

REGULATORY ROADMAP FOR NANOTECHNOLOGY BASED MEDICINES

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REVIEW ARTICLE

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ABSTRACT

Nanotechnology is emerging as one of the key technologies of the 21st century and is expected to enable developments across a wide range of sectors that can benefit citizens. Nanomedicine is an application of nanotechnology in the areas of healthcare, disease diagnosis, treatment and prevention of disease. Nanomedicines pose problem of nanotoxicity related to factors like size, shape, specific surface area, surface morphology, and crystallinity. Currently, nanomedicines are regulated as medicinal products or as medical devices and there is no specific regulatory framework for nanotechnology-based products neither in the EU nor in the USA. This review presents a scheme for classification and regulatory approval process for nanotechnology based medicines.

Keywords: Nanotechnology, Nanomedicine, Nanotoxicity, Approval, Regulations.

INTRODUCTION

All human endeavors in drug development and therapeutics revolve around their optimization to offer efficacious proactive healthcare so as to improve public health with assured safety and market accessibility of the new products to people. Nanotechnology is emerging as one of the key technologies of the 21st century and is expected to enable developments across a wide range of sectors that can benefit citizens. The dawn of nanotechnology can be traced back to 1959, when Caltech physicist Richard Feynman painted a vision of the future of science. In a talk titled "There's plenty of room at the bottom", Feynman hypothesized that atoms and molecules could be manipulated like building blocks. (1) Nanotechnology began to emerge as a realistic scientific endeavor during the 1980s. In 1982, IBM researchers introduced the scanning tunneling microscope (STM), a microscope that could display individual atoms of gold. (2) Scientists' abilities to utilize advancing nanotools were highlighted in 1989 when IBM scientists manipulated thirty-five atoms of xenon to form the letter IBM. (3) The last decade has witnessed rapid technological advancements.

Nanotechnology is the science of studying phenomena and the manipulation of materials at

atomic, molecular and macromolecular scale. Use of the prefix "nano" in this context refers to a nanometer (nm). A nanometer is one-billionth of a meter. Dimensions between approximately 1 and 100 nanometers are known as the "nanoscale". (4)

Over millennia, nature has perfected the art of biology at the nanoscale. Many of the inner workings of cells naturally occur at the nanoscale. For example, hemoglobin, the protein that carries oxygen through the body, is 5.5 nanometers in diameter. A strand of DNA, one of the building blocks of human life, is only about 2 nanometers in diameter.(5) Things like nanotubes are the nanomaterials that are engineered by picking up some members from Carbon family. The single walled nanotube is very popular for its applications in electronics. (6) But, a formulation scientist can make it functionalize to work as advanced drug delivery system for delivery of anticancer drug to the targeted tissue. (7)

DISPARITIES IN DEFINING NANOTECHNOLOGY AND NANOMEDICINE

Nanotechnology

One of the major problems that regulators, policy-makers, researchers, and lawyers continue to face regarding nanotechnology is the

confusion about its definition. (8, 9) Medicines and Healthcare products Regulatory Agency (MHRA) defines nanotechnology as the Production and application of structures, devices, and systems by controlling the shape and size of materials at nanometer scale. Scale ranges from the atomic level at around 0.2 nm up to around 100 nm.(10) The MHRA believes that current EU regulations for medicines and medical devices are sufficiently stringent and broad in scope to cover theoretically risks associated with nanotechnologies. (11) The USA National nanotechnology initiative, (NNI) defines nanotechnology as: "Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometres, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale. (12) The NNI definition excludes numerous devices and materials of micrometer dimensions (and also of dimensions less than 1 nm), a scale that is included within the definition of nanotechnology by many nanoscientists. (13)

Japanese authorities in their Second Science and Technology Basic Plan have defined nanotechnology an interdisciplinary science and technology that encompasses IT technology, the environmental sciences, life sciences, materials science, etc. It is for controlling and handling atoms and molecules in the order of nano (1/1 000 000 000) meter enabling discovery of new functions by taking advantage of its material characteristics unique to nano size, so that it can bring technological innovation in various fields. (14)

One definition, not constrained by size, yet correctly emphasizing that controlled manipulation at the nanoscale results in medical improvements and/or significant medical changes, comes from the European Science Foundation (15): "The science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.

From the perspective of its applications in diverse fields, Nanotechnology cannot be

considered as one technology but encompasses many technical and scientific fields such as medicine, chemistry, physics, engineering, biology, etc.

Nanomedicine

Nanomedicine is an application of nanotechnology in the areas of healthcare and disease diagnosis and treatment and prevention of disease. Nanomedicine has been defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures. (16) Although nanoscales range from 1nm to 100 nms, in practice, nanomaterials beyond this scale often go into Nanomedicine development. For example, drug developed using nanotechnology (Abraxane's albumin-paclitaxel nanoparticles) demonstrates therapeutic efficacy and bioavailability and desired properties at scales greater than 100nm, (17) on the other hand, certain medical devices in Nanomedicines scale below even 1 nm. (18) At present, there are no uniform, internationally accepted definitions of nanotechnology as well as Nanomedicine and it continues to be the major area of controversy.

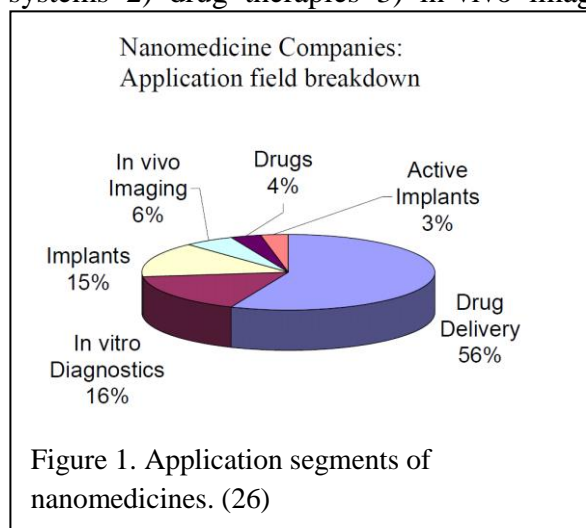
FDA has neither adopted the NNI's definition for its own regulatory purposes nor has it established a formal regulatory definition of nanomaterials, nanoscale, nanotechnology or Nanomedicine. Some experts suggest that the size limitation imposed in NNI's definition should be removed especially for Nanomedicines where the phrase "small technology" may be more appropriate to accurately encompass both nanotechnologies and micro-technologies. (19)

NANOMEDICINE MARKET The market projections for medically oriented Nanotechnologies show that Nanomedicine market was USD 78.54 billion in 2012 and is expected to reach a value of USD 177.60 billion in 2019, growing at a CAGR of 12.3% from 2013 to 2019.(20) Increase in the Compound Annual Growth Rate (CAGR) for Nanomedicines market is due to two reasons: 1) Increased funding by Government and Private Institutions to foster R&D and commercialization of Nanomedicines in the area of neuro, cardiovascular and oncology

applications (21), and 2) Increase in the geriatric population, rise in the chronic diseases/disorders and high unmet medical needs where Nanomedicines is a great hope! (20) There are over 70 Nanomedicine products marketed Worldwide. (22) The growth of nanotechnology is exponential, during the year 2000 to 2008, worldwide growth of nanotechnology patent applications was about 34.5%. USA has filed 19,665 patent applications followed by China 18,438 and Japan with 10,763 patent applications during the year 1991 to 2008. (23-25)

APPLICATIONS OF NANOMEDICINES

Figure 1 represents Nanomedicine application field breakdown. Among the different application fields of Nanomedicines, the drug delivery market is the largest contributing segment. (26) Nanomedicine includes several distinct application areas that fall under 6 medical sectors: 1) advanced drug delivery systems 2) drug therapies 3) in-vivo imaging



4) in-vitro Diagnostics 5) biomaterials and active implants and 6) cosmetics

CURRENT REGULATIONS FOR APPROVAL OF NANOMEDICINES

At present, Nanomedicine products are regulated as medicinal products or as medical devices and there is currently no specific regulatory framework for nanotechnology-based products neither in the EU nor in the USA. Current regulation for Nanomedicines in the USA follows FDA Guidelines effective from 3 June 2010 CDER MAPP 5015.9. (27) In EU, Nanomedicines are considered within existing guidelines on a product-by-product basis. There

is a “reflection” paper on nanotechnology based medicinal products for human use (EMA/CHMP/79769/2006). In Japan, Nanomedicines are regulated within the framework of the Pharmaceutical Affairs law on a product-by-product basis. (27)

New drug delivery systems (NDDS) are always approved in combination with the drug they deliver and they are regulated as drugs because the delivery system interacts with the drug and can change its efficacy and safety profile. Some therapies in which nanoparticles have no direct therapeutic effect are regulated as medical devices. Examples are hyperthermia with iron nanoparticles or cell therapy using nanoparticles for cell sorting. (28) Nanoparticle-based contrast agents that are administered intravenously, on the other hand, are regulated as drugs.

REGULATORY PROBLEMS / ISSUES FOR NANOMEDICINES

Emerging technologies bring with them concerns and uncertainties about how they should be regulated. (29) To facilitate the regulation of nanoproducts, the FDA has formed an internal nanotechnology interest group (NTIG) composed of representatives from all its regulatory centers. The Nanotech Task Force in 2007 issued an FDA task force report, but as of March 2011, no clear guidelines or regulations have been proposed by the task force. (30) So, the FDA currently regulates nanoproducts but not the technology. The conclusion by the FDA has been criticized by many experts because of the questionable assumption on which it is based. (31) In other words, the nanoproducts were approved based on the safety data of their ‘non-nano versions’ (bulk counter parts).

CHALLENGES POSED BY NANOMEDICINES

The two main regulatory problems posed by Nanomedicine are as follows: 1) classification problem, and 2) problem of scientific expertise Substantive steps are needed to prepare for these problems in the context of Nanomedicine.

1) Classification problem: The first significant regulatory dilemma posed by products based on nanotechnology is that of classification. Although the current classification system has been applied to other emerging technologies, the

miniaturization of medical products compounds the problems associated with regulating combination products and blur the distinction between the different categories of products to a greater degree than ever before. Till the advent of advancing medical technologies, FDA classified medical products for regulatory purposes as drugs, devices, and biologics. Advancing medical technologies combine drugs, devices and biologics often; hence the fourth category for combination products was created in 1990. (31) In 1991, agreements were formed between CDER and CBER, CDRH and CDER (32) and CDRH and CBER (33) establishing guidelines for determining which center has primary jurisdiction over a combination product. In 1999, a Device Action Plan was launched to make CBER's review of combination products more consistent with how they would be reviewed by CDRH. (34) If a product combines a drug and biologic, a drug and device, or a biologic and device, it is a combination product. (35) The product's primary mode of action determines which center has primary jurisdiction over the product. A manufacturer can submit a request to have the product characterized as a drug, biologic, device, or combination product and the intent of the manufacturer is often evaluated as evidence of how the product should be classified. (36, 37)

The request for the product class comes from the Manufacturer. (38) The manufacturer may prefer to target a particular center for its tendency to evaluate certain types of evidence or the fact that it does not charge user fees! The real challenge faced in classification of nanotechnology based products lies in their difficulty in characterizing the primary mode of action. This is due to the fact that the miniaturization of medical products would lead to an increase in the combination products. (37) For example, when dendrimers or nanoshells are the drug delivery devices, they are activated by IR light. (39) So it's unclear how these novel drug delivery systems should be regulated.

2) Lack of scientific expertise. It is undoubtedly true that scientific expertise is critical to effective Regulation. The regulatory authorities have recognized the importance of strong science base since 2001 and it is reflected in performance plan. (40) However, taking an

example of nanorobots, they can enter into our systemic circulation and deliver the drug just in right dose and at the right place. A big question is whether the decision makers are scientifically able to judge the advanced technology and safety of such products for marketing especially when the tissue toxicity with Nanomedicines is not well understood. (41) A dedicated nanotoxicological evaluation system is still lacking. (27)

Toxicity of the engineered nanoparticles: Engineered Nanoparticles could themselves induce toxicity if they are sensed as antigenic challenge by our immune system. (42) This cannot be overlooked as it would create a worse situation for the patients. The most significant parameters of the engineered nanoparticles with respect to nanotoxicity are size, shape, specific surface area, agglomeration/aggregation state, size distribution, surface morphology, crystallinity, solubility, molecular structure, composition of nanoparticles, phase identity, surface chemistry including composition, charge, tension, reactive sites, physical structure, photo-catalytic properties and zeta potential. (43) The need for separate toxicological assays of nanoproducts is because nanoparticles not only possess unique size specifications, but the novel properties they show are different from their bulk counterparts. There are Nanomedicines that involve subcutaneous or intravenous injectible Nanoparticulate systems. (44) These carry and deliver the drug directly into human body bypassing the normal absorption processes. These Nanoparticulate carriers may be responsible for the toxicity as they would interact with the biological macromolecules and result in toxicity. Alternately, insoluble NPs can accumulate inside tissues or organs and lead to toxicity. The risks of toxicity associated with exposure to nanoparticles are as shown in figure 2.

OUR PROPOSAL:

Having seen the gravity of the problems in regulation and toxicity issues related to Nanomedicines, the authors wish to propose certain measures towards managing these better if not completely.

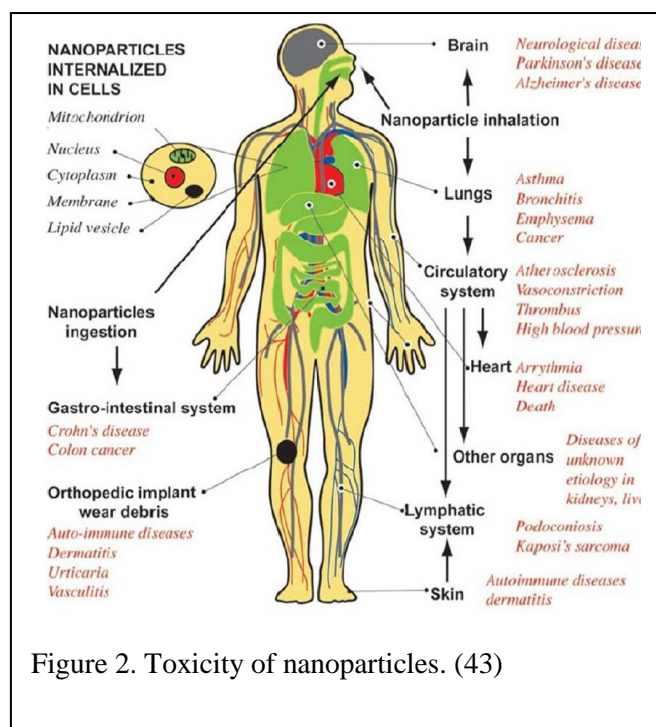


Figure 2. Toxicity of nanoparticles. (43)

The proposal has 8 steps: 1) Identify Unique safety issues, 2) Correlate physicochemical properties of nanoparticles with in-vivo behaviour and therapeutic outcome, 3) Improve the understanding of transport process of these nanoproducts in cell membranes 4) Determine the complete Pharmacokinetic Profile of the product 5) Develop standards to correlate biodistribution with safety and efficacy 6) Create a robust Databank of interactions between nanomaterials and biological systems 7) Standardization of nanomaterials, protocols, refining of definitions and classification, explore International Harmonizing efforts and treaties and 8) Specify regulatory submissions.

Step 1: Identify safety issues unique to Nanomedicines

Safety issues unique to Nanomedicines have to be identified by carrying out *In vitro* toxicity studies, *In vivo* toxicity studies and QNAR Modeling. *In-vitro* toxicity studies for Nanomedicines offer rapid and effective end points to assess the toxicity of the engineered Nanomedicines. These studies offer the following advantages:

- Mechanism-driven evaluations,
- Dose-response relationships,
- Suitable for high throughput screening,
- System for studying the structure activity relationships,

- Identify the mechanisms of toxicity in the absence of physiological and compensatory factors that confound the interpretation of whole animal studies,
- Efficient and cost-effective,
- Assist in designing in-vivo animal studies.

Toxicity	OECD guideline with test number
Skin Sensitisation	Local lymph node assay (429)
	Acute dermal toxicity (402)
	Acute dermal irritation/corrosion (404)
Dermal Toxicity	Subchronic dermal toxicity: 90-day study (411)
	Acute eye irritation/corrosion (405)
Ocular toxicity	Acute inhalation toxicity (403)
	Subchronic inhalation toxicity: 90-day study (413)
Inhalation Toxicity	Acute oral toxicity: Up-and-Down procedure (425)
	Repeated dose 90-day oral toxicity study in rodents (408)
	Repeated dose 90-day oral toxicity study in non-rodents (409)
Oral toxicity	Neurotoxicity study in rodents (424)
	Developmental neurotoxicity study (426)
	Carcinogenicity study (451)
Cytotoxicity	Reproduction/developmental toxicity screening test (421)
	Two-generation reproduction toxicity (416)
Developmental Toxicity	Reproduction toxicity (416)
	Genotoxicity

Figure 3. OECD guidelines for toxicity testing. (43)

***In-vivo* toxicity studies** for establishing safety of the engineered nanoparticles use the constitution of organism outside the organism. The influence of various factors may not be available in *in-vitro* experimental environment. Hence, it is essential to confirm the result using appropriate animal model. The organisation for economic co-operation and development (OECD) guideline for the testing of chemicals has been implemented for many toxicological endpoints.

The guidelines given by OECD as shown in fig. 3 should be applied for nanoengineered materials in their nano versions and not in their bulk counterparts.

Quantitative Nanostructure - Activity Relationship (QNAR) Modeling:

Presently, the FDA has not established or applied comparable PbPK or QSAR models to nanomaterials. (45) Experimental toxicological

studies are lengthy, costly, and often not feasible. In such cases, *In silico* structure activity relationship assays should be developed for nanostructured materials/ nanoproducts. This would be economically feasible, yet with a high predictive power in the early stages of drug discovery and development.

Step 2: Correlate physicochemical properties with *In vivo* biological behaviour and therapeutic outcome.

Physico-chemical properties of nanoparticles such as size, surface charge, stability, density, crystallinity, surface characteristics, and solubility can impact on biodistribution. Since the nanoscaled products show distinct and unique physicochemical properties, they must be evaluated to establish correlation with the biological behavior, or pharmacokinetic profile (ADMET) profile and mechanism of action to finally the therapeutic outcome.

Step 3: Improve understanding of mass transport across membranes and body compartments.

Membrane permeability assays using cell culture techniques have been used for pharmacokinetic studies, they should also be used for nanomedicinal products. There is a need to search for suitable model systems fit for the permeation assays while testing nanomaterial based products.

Step 4: Determine complete pharmacokinetic profile of the product.

Information about accurate bio-distribution profiles following systemic administration via any route is valuable to determine bioavailability, dose and dosing regimen of the product.

Step 5: Develop standards to correlate bio-distribution with safety and efficacy

This should be done by using parameters like size, surface charge, stability, surface characteristics, solubility, crystallinity, density, etc.

Step 6: Create a robust databank relating the interactions between nanomaterials and biological systems

Adapt existing methodologies and develop new paradigms for evaluating safety and efficacy data of Nanomedicines.

- Develop the guidance that provides specifics as to what kind of data is needed.
- Share the data in an internationally harmonized environment.

Data evaluation, Data sharing in international harmonized environment should be done taking into consideration additional dimension in addition to classical immunological, metabolic and pharmacological functions. What we mean by this is the novel properties intrinsic to nanomaterial and products thereof should be studied and standardized using validated analytical methods and, both qualitative and quantitative data should be generated.

Step 7: Standardization of nanomaterials, protocols, refining of definitions and classification, explore International Harmonizing efforts and treaties.

- Create reference classes for nanomaterials that are synthesized and characterized.
- Develop consensus testing protocols to provide benchmarks for the creation of classes of Nanomedicines.
- Create uniform standards for and/or working definitions of nanomaterials.
- Refine the current definitions of nanomaterial, nanotechnology, nanoscale and Nanomedicine.
- Explore international harmonization efforts and formal treaties.
- Involve standard - setting organizations such as the International Organization for Standardization (ISO) and ASTM International.
- Consult and collaborate with other federal agencies in a more effective manner.

Step 8: Classification and Regulatory submissions

Re-evaluation of the current FDA classification scheme developing a system of classification based on function and/or risk of potential harm is required. Nanoverions of therapeutics should be subjected to completely new drug application process (NDA) and not merely the current Abbreviated New Drug Application (ANDA) process. (19) The screening and evaluation of

novel nanomedicinal products should incorporate dedicated screens for nanomaterial used in the product development.

CONCLUSION

Although the FDA's current approach of classification and approval of nanotechnology based products lacks specificity, the FDA cannot develop more specific guidelines until it collects more data, establishes valid testing criteria, and answers important questions regarding the regulation of these products. (45-47) The FDA needs to acquire a greater understanding of the toxicity and other properties of nanomaterials before it can establish new guidelines for nanoproducts. More data are also needed to help the FDA determine what, if any, additional testing should be required during agency evaluation of products containing nanomaterials. For example, the size boundary at which data regarding larger particles of a particular material become irrelevant to NPs is currently unknown. In addition, only limited data are available regarding the metabolism and toxicity of NPs, including excretion, translocation, carcinogenicity, and immunological or genotoxic effects. Such findings are relevant to evaluating toxicity, biocompatibility, and the potential distribution of NPs in the body. Long-term toxicity data for many nanomaterials are also currently unavailable. The biopersistence of inorganic NPs, which can build up in the body, must also be studied extensively in animals before they can be approved for use in human applications. As Nanomedicines are evolving rapidly on the pharmaceutical landscape, it is also important to continuously distribute new information and provide ongoing training in order to conduct an FDA review process that is timely, informed, and based on the most current science. Regulation of Nanomedicines requires a proper balance between "underregulation," which could cause inappropriate and possibly harmful product approvals, and overregulation, which could limit innovation. (45)

In a nutshell, to dive successfully in the tide of innovation; regulation of Nanomedicines should be based on the strong evidence based scientific knowledge of the nanomaterial gained by harmonized efforts with advanced validated methods of evaluation where scientists of varied

disciplines as well as regulatory agencies join hands to support the development of product that fits for the challenging unmet medical needs and yet regulated with scientific confidence to ensure safe, efficacious product reaching the market place and protection of public health.

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CONFLICT OF INTEREST

No conflict of interest declared.

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