approval Probabilities for New Nanomedicines

As of 2015, the US FDA had approved 13 Nanomedicines for various disease treatments. Recently, there has been a significant increase in the number of clinical trials involving Nanomedicines. According to data from 2021, there are currently 100 Nanomedicines available in the market, with an additional 563 undergoing clinical trials or at other developmental stages. Notably, a substantial proportion of these clinical trials are in the early phases, with 33% in Phase I and 21% in Phase II. The primary therapeutic targets for these Nanomedicines include cancer, accounting for 53% of the focus, followed by infections at 14%, along with a range of other conditions such as blood disorders, endocrine and metabolic diseases, nervous system disorders, immunological diseases, cardiovascular issues, ocular diseases, and skin conditions. Furthermore, Nanomedicines play a role in vaccine development and imaging diagnostics.

9. Current Regulations for Approval of Nanomedicines

At present, Nanomedicine products are classified under the regulations governing either medicinal products or medical devices, and there is an absence of a dedicated regulatory

framework for Nanotechnology-based products in both the European Union and the United States. In the United States, the regulation of Nanomedicines adheres to the FDA Guidelines that have been in effect since June 3, 2010, specifically outlined in CDER MAPP.

10. Challenges in the Regulation of Nanomedicine Development

Unlike traditional pharmaceutical products that typically utilize a single active ingredient, pharmaceutical Nanoparticles are characterized by their intricate composition, comprising multiple components and heterogeneous structures. This complexity allows for the interaction of various elements, which can influence the pharmacological properties of the active substance. Consequently, the regulation of Nanomedicines may encounter numerous challenges due to these multifaceted characteristics.

11. Regulatory Databases Accessed

A regulatory database has been compiled, encompassing guidelines and various regulatory documents pertinent to natural health products (NHPs). This database incorporates references collected from multiple sources, with the latest updates recorded until August 31st, 2023.

Aim

This research endeavors to conduct a thorough assessment of the regulatory frameworks that oversee the approval and development of Nanomedicines in various regions worldwide, specifically focusing on the United States, Europe, India, and Australia. The objective is to pinpoint and scrutinize the challenges associated with current regulatory practices, evaluate the efficacy of existing guidelines, and investigate possible approaches to harmonize these regulations. Furthermore, the study aims to shed light on the influence of government initiatives in promoting Nanotechnology research and to analyze the data that underpins the approval processes for Nanomedicines across different jurisdictions.

Objective

This study aims to perform an in-depth examination of the regulatory frameworks that govern the development of Nanomedicine, particularly emphasizing their use in drug delivery systems. The research will investigate the function of Nanoparticles in improving drug delivery, highlighting their distinctive characteristics and the advantages they present compared to traditional methods.

DISCUSSION

The review discusses and correlates the data collected concerning the regulatory processes governing human-use pharmaceuticals, as well as the initiatives undertaken by regulatory bodies and governments to establish a regulatory framework for Nanomaterials. This response is a direct result of technological advancements that have facilitated the integration of Nanotechnology across multiple healthcare domains. The discussion underscores the significant challenges faced in successfully navigating a Nanomedicine through the complete preclinical and clinical development stages, ultimately leading to the attainment of market authorization.

Based on the information analyzed, it can be concluded that a major challenge facing Nanomedicines is the considerable scarcity of data available to manufacturers, which arises from the substantial variability inherent in these materials. In this context, the regulatory approach being adopted by the FDA and EMA is appropriate. The establishment of technical centers such as the Nanotechnology Characterization Laboratory (NCL) and the Centre for Drug Evaluation and Research (CDER) in the United States, along with the European Nano-Characterization Laboratory (EU-NCL) in Europe, plays a crucial role in facilitating the comprehensive characterization of Nanomaterials intended for healthcare applications.

Approved Nano-formulations for cancer therapy

Since the early 1990s, Nano-formulations have been introduced for medical applications in the fight against cancer, with notable examples including the polymer–protein conjugate Zinostatin stimalamer, which received approval in Japan for hepatocellular carcinoma, and the pegylated liposome Doxil®, which was launched in the United States as a treatment for ovarian cancer. Over the years, a variety of Nano-formulations have emerged, such as liposomes, metal and metal oxide Nanoparticles, polymeric micelles, and lipid Nanoparticles, all of which have been authorized for medical use by various regulatory bodies worldwide, while numerous others are currently undergoing clinical and preclinical evaluations. Doxil® marked a significant milestone as the first liposomal product to gain approval in the United States in 1995.

CONCLUSION

The oversight of pharmaceutical products designed for human consumption constitutes a complex field that has undergone significant evolution over time. The introduction of Nanomedicines introduces an additional layer of intricacy, revealing that existing regulatory

frameworks are insufficiently prepared to address these advancements, despite the considerable efforts of agencies such as the FDA and EMA. A review of the current literature highlights that regulatory authorities and governments, particularly in the United States and the European Union, have been proactive in initiating programs aimed at revising regulatory structures to better accommodate the distinctive features of Nanomedicines. Therefore, the regulation of Nanomedicines necessitates the engagement of all stakeholders from the initial stages of development to ensure that clinical trials are conducted with a high degree of assurance regarding the quality, efficacy, and safety of the products in question.

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