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Research

Nanomedicine

De-Coding Nano-Regulation in India and Considerations for the Future

July 2022

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1. Introduction

I. What is Nanomedicine?

Nanotechnology is a branch of science which has marvelled the world for many decades. It is often regarded as a perplexing field as it has emerged across multiple disciplines simultaneously therefore making it rather difficult to define. To put it simply, "nanotechnology" or "nanoscience" is a broad area of science which involves the study, manipulation and application of a particle. The conception of nanotechnology is credited to Richard Feyman, an American physicist. His 1959 lecture titled "There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics"[1] described the process of manipulation and control of atoms and molecules, thus, setting the wheels of nanotechnology in motion.

Nanotechnology in recent years has come to be applied to numerous fields. At the heart of innovation in nanotechnology lies "nanomedicine". Nanomedicine is the application of nanotechnology for medical purposes.[2] Robert A. Freitas, Jr., who authored the first technical book series on medical nanorobotics, has captured the essence of nanomedicine through the following definition:

> *"the science and technology of diagnosing, treating, and preventing disease and traumatic injury, relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body and as the employment of molecular machine systems to address medical problems, at the molecular scale."*[3]

Nanomedicine is not a single class of medical interventions,[4] but refers collectively to a wide range of applications, research and ideas in medicine and healthcare. However, it may be understood as the use of nanomaterials for the diagnosis, control, monitoring and treatment of diseases. As with nanotechnology, this definition lacks consensus and is continuously evolving as it possesses novel characteristics and properties which are transitional between molecular and bulk regimes.[5]

They are often regarded as a disruptive field in medicine and healthcare, revolutionizing multiple existing medical interventions and techniques. Over the years, there have been several successful and unsuccessful applications of nanomedicine. These have highlighted the gaps in innovation and regulation of this technology.[6]

1. Richard P Fynnman, There is Plenty Of Room At The Bottom, available at: https://media.wiley.com/product_data/excerpt/53/07803108/0780310853.pdf (Last accessed on July 4, 2022).
2. Michael Berger, Ethical Aspects of Nanotechnology in Medicine, NANOWERK.COM, January 8, 2008,
3. Robert A. Nanomedicine, VOL. 1: Basic Capabilities (1999), available at: http://www.nanomedicine.com/NMI.html. (Last accessed on July 4, 2022).
4. Michael Berger, Ethical Aspects of Nanotechnology in Medicine, NANOWERK.COM, Jan. 8, 2008, http://www.nanowerk.com/spotlight/spotid=3938.php#ixzz2W75VqPAp (Last accessed on July 4, 2022).
5. Tinkle, S., McNeil, S. E., Mühlebach, S., Bawa, R., Borchard, G., Barenholz, Y. C., Nanomedicines: addressing the scientific and regulatory gap. Ann. N. Y. Acad. (2014), available at: https://nyaspubs.onlinelibrary.wiley.com/doi/10.1111/nyas.12403 (Last accessed on July 4, 2022).
6. Medicines Agency, Committee for Medicinal Products for Human Use, Reflection Paper on Nanotechnology-Based Medicinal Products for Human Use EMEA/CHMP/79679 p.2 (2006), available at: http://wwwema.europa.eu./docslenGB/documentlibrary/Regulatoryproceduralguideline/2010/01/WC500069728.pdf (Last accessed on July 4, 2022).

II. What is the purpose of this paper and how is it relevant?

The role of nanomedicine in healthcare is ever-increasing with its applications being tested in detection, monitoring and treatment of disease conditions in human beings. The reason for the rise in nanotechnology applications in medicine is the prospect of improving effectiveness by the biological targeting of drugs in current clinical use. In the absence of in-depth research on the application of nanotechnology to healthcare and the regulation of nanotechnology in India, we have attempted to address topics pertaining to the technologies embedded within the concept of nanomedicine, categorisation of nanomaterial into drugs and medical devices, applications of nanomedicine, etc. In the absence of a definition for the term nanomedicine in existing statutes in India, it becomes important to understand the potential regulation and compliances that would be required in the application of nano technology to the field of healthcare and pharmaceuticals in the country.

In this paper, we have analysed numerous international legislations governing or seeking to govern nanomedicine to understand the possible approach that may be adopted in regulating nanomedicine in India based on their proposed use.

III. Nanomedicine and Allied Terminologies

The following terminologies are key to understanding the concepts of nanomedicine:

a. **Nanotechnology:** It is the branch of science involving the manipulation of size of atoms and molecules to a nanoscale to enable its use across several different applications.

b. **Nanomedicine:** A subset of the field of nanotechnology. It is the application of nanotechnology across healthcare, pharmaceuticals and medical technologies.

c. **Nanoparticle or nanomaterial:** It is a nano scaled particle which ranges between 1 to 100 nanometer in size. In comparison to their larger counterparts, their size allows them to inhibit different physical and chemical properties.

d. **Nanopharmaceutical:** Nanopharmaceuticals are therapeutic products containing nanoparticles. They may either be a drug which is combination of a nanoparticle with an active pharmaceutical ingredient or a nanosized drug itself.

e. **Nanocarrier:** A nanocarrier is a form of nanopharmaceutical. These are drug delivery agents made of nanomaterial which is used to transport a drug to a target area in the body.

f. **Nanodevices:** The incorporation of nanotechnologies and nanomaterials in medical devices such as instruments, appliances and implants.

g. **Nanopharmaceutical biologics:** Nanopharmaceuticals which contain biologic components.

h. **Nano-regulation:** Legal and regulatory framework for nanotechnology.

2. Applications of Nanomedicine

Applications of nanotechnologies in medicine are promising and constantly evolving and areas such as disease diagnosis, detection, targeted drug delivery, molecular imaging, and the use of nanomaterials in medical devices are being investigated. Additionally, nanomaterials are also being used in a unique manner as biomarkers to identify and create a "contrast" at the site of interest in the human body, to aid procedures such as imaging as well as identification of components in samples extracted from the human body.[7]

The potential for nanomedicine is immense, because nanotechnology is a divergent innovation in science which is based upon the premise of nano-scaling particles. Hence, any form of application in the medical field which involves the use of nanoparticles will invariably be a nanomedicine application.

While the application of nanotechnology to the field of healthcare is ever evolving with new applications being tested for their effectiveness and efficiency. Some applications of nanotechnology in healthcare are discussed in brief below.

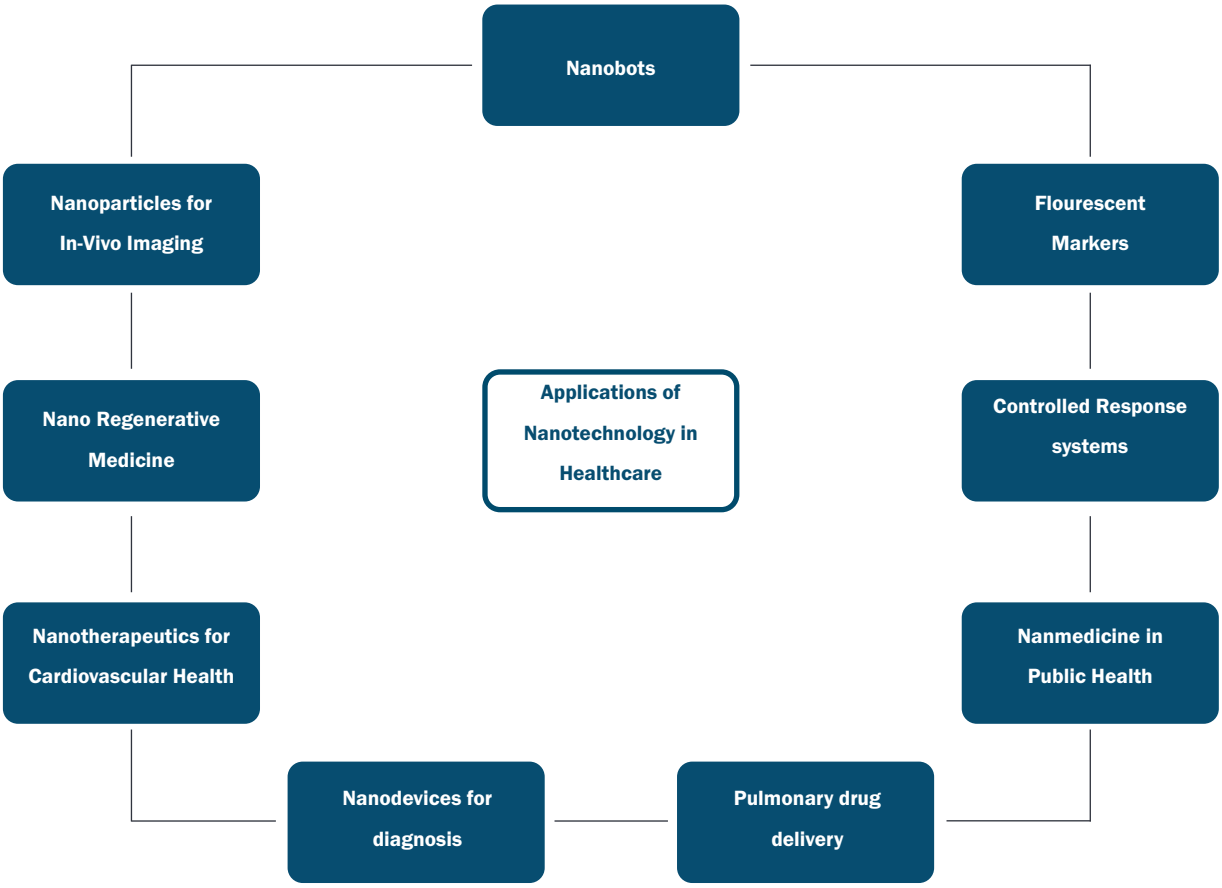

Figure 1: Nanotechnology in Healthcare

7. Chow E., Cancer Nanomedicine: From Drug Delivery to Imaging. Sci. Transl. Med. 2013, 5, available at: https://www.science.org/doi/abs/10.1126/scitranslmed.3005872 (Last accessed on July 4, 2022).

2.Applications of Nanomedicine

I. Nanobots

One of the most important applications of nanotechnology to medicine is the engineering marvel of nanobots. Nanobots as the term suggests serve as miniature surgical assistants which can be used for repairing damaged cells or even replace the intracellular structures within the human body. They are being developed to become capable of replicating themselves for correcting a genetic deficiency or replacing certain molecules for disease eradication in the human body.

II. Nanoparticles for In-Vivo Imaging

Given the nature of nanoparticles and the ease of mobility within the human body, nanoparticles are becoming pivotal in generating high-resolution, high-contrast images needed for accurate imaging and precision diagnostics. Nanomaterials are playing major roles in imaging by delivering highly reliable imaging results, allowing improved sensitivity to target areas by a modularity of design and flexibility in application. Nanomaterials enable physicians to differentiate between healthy and diseased cells by attaching to the targeted diseased cells in the human body and acting as contrast agents for imaging purposes.

III. Fluorescent Markers

Nanoparticles enable their use as fluorescent markers for imaging, diagnosis and screening purposes in the human body even for remote tissues and organs. Nanotechnologies offer the possibility of intracellular imaging through attachment of quantum dots to selected molecules encouraging their application in diagnosis and analysing extracted samples from the human body for detecting alterations at the molecular level as well as the biological markers which may be present. These nanoparticles are termed as nanotools as they assist in the process of detection and prevention. This enables greater potential for improving diagnostic precision and such nanoparticles may be developed to undertake numerous functions individually such as diagnosis and drug delivery which assists in the process of treatment and may even be retained at the targeted site for monitoring progress.

IV. Nanotherapeutics for Cardiovascular Health

The human cardiovascular system is fairly complex for in-depth imaging and diagnosis in addition to the difficulty in targeted drug delivery in the system. Strategies are being discussed to utilize the unique properties of nanoparticles to enable targeted drug delivery for increasing nanotherapeutic effectiveness in cardiovascular and other inflammatory diseases. However, achieving sufficient and heterogeneous delivery remains to be a critical issue in utilization of nanoparticles for treatment of cardiovascular diseases.

V. Nano Regenerative Medicine

Stem cell technology is a rapidly developing field of life sciences wherein stem cells from the human body are utilized as progenitors capable of self-renewal and differentiation enabling in-vitro manipulation and cell replacement in the body for treatment of diseases.[8] Combining nanotechnology with stem cell technology has led to the creation of a new field of medicine known as regenerative medicine. For example, nano diamond polymer

8. Paulo F., Angus T., Stem Cell Technology, BMJ,1999 Nov 13; 319(7220):1308, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1129084/ (Last accessed on July 4, 2022).

composites can be used in tissue engineering and regenerative medicine which enables restoring of damaged tissue. Similarly, certain bioengineered nanoparticles are being tested for bone regeneration.

VI. Nanoparticles in Cancer therapy

Nanoparticles are being designed to treat various kinds of diseases, an important breakthrough in their application remains to be the focus on detection and treatment of cancer. The drug delivery process in cancer treatment consists of five steps, known as 'CAPIR' wherein circulation of the nanoparticle in blood takes place followed by accumulation and penetration into the cancer tumor. This is followed by internalization into the cell and drug release through the use of nanoparticles.[9] The nanometals enhance drug dissolution and adhesion to targeted tumor surfaces, resulting in rapid onset of effective therapeutic action.[10] Drug-loaded delivery vehicles or nanoparticles are attractive because they can be passively or actively targeted to cancer tissues to improve anticancer drug delivery and thereby reduce severe side effects.

Another approach being explored is the application of nanoparticles by combining various drugs into one carrier in order to address the concern of poor drug delivery achieved by the use of present-day medicine and the need for enhancement. This would also enable multiple tumor targeting for better diagnosis and treatment of cancer.

VII. Nanodevices for Diagnosis

The nanomaterial offers enormous scope to be developed as an advanced diagnostic tool. A nanoscale device or nanomaterials could affect direct interaction with the biological system at the subcellular and molecular level and thus can be developed as a more sensitive and accurate molecular probe and biosensor which enables diagnosis. For example, some companies are attempting to develop microchips that use electrodes to identify the dielectric properties of cancerous cells, viruses, and bacteria in body fluids.

VIII. Pulmonary drug delivery

The treatment of respiratory infections is challenging because the infections may possess multidrug-resistance, and the microbes may reside deep inside the airways. Delivery of drugs to such deeper parts of the airway system remains to be a major milestone to be accomplished in the future for nanomedicine by the use of such characteristic nanoparticles and their ability to cross biological barriers in the human body with ease.

IX. Controlled Response systems

Nanoparticles may be engineered to enables sustained release systems within the body which may be able to address the concerns pertaining to toxicity and drug release raised by numerous researchers in the use of nanoparticles in drug delivery in human body.[11] The nanoparticles are developed in a way to allow release of the drug upon receiving certain stimuli and as a response this approach is currently being researched further for application in medicine.

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9. Diverse Applications of Nanomedicine, ACS Nano, 2017 Mar 28; 11(3): 2313–2381, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371978/ (Last accessed on July 4, 2022).
10. Ahmed Alalaiwe, Bioconjugated nanometals and cancer therapy: a pharmaceutical perspective, Available at: https://www.futuremedicine.com/doi/10.2217/nnm-2021-0010 (Last accessed on July 4 , 2022).
11. Singh R.; Lillard J., Nanoparticle-Based Targeted Drug Delivery, Exp. Mol. Pathol. (2009) 215–223, available at: https://pubmed.ncbi.nlm.nih.gov/19186176/ (Last accessed on July 4 , 2022).

X. Nanomedicine in Public Health

Given the advancements being made in the field of nanomedicine it has enormous potential to improve various facets of public health such as promoting general health, improving quality of life, increasing lifespan, preventing and treating disease conditions and curing life-threatening disorders. It can also assist in addressing community-based or social health issues including vaccination, infection control, civic sanitization, environmental infection control, early detection and prevention of infectious diseases.

3. Categorizing Nanomedicine in India

There is no universally accepted legal definition of nanomedicine. As discussed, any application of nanoscale products in the medical field will be termed as "nanomedicine." This understanding of nanomedicine can encompass a limitless range of applications. Hence, for the ease of understanding, a nanomedicine may be classified into these categories:

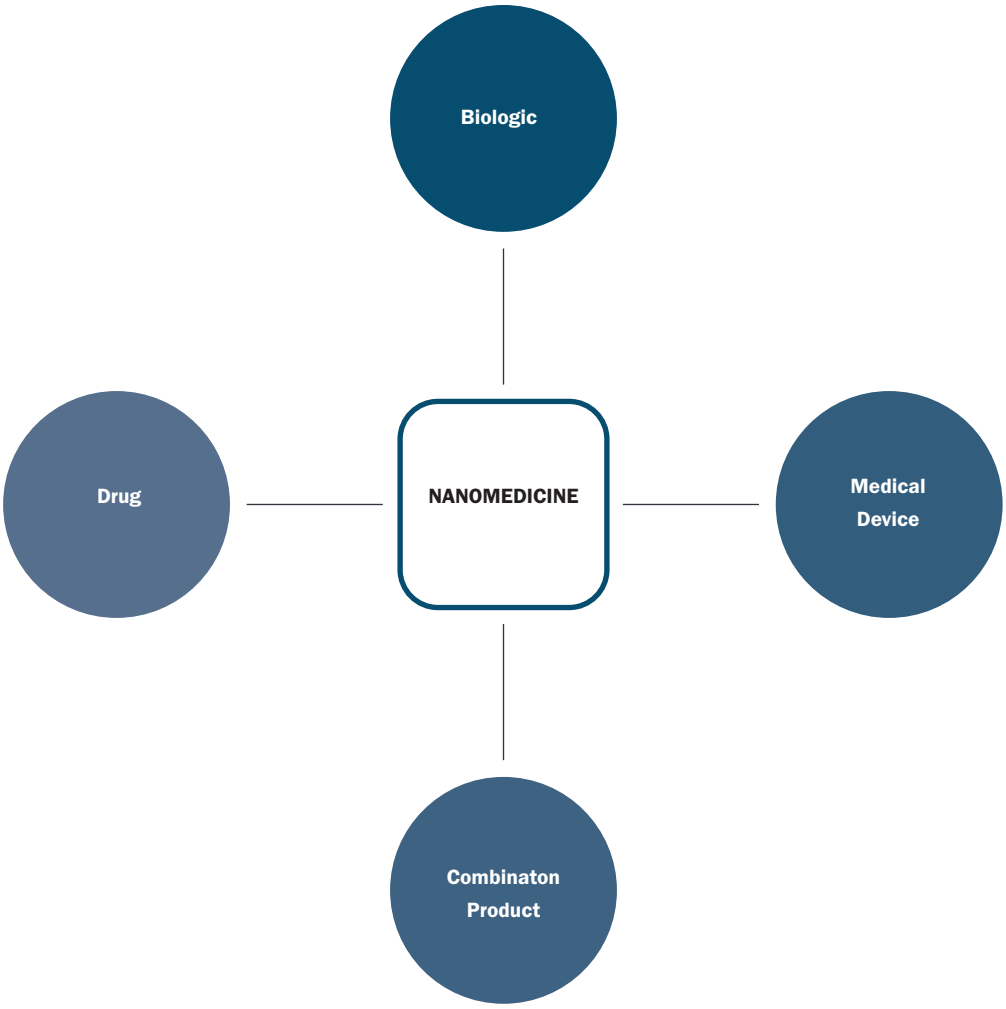


Figure 2: Classification of Nanomedicine

a. **Drug:** Drug delivery mechanisms, use of nanoparticle raw materials in medicines, etc.

b. **Medical Device:** Nanobots, scanners, health monitors, in-vivo imaging, implants, etc.

c. **Biologic:** Incorporation of nanomaterials into biologic pharmaceutical drug products such as vaccines, therapeutic serums, anti-toxins, etc.

d. **Combination Product:** A nanomedicine application which may perform more than one of the above functions. For instance, smart pills which involve sensing, imaging and drug delivery are said to be a hybrid of medical device and a drug.

In the absence of a specific law defining or governing nanomedicine, based upon the therapeutic effect, all nanomedicines will fall under the definition of a "drug." In India, the definition of drug under the Drugs and Cosmetics Act, 1940 (**"DCA"**) is of wider import and includes pharmaceutical drugs, biologics and medical devices:

3. Categorizing Nanomedicine in India

i. all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;

ii. such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of vermin or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;

iii. all substances intended for use as components of a drug including empty gelatin capsules; and

iv. such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board.[12]

Further, a "medical device" is defined under the Medical Device Rules, 2017 (**"MDR"**) to include all devices including an instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including a software or an accessory, intended by its manufacturer to be used specially for human beings or animals which does not achieve the primary intended action in or on human body or animals by any pharmacological or immunological or metabolic means, but which may assist in its intended function by such means for one or more of the specific purposes of:

i. diagnosis, prevention, monitoring, treatment or alleviation of any disease or disorder;

ii. diagnosis, monitoring, treatment, alleviation or assistance for, any injury or disability;

iii. investigation, replacement or modification or support of the anatomy or of a physiological process;

iv. supporting or sustaining life;

v. disinfection of medical devices; and

vi. control of conception.[13]

Devices which have not been specifically notified under the MDR are not regulated as a medical device, instead they will be regulated as a drug under DCA and Drugs and Cosmetics Rules, 1945 (**"DCR"**). Although, both pharmaceuticals and medical devices are regulated as drugs, the MDR provides specific provisions for the regulation of notified medical devices which apply in addition to the general law under DCA. By virtue of being a specific law, the MDR overrides the DCA in instances of overlap of the provisions. Additionally, the Clinical Trial Rules, 2019 (**"CT Rules"**) widens this distinction by providing certain exemptions in the conduction of clinical trials for medical devices.

This difference in the regulatory approach towards drugs and medical devices leads to the consideration as to which of these two categories do nanomedicines fall under. Owing to the absence of a specific law governing nanomedicines, a nanomedicine application will be compartmentalized into the existing categories based on its functionality on a case to case basis.

12. Section 3(b), Drugs and Cosmetics Act, 1940.

13. Rule 3(zb), Medical Device Rules, 2017.

3. Categorizing Nanomedicine in India

Currently, majority of commercial applications of nanomedicine is geared towards drug delivery and targeting of diseases in the human body.[14] Given the nature of application of nanomedicine these would traditionally fall within the ambit of the definition of a drug under DCA. Further, the Guidelines for Evaluation of Nanopharmaceuticals in India, 2019 (**"Nanopharmaceuticals Guidelines"**) defines nanopharmaceuticals to mean a pharmaceutical preparation containing nanomaterials intended for internal use or external application on human body for the purpose of therapeutics, diagnostics and health benefits.[15]

Similarly, a direct approach is adopted in categorizing nanodevices. All nanotechnology applications which are akin to devices or implants and assist with functions such as diagnosis, mitigation and treatment will be a medical device for the purposes of application of MDR.

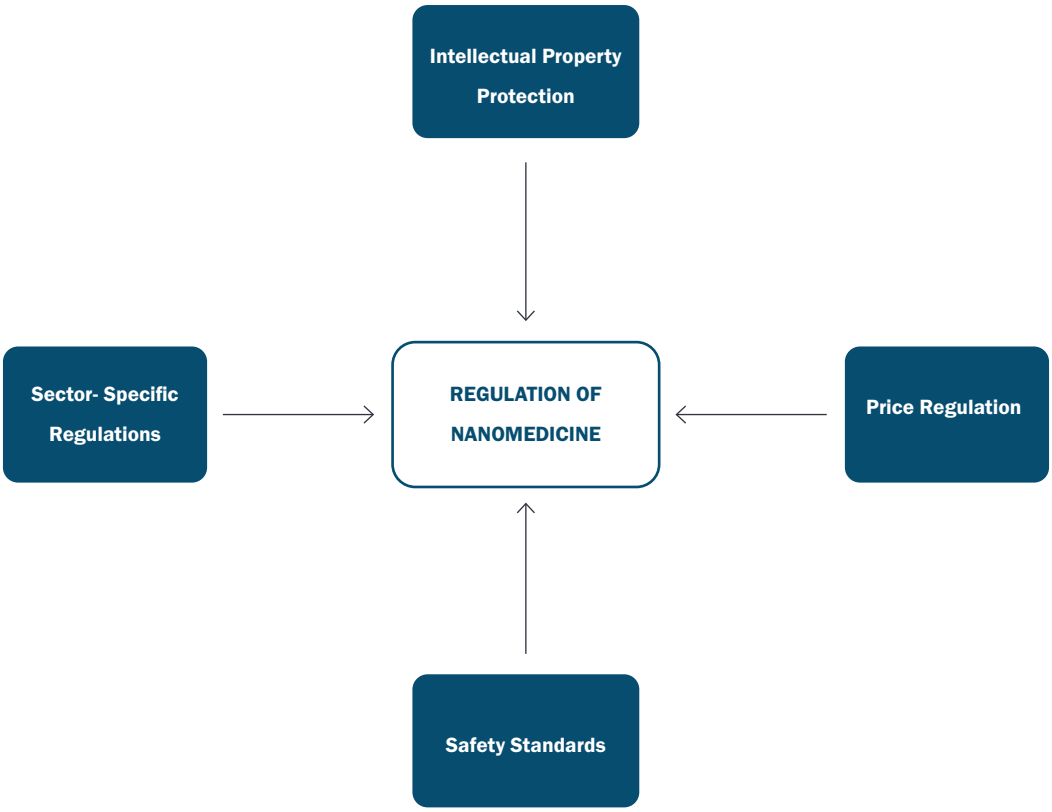
However, due consideration must be given in assigning a legal character to combination nanomedicine products. As per the definition prescribed under MDR, a device, instrument or apparatus which "assists" in functions as opposed to having a direct pharmacological, immunological or metabolic effect will be a medical device. This creates an uncertainty as to whether a combination product such as a smart pill, which performs functions similar to a medical device in assisting with diagnosis and recognition of a target area and may subsequently also act as a drug with pharmacological efficacy will fall under this definition of a medical device in MDR. In such instances, the classification will be based upon an assessment of the likeness of the product in terms of its functions to a drug or a device.

14. Eur. Medicines Agency, Committee for Medicinal Products for Human Use, Reflection Paper on Nanotechnology-Based Medicinal Products for Human Use EMEA/CHMP/79679 p. 2 (2006), available at: https://etp-nanomedicine.eu/wp-content/uploads/2018/10/reflection-paper-nanotechnology-based-medicinal-products-human-use_en-1.pdf. (Last accessed on July 4 , 2022).

15. Guideline 4.1, Guidelines for Evaluation of Nanopharmaceuticals in India, 2019.

4. Current Regulatory Framework for Nanomedicine

Under the present laws, a nanomedicine application may be regulated as a drug, medical device or a biologic. The primary legislation governing all forms of nanomedicine is the DCA, however, depending upon which of these categories the application falls into, additional legal nuances will have to be considered. In the absence of a definition for nanomedicine and the absence of specific regulations for the same, nanomedicine is categorized for regulation on the basis of its application.



I. Regulation of Nanomedicine as a "Drug"

The primary statute which regulates drugs in India is the DCA and DCR. DCA and DCR regulate the manufacture, import, distribution and sale of drugs although it does not explicitly define and regulate nanomedicine. The Central Drugs Standard Control Organization (**"CDSCO"**), headed by the Drug Controller General of India (**"DCGI"**) is responsible for implementation of DCA and DCR. The CDSCO also formulates policies, handles product approvals and standards and issues licenses under the DCA. Additionally, there are also State Drug Licensing Authorities (**"SLA"**) under the CDSCO which aid in carrying out these functions within individual states.

For manufacturing a nanopharmaceutical product, both the manufacturing premises and the drug have to be licensed. Manufacturing includes any process (or part) for making, altering, ornamenting, finishing, packing, labelling, breaking up or otherwise treating or adopting any drug with a view to its sale or distribution. However, it does not include dispensing or packing at the retail sale level. Therefore, for the retail of a nanopharmaceutical i.e. making it available to an end consumer an additional license will have to be obtained.

In case of import of nanopharmaceutical, an import license must be obtained similar to the requirements placed on the import of a drug in the country. Additionally, the foreign manufacturing facility as well as the drug itself must be registered with the DCGI. It is also a requirement for the importer to be based out of India and to have either a license to manufacture any type of drug or a license to sell drugs by wholesale in India.

It is also important to note that the DCR categorises certain drugs into schedules based on various considerations and additional conditions provided under the relevant licenses which may be obtained for the drugs listed under specific schedules. These scheduled drugs are required to comply with additional norms such as labelling requirements, restrictions on sale, etc. which is specific to the schedule it has been listed under, to be in compliance with the conditions of the license obtained. Further, DCA provides that a bioequivalence study for Schedule C, Schedule C (1) and Schedule X drugs is mandatory to obtain a manufacturing license.

Although a nanopharmaceutical is not directly listed in any of the DCR schedules, as a drug nor is it listed as a combination product, there are two instances when it may be a scheduled drug. First, in the case of multi-component nanopharmaceuticals where the nanomaterial is one of the components along with a scheduled drug which has the primary therapeutic effect. Secondly, in the case of nanocarriers and nanoparticles of drugs listed in the schedules.

Further, all drugs to be sold in India must also comply with requirements such as packaging and labelling. In the case of imports, the drug package must be re-labelled to contain India-specific declarations in accordance with DCR prior to distribution for consumption.

II. Regulation of Nanomedicine as a "Medical Device"

The MDR notified under the DCA governs medical devices in India in pursuance of which the CDSCO and SLAs are made responsible for the enforcement of MDR. The definition of medical device, as discussed, is not a catch-all definition, instead only medical devices notified by the government shall be governed under MDR. Therefore, non-notified nanotechnology medical devices will be governed as drugs as per the procedures discussed in the previous section. While notified nanotechnology-based medical devices will be governed under the MDR.

A recent development in the regulation of medical devices requires all medical devices to be registered upon obtaining and ensuring the required compliances. The registration requirement is a part of the process to regulate all medical devices in a phase wise manner.[16]

All notified medical devices are categorized into four classes in ascending order of risk:

i. Class A - low risk;

ii. Class B - low moderate risk;

iii. Class C - moderate high risk;

iv. Class D - high risk.

Presently, the risk classification for medical devices is based on the intended use of the device and the risk associated as per the parameters provided under the First Schedule of the MDR as opposed to the materials used in the production. Hence, the mere incorporation of nanotechnology into medical devices would not lead to them being classified as high-risk devices under the present law.

16. Accessible at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NzczMA== (Last accessed on July 4, 2022).

4.Current Regulatory Framework for Nanomedicine

The risk classification of a medical device determines the regulatory requirements for obtaining approvals and licenses in respect of the device, with manufacturers and importers of Class C and D devices having to comply with more rigorous documentation and inspection requirements than those of Class A and B devices.

Further, a license is required for the manufacture and import of a notified medical device. A separate license is required for each manufacturing facility as well. For import, an authorized agent of the foreign manufacturer in India must also hold a wholesale license for sale or distribution of the notified nanotechnology medical device in India. In case, the device falls under the definition of an investigational medical device or new in-vitro diagnostic medical device under the MDR, the interested manufacturer/importer will have to obtain a special permission to market the device in India from the Central Licensing Authority.

A detailed analysis of the MDR and the regulatory framework regarding medical devices can be accessed in our research paper on medical device regulation here

III. Regulation of Nanomedicine as a "Biologic"

Biologics are preparations derived from living organisms for medicinal use. These include vaccines, serums, antitoxins, etc. They are listed in Schedule C of DCA. Similar biologics i.e. genetically engineered biologics are regulated under Guidelines for Similar Biologics, 2016 **("Biosimilar Guidelines")** and Rules for the manufacture, use, import, export and storage of hazardous microorganisms/ genetically engineered organisms or cells, 1989 **("Genetically Engineered Microorganisms Rules")** notified under the Environment Protection Act, 1986 **("EPA").**

Since biologics are regulated as drugs, the procedure for import and manufacture of drugs detailed previously is applicable. Part X of DCR provides for additional compliances such as packaging and labelling of biologics. Additionally, a license must be issued by Genetic Engineering Approval Committee under the Genetically Engineered Microorganisms Rules for all biologic products. These Rules are applicable to manufacturing, import, sales and export of biologics in addition to the DCA and DCR. Primarily governs aspects of safety and handling procedures of biologics.

IV. Regulation of Nanomedicine as a "Combination Product"

A combination product is a combination of two or more types of applications – as a drug, device and biologic. As discussed above, nanomedicine products are difficult to bucket into a single category of application given its diverse characteristics. Therefore, licensing and regulating nanomedicine products as a 'combination product' will enable the regulators to give due attention to the unique features of the product and regulate them accordingly.

In India, at present, the CDSCO does not specifically regulate combination products as a separate category. However, there are multiple combination products which are currently marketed in India, such as In-Vitro Diagnostic Devices **("IVD(s)")**. Typically, depending upon the likeness of the product to the characterises of a drug or a medical device, the manufacturer/importer opts to apply for a drug or a medical device approval.

With increasing rate of innovation in the pharmaceutical and medical device industry it is only a short span of time before specific rules and regulations for combination products are introduced.

V. Marketing Approval for Nanomedicine

A. Nano-products as drugs

The governing framework for clinical trials in India is the CT Rules, National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 issued by the Indian Council for Medical Research (**"ICMR Guidelines"**) and Guidelines on Good Clinical Practice in India, 2001 (**"CDSCO-GCP"**). These are triggered depending upon the nature of the study:

i. Interventional Clinical Studies: Clinical studies which involve the administration of an intervention- new drug or investigational new drug for a commercial purpose should comply with CT Rules, ICMR Guidelines and CDSCO-GCP.

ii. Academic and Biomedical Clinical Studies: Biomedical and health research includes research where no investigational new drug or new drug is involved and is primarily conducted for the purpose of collecting scientific knowledge about diseases and conditions. While, academic clinical trials are conducted for drugs already approved for a certain claim and initiated by an academic or research institution or an investigator for a new indication, dosage form or route of administration. Such studies are only required to comply with the ICMR Guidelines.

If the nanomedicine application is a "new drug"[17] as per the CT Rules i.e. a drug which is not in substantial use in India, then manufacturers and importers must demonstrate its safety and efficacy prior to marketing in India. A drug within the definition of DCA includes both a pharmaceutical drug and a medical device.

Typically, there are four phases of clinical trials for new drugs in India. The safety and efficacy of the drug must be established with animal and human data through these trials. Permission from CDSCO is required prior to proceeding with each phase of the which will be granted by the CDSCO on the basis of the findings of the previous phase. If the CDSCO is dissatisfied with the reports submitted for a particular phase, studies in the particular phase may have to be re-conducted.

There are certain exemptions to of all four phases of clinical trials in India under the CT Rules. They are as follows:

- For drugs developed outside India, Phase I global clinical trial data may be submitted and the CDSCO may grant permission to directly conduct Phase II trials in India alongside the global trials.
- A local clinical trial requirement may be waived off, if the new drug has been approved in countries which are notified by the Ministry of Health and Family Welfare (**"MoHFW"**) under Rule 101 of CT Rules. These include United States, Japan, United Kingdom, Canada and Australia. The pre-requisites for claiming this waiver is that no serious adverse events should have occurred during the prior clinical trials and there must be no evidence or possibility that the drug may be unsuitable for Indian population despite demonstrating

17. As per Rule 2(w) New Drugs and Clinical Trial Rules, 2019 "new drug" means, -
i. a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licensing Authority with respect to its claims; or
ii. a drug approved by the Central Licensing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or
iii. a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or
iv. a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licensing Authority; or
v. a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;
Explanation. – The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licensing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs.

safety in the tested population. Lastly, the applicant for marketing authorization must undertake to conduct Phase IV trials in India to prove the long-term efficacy of the drug to the population.

- The CDSCO is also empowered to provide an expediated approval where the drug is indicated for an unmet medical need or serious life-threatening disease. In doing so, factors such as the severity, rarity, prevalence, nature of the disease and the availability of alternate treatments is taken into account.

Additionally, there are certain specific relaxations provided for medical devices as well. For example, for Class A medical devices i.e. low risk devices there is no requirement to submit performance evaluation data unless the CDSCO mandates it.

In addition to the CT Rules, the Nanopharmaceuticals Guidelines provide guidance for specific requirements of nanopharmaceuticals such as providing their chemical and pharmaceutical information, non-clinical and clinical data relevant for any nanotechnology based pharmaceutical product in recognition of the inherent complexity of nanotechnology applications:

- Stability testing of nanopharmaceuticals must be in accordance with Second Schedule of CT Rules and the Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products, 2018. [18] Further, the testing must be done in consideration of conditions such as functionality, size, carrier material stability, drug stability and degradation of the nanomaterial.
- Animal pharmacology data generated during pre-clinical studies must evaluate enhanced therapeutic efficacy, possible accumulation of the drug at the disease target site. Further, data must also be presented on the effect and circulation of the nanopharmaceutical beyond the target area.
- Studies on animal toxicology must be based upon the pharmacology of the nanopharmaceuticals and the dosage must be based upon the toxicity of the nanoparticles.
- Clinical trials must also be based upon the toxicity and efficacy profile of the nanopharmaceutical drug. Appropriate design of the study, patient selection and biomarkers are critical to providing a clear understanding of parameters driving the efficacy of the free drug and the in vivo behaviour of the delivery system.
- The data required for evaluation of nanopharmaceuticals is to be decided on a case to case basis. The Nanopharmaceuticals Guidelines list out some categories of information which must be provided to the regulatory authorities for approval such as the physiochemical characterization data, analytical data of nanocarriers, API and nanopharmaceutical, stability studies, regulatory status in other countries of the specific nanopharmaceutical etc.
- Pharmacovigilance studies are recommended to be carried out throughout the entire lifecycle of the nanopharmaceutical.

B. Nano-products as medical devices

In the case of medical devices, a clinical investigation/clinical performance evaluation will need to be conducted in accordance with the MDR to assess the safety, performance, or effectiveness of the device. If the nanomedicine application is categorised as an 'investigational medical device,' then a clinical investigation is required to be carried out as pre-condition to manufacturing/importing the investigational medical device for sale in India.

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, available at: https://database.ich.org/sites/default/files/Q1F_Stability_Guideline_WHO_2018.pdf (Last accessed on July 4 , 2022).

Whereas, if the nanomedicine application is an in-vitro medical device, then a clinical performance evaluation will need to be conducted.

There are certain exemptions to a clinical investigation/clinical performance evaluation:

- The CDSCO may abbreviate defer or omit the requirement for local clinical investigation/ clinical performance evaluation if the device is indicated for a life threatening, serious diseases or diseases of special relevance to the Indian health scenario, national emergencies, extreme urgency, epidemic and medical devices indicated for conditions, diseases for which there is no therapy. There is no requirement to submit clinical investigation data for Class A (low-risk) devices.
- Local clinical investigation may not be required if the investigational medical device has been marketed in the United Kingdom, United States, Australia, Canada or Japan for at least two years subject to certain additional conditions under the MDR.

VI. Price Regulation of Nanomedicine

The Drug Price Control Order (**"DPCO"**) issued under Section 3 of the Essential Commodities Act, 1955 regulates price of all drugs in India. It provides for the procedures for fixing the prices of drugs, methods of implementation of fixed prices and penalties for contravention of provisions. The National Pharmaceutical Pricing Authority (**"NPPA"**) is the authority which discharges the functions under DPCO.

The DPCO distinguishes between scheduled and non-scheduled formulations. DPCO provides that "Scheduled formulations" are the drugs contained in the appended First Schedule which is the National List of Essential Medicines (**"NLEM"**). All scheduled formulations are subject to a ceiling price which is fixed by the NPPA on the basis of a formula by taking a simple average of the price of drug brands selling the same scheduled formulation and adding the margin to the retailer to arrive at a Maximum Retail Price ("**MRP"**) for the drug. Whereas, a "Non-scheduled formulation" does not have a MRP determined by the NPPA, however, the prices of such drugs are also monitored by the Central Government, who may fix the ceiling price for such a drug under certain extraordinary circumstances in the interest of public.[19] In the recent past, this provision has also been extended to medical devices to bring them under price control in the interest of public.

Further, the DPCO lays down that the MRP of all drugs, including the non-scheduled formulations cannot be increased by more than ten percent of MRP during preceding twelve months.

In the context of nanomedicine, if the nanomedicine application (drug or medical device) is specified in Schedule I, it will be regulated as a "scheduled drug." Consequently, it will be price controlled and the MRP of the product should be within the ceiling price notified by the NPPA. Whereas, if the nanomedicine application is not specified in Schedule I, it will be regulated as a "non-scheduled drug." There are no ceiling prices prescribed for non-scheduled drugs and hence, the produced will not be price controlled. However, manufacturers of non-scheduled nanomedicine formulations can only undertake a price increase of 10% in given twelve months.[20] There is no restrictions on fixing the initial MRP in this respect. Hence, they are are price-monitored.

In addition, the NPPA is vested with a discretionary power to price- control any drug including non-scheduled formulations in the interest of public as discussed above. If a nanomedicine application is specifically notified by the NPPA for this purpose, there may certain limits imposed on the trade margins in respect of the products and/ or ceiling prices may be prescribed.

19. Paragraph 19, Drug Price Control Order, 2013.
20. Paragraph 19, Drug Price Control Order, 2013.

VII. Safety Standards

In the absence of a specific law governing nanotechnology applications, the general broad legislative framework is the EPA and the rules and guidelines issued thereunder. EPA is an umbrella legislation which seeks to prevent and prohibit activities which may cause environmental hazards. A hazardous substance has been defined as any substance or preparation which, by reason of its chemical or physio-chemical properties or handling, is liable to cause harm to human beings, other living creatures, plant, micro-organism, property or the environment.[21] This definition is wide enough to bring nanomaterials under the regulatory ambit of EPA. The Pollution Control Boards at the Central and State Levels overlook the functioning of EPA and rules issued under it.

Under the EPA, the Hazardous Waste (Management, Handling and Transboundary Movement) Rules, 2008 (**"Hazardous Waste Rules"**) will have to be complied with at nanomedicine manufacturing facilitates. Additionally, in case of biologics, the Genetically Engineered Microorganisms Rules have been issued under the EPA which provide for specific safety management standards for biologic and genetically engineered products.

Aside from the EPA, the nanopharmaceuticals Guidelines lay down that in respect of production of nanopharmaceuticals, the waste disposal mechanisms should also be laid down. In case of liposomal formulations, specific Food Drug Administration guidelines adopted in the United States for 'Liposomal Drug Products' in April 2018[22] may be referred to.

The Nanoregulatory Task Force has also issued Draft Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries in India.[23] This document lays down exposure control strategies, best practices for handling nanotechnology and other incidental safety practices which may be voluntarily complied with.

VIII. Intellectual Property Protection

Although at present, commercialization of nanotechnology has been modest, it is an emerging sector with inventors seeking to protect their inventions and products. India's intellectual property regime has undergone a transformation to be aligned with the Trade Related Aspects of Intellectual Property Rights Agreement (**"TRIPS"**). Prior to the adoption of TRIPS, protection of intellectual property rights (IPRs) in India was of concern to global pharmaceutical/medical device companies seeking to enter India. Post-TRIPS, India has developed a well-established statutory, administrative, and judicial framework to safeguard IPRs.

The National Intellectual Property Rights Policy, 2016,[24] is a vision document for intellectual property protection in India. This policy recognises nanotechnology as an emerging technology and targets the promotion of innovation in this sector.

A. Patent Protection

The grant, revocation and regulation of patents takes place under the Patents Act of 1970 (**"Patents Act"**) and is supported by the Patents Rule, 2003. A patented invention is given twenty years of protection in India under the Patents Act, 1970. India's patent law is also well placed to provide protection for both product and process patents.

21. Section 2(e) of the Environmental Protection Act, 1986.
22. United States Food Drug Administration, Liposome Products- Guidance for the Industry, 2018, available at: https://www.fda.gov/media/70837/download (Last accessed on July 4 , 2022).
23. Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries, available at: https://dst.gov.in/sites/default/files/Draft-Guidelines%20.pdf (Last accessed on July 4 , 2022).
24. The National Intellectual Property Rights Policy, 2016 issued by Ministry of Commerce and Industry under Government of India on May 12, 2016, available at: https://www.meity.gov.in/writereaddata/files/National_IPR_Policy.pdf (Last accessed on July 4 , 2022).

The Patents Act grants a patent to 'inventions' which is a new product or process involving an inventive step[25] and capable of industrial application. However, some innovations though falling within the definition of invention, would not be considered to be 'inventions' under the Patents Act and therefore would not be eligible for a patent. One such exception is for a process for the medicinal, surgical, curative, prophylactic, diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease. Therefore, while the process/ method of performing a treatment is not patentable, the tools used to perform such treatments may be patented. Hence, nano-products may be patented without triggering this restriction.

B. Copyright Protection

Software in the field of nanotechnology may be protected by copyright. In the past, as an alternative to protecting software as a trade secret, some companies have opted to protect the source codes and object codes through copyright. The Indian copyright law- the Copyright Act, 1957 grants protection to original literary, dramatic, musical and artistic works and cinematograph films and sound recordings from unauthorized uses. A computer program is protected as literary work under the Copyright Act. A "computer program" is a set of statements or instructions to be used directly or indirectly in a computer in order to bring about a certain result. Copyright for computer programs prohibits copying of program structure and design.

The copyright protection commences as soon as the work is created and lasts for the life of the author plus an additional sixty years. Non-registration does not disentitle the author of the work from claiming copyright. However, from the perspective of enforcement, registration of the copyright under the Copyright Act attaches evidentiary value.

C. Trademark Protection

Since nanotechnology across all industries including healthcare is at a nascent stage currently, the trade names and devices of nanotechnology inventions we see today may be susceptible to genericide as the industry grows. Therefore, protection of trademarks is key from an early stage.

In India, trademarks are protected both under statutory and common law. The Trademarks Act, 1999 (**"TM Act"**) is the statutory framework for protection, registration, licensing and infringement of trademarks in India. Upon the conditions set-forth in the TM Act, a trademark may be registered in India. Specifically, the TM Act sets forth absolute and relative grounds of refusal of trademark registration. Once registered, the term for statutory protection is ten years which may be renewed subsequently.

Under the Indian law, registration of trademark is the prima facie evidence for validity of the trademark itself. However, a trademark can be used even without registration and can be protected under common law. In such instances, it is the liability of the owner of the trademark to prove the value and the goodwill attached to the goods or services. Further, the statutory remedies under the TM Act cannot be exercised in relation to the unregistered marks. Only common law remedies may be exercised to defend the use of the unregistered trademark.

D. Machine to Machine Laws

Recently, the Government has been working towards the regulation of new and emerging technologies. One such regulation which will impact the nanomedicine industry is Machine to Machine Communications (**"M2M"**) regulation. M2M covers any technology that enables networked devices or machines to exchange information and perform actions without or with minimal human intervention. In an effort to regulate the M2M industry, the

25. Under Section 2(1) (ja) of the Patents Act: 'inventive step' means "a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art."

4. Current Regulatory Framework for Nanomedicine

Department of Telecommunications (**"DoT"**) has amended the Unified License (**"UL"**).[26] The amended UL now contains a new service authorisation for M2M. Accordingly, entities licensed by the DoT (such as internet service providers, telecom service providers etc.) are permitted to provide connectivity and related services to M2M service providers i.e. entities that collect and analyse data from M2M devices and platforms for a commercial purpose. The amended UL also imposes certain data-related obligations on licensed entities such as maintaining records of M2M devices, make, model, registration number etc. of the M2M devices, physical custodian's (end user) name and address etc. The DoT has also published the Guidelines for Registration Process of M2M Service Providers[27] (**"M2M Guidelines"**) which builds upon the amended provisions of the UL.

This development will particularly impact the importers and manufacturers of nanomedicine products which operate on M2M technologies. These applications may include nanobots, sensors, continuous monitoring devices etc.

26. Accessible at: https://dot.gov.in/sites/default/files/UL%20VNO%20with%20M2M%20without%20INSAT%20MSSR%2017012022.pdf?download=1 (Last accessed on June 27, 2022).

27. Accessible at: https://dot.gov.in/sites/default/files/M2MSP%20Guidelines%20.pdf?download=1 (Last accessed on June 27, 2022).

5. Global Perspective on Regulation of Nanomedicine

Although there is great anticipation surrounding the regulation of nanomedicine and its influence on the pharmaceutical industry, currently there is little to no regulatory guidance across the globe. Researchers and legislators have evaluated application of current regulatory laws for nanotechnology in general and its application in healthcare, however, no consensus has been reached. In the absence of specific laws, like in India, general drug laws have been extended to nanomedicine with some modifications since it is directly associated with human health, nanomedicine poses unique challenges and solicits development of a specific governance framework worldwide.

The regulatory approach towards nanomedicines in some jurisdictions has been discussed below:

I. United States of America ("USA")

In the USA in 2008, the US National Research Council issued a report calling for greater regulation of nanotechnology. Presently, the US Food and Drug Administration (**"US FDA"**) is regulating nanotechnology products, including nanomedicines, using the statutory and regulatory authorities surrounding drugs and medical devices. In 2017, US FDA produced a draft guidance on drug products, including biological products, that contain nanomaterials. In addition, the US FDA does not attempt to categorize nanotechnology as safe or harmful but evaluate each nanotechnology on a case-by-case basis.[28]

The US FDA formed the Nanotechnology Task Force and Nanotechnology Interest Group comprised of representatives from many regulatory centres in order to tackle the issue of regulating nanotechnology worldwide in 2018. Despite this, the US FDA is yet to produce a clear set of guidelines. [29]

II. European Union ("EU")

Currently, in relation to nanomaterials, within the EU, regulation is based on both legal acts with binding force (regulations, directives), as well as non-binding acts such as recommendations concerning the fair conduct of scientific research or the application of a uniform definition of nanomaterial. There is no adequate legislation, even though since 2004 the EU has introduced provisions relating to nanotechnology to tighten control and to improve regulatory adequacy and knowledge of nanotechnology risks. Currently, specific provisions on nanomaterials have been introduced for biocides, cosmetics, food additives, food labelling and materials in contact with foodstuff.

In the EU progress has been made with consortiums coming together to put down a definition for what constitutes nanomaterial bringing within its ambit the aspects of health, environment and food. In common with the US, other organizations such as the European Nanomedicine Characterization Laboratory (EU-NCL) which are based across the UK and EU provide and constantly refine knowledge on preclinical characterization assays of nanomedicine. The regulatory body in the EU, the European Medicines Union has published a range of specific preliminary guidelines for a range of nanomedicine preparation standards.[30]

28. United States Food Drug Authority , Nanotechnology Fact Sheet, 2018, available at: https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm402230.htm (Last accessed on July 4 , 2022).

29. Id

30. R. Pita, F. Ehmann and M. Papaluca, AAPS J., 2016, 18(6), 1576–1582 available at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-nanomedicines (Last accessed on July 4 , 2022)

The current regulations, as regards the application of nanomaterials, consist mainly of two regulations, the so-called REACH (Registration, Evaluation and Authorisation of Chemicals) (EC) No 1907/2006) and CLP (Classification, Labelling and Packaging) ((EC) No 1272/2008). [31]The provisions on nanomaterials can also be found in sectoral regulations. The regulations concern the use of biocides, cosmetic products ((EC) No 1223/2009), transmission of information to consumers about food and food additives ((EC) No 1169/2011). [32]Since nanotechnologies are also used in medicine, a Directive on the Community Code relating to medicinal products for human use (Directive 2001/83/EC) appeared in 2001.

III. Japan

Medicines or drugs in Japan are regulated by the Ministry of Health, Labour and Welfare (**"MHLW"**) or the Pharmaceuticals and Medical Devices Agency (**"PMDA"**). The regulatory bodies are still in the process of laying down a definition for nanomedicine and the regulatory framework surrounding this technology and application. [33]Nanomedicines are regulated under the act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices in Japan which provides for a framework on manufacturing, importation, and sale of drugs, medical devices and medical software on a case-by-case basis. [34]Regulators and reviewers are in the process of assembling and analysing nanomedicine data in Japan.

IV. Australia

In Australia nanotechnology is regulated in a sector-specific manner. Existing individual regulatory bodies regulate their industry specific nanotechnology applications. The Therapeutic Goods Administration (**"TGA"**) manages nanoparticles in therapeutic goods and medical devices in Australia. [35] Existing laws governing conventional medicines apply to nanomedicines as well. In application, the regulatory body also seeks guidance of the National Nanotechnology Strategy, 2012 and the Monash Review, 2007 and other regulatory documents for the application of general laws to nanomedicines.

V. Canada

As with other countries, Canada uses existing legislations to regulate nanomedicine. Additionally, the federal body on Health in Canada has adopted the Policy Statement on Health Canada's Working Definition for Nanomaterial to supplement the laws. In addition, the Canada-US Regulatory Cooperation Council has finalized a Nanotechnology Work Plan to develop joint approaches on regulatory aspects of nanomaterials, including terminology and nomenclature.

31. European Chemicals Agency, Nanomaterials, available at: https://echa.europa.eu/regulations/nanomaterials (Last accessed on September 21, 2021)

32. Id.

33. Current Initiative in Japan for nanomedicines, available at: https://www.ema.europa.eu/en/documents/presentation/presentation-nanomedicines-current-initiatives-japan-kumiko-sakai-kato-toru-kawanishi-national/mhlw_en.pdf (Last accessed on July 4 , 2022).

34. Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi Drugs, available at: https://www.pmda.go.jp/files/000153399.pdf (Last accessed on July 4 , 2022).

35. Nanotechnology Regulation In Australia, https://www.science.org.au/curious/technology-future/nanotechnology-regulation-australia (Last accessed on July 4 , 2022).

6. Legal Issues with Nanomedicine

Nanotechnology is regarded as a double-edged sword. One edge depicts potential health benefits and the other points towards the difficulty in regulation of nanotechnology given its complex and varying nature based on the application being considered for regulation. Some key areas of legal concerns have been discussed here:

I. Lack of Commonly Accepted Definition and Regulations

There is no general international consensus on the classification of nanomedicine applications. Each jurisdiction has a different system of evaluation on the basis of existing pharmaceutical and medical laws. This creates a bout of confusion in regulating nanomedicine as a drug, medical device, etc.

In India, the categories of nanomedicine have not been defined. However, the Nanopharmaceuticals Guidelines have categorized pharmaceutical applications of nanomedicine while the other applications of nanomedicine remain undefined. The lack of settled legal definition and categories will disadvantage the regulatory bodies understanding the operation of the nanomedicine applications which is essential for grouping them into drugs, medical devices and biologics. This may also cause disparities in regulations of identical products since each application needs to be examined on a case to case basis without a uniform threshold

While it is arguable that existing regulation can be applied to medical uses of nanoparticles, yet in some cases it may not be enough, and more specific regulation might be needed to [36]avoid a situation of under-regulation. The lack of classification gives rise to several granulated issues. For instance, a nanocarrier may act as both a drug and a carrier, then it will possess inherent therapeutic characteristics. In such a scenario, compartmentalizing it as its traditional drug molecule counterpart or as an ordinary drug carrier will lead to ignorance of all potential risks and it may be under-regulated.

II. Consent in Nanomedicine

New technologies often pose unknown risks which come to the forefront only upon application and use on individuals with unique conditions. Unlike clinical trial conditions where obtaining informed consent of the participants and the associated risks and consequences are covered within the ambit of separate regulations. [37]Hence, obtaining informed consent from individuals may pose a serious problem in the application and use of nanomedicine for diagnosis, treatment, imaging and prevention of diseases.

The growing requirement of continued consent in application and use of medicines, and in-vivo application of nanomedicine is deemed to impact the liabilities and duties of doctors worldwide. Such a consent is not merely considered to be a formality for administration of medical help but is developing on the lines of patient's right to determine the kind of medical assistance and treatment being administered. The idea of continued informed consent is on diverging lines with the existing traditional approach and researchers and doctors worldwide would require adapting to this change.

36. Rachel F., Ernest M., Jasmine T., Suet Y. Abigail J. Clare H., The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives, Biomater. Sci., 2020, 8, 4653-4664, available at: https://pubs.rsc.org/en/content/articlehtml/2020/bm/dobm00558d (Last accessed on July 4 , 2022).

37. Ezekiel Emanuel, David Wendler & Christine Grady, What Makes Clinical Research Ethical, 283 JAMA 2701 (2000), Available at: http://demvstifyingmedicine.od.nih.Lov/DM13 /2013-02-2 6/IAMA-v2000-v283-p2 701.pdf (Last accessed on July 4 , 2022).

III. Product Liability for Nanodevices

A. Nano-products as medical devices

While new technologies are consistently evolving, the uncertainty in the extent of and reasons for liability are not always foreseeable by researchers, medical practitioners, manufacturers and other industry stakeholders as risk disclosures in this developing technology becomes a challenge. Liabilities arising out of use of nanomedicine may be covered within the ambit of the general applicable law i.e. the Consumer Protection Act, 2019. Under this legislation product liability has been defined as "responsibility of a product manufacturer or product seller, of any product or service, to compensate for any harm caused to a consumer by such defective product manufactured or sold or by deficiency in services." The CPA divides responsibility between the product manufacturer, product seller and product service provider. Broadly, the liability is divided based on the entity who is directly responsible for causing the damage.

B. Nano-products as drugs

Similarly, under the Drugs and Cosmetics Act, which is the parent legislation of the MDR, the import, manufacture and sale of medical devices which are prohibited under any applicable law, which are not of standard quality, adulterated, misbranded or spurious is forbidden and penalised. Hence, in the absence of specific legislations imposing product liability for nano-products within the ambit of drugs in India, the said two legislations may be relied on for imposing liability.

Further, the field of nano torts is also developing internationally in order to address concerns arising out of the use of nanotechnology in medical applications of nanotechnology to life sciences. Such claims may be raised under the tort laws, consumer laws, fraud or contract law.[38] The unique and ever enhancing qualities of nanoparticles lead to further difficulties in creating a basis for deciding whether possible defects or side-effects are foreseeable, predictable and can cause damage. Informed consent of individuals will play an important role in minimizing the liability of exposure of healthcare professionals in the application of nanomedicine.

IV. Intellectual Property Concerns

Nanoparticles remain to be in a grey area in terms of claiming intellectual property protection under the laws. In order to encourage innovation by application of technical know-how and monetary investments in any sector, the patenting system in a country is the key. As far as the field of contribution to the total number of nanotechnology patents is concerned, 14.8% are contributed by medicine and biotechnology.[39]

Patenting laws in India require an invention to have a novelty criterion,[40] which poses a challenge to the nanotechnology as use of nanoparticles entails reduction in the mere size of the existing inventions for enhanced and efficient use. Novelty has been defined and standards have been laid down in various judgments by the courts such as in the case of Monsanto Company v. Coramandal Indag Products,[41] Nanotechnology and nanomedicine face the challenge of establishing the novelty criteria due to the pre-existing technologies based on which nanotechnology is said to be derived to generate more efficient functioning. This is brought within the ambit of

38. Michael L. Lisak & James W. Mizgala, Mitigating Risk In Mass Nano Torts, LAw360.coM, Feb.1, 2012, http://www.law360.com/articles/304091/mitigating-risk-in-mass-nano-torts. (Last accessed on July 4 , 2022).

39. Kanika Sharma & Archana Chugh, Legal Aspects of Nanobiotehnology Inventions: An Indian Perspective, Vol. 6 Issues 2 SCRIPTed 433 (2009).

40. As per Section 2(j), Indian Patents Act, "invention" is defined as " a new product or process involving an inventive step and capable of industrial application." AIR 1986 SC 712.

41. AIR 1986 SC 712.

anticipated prior art. Another challenge faced in the patenting process is the failure to meet the bar of enhanced efficacy[42] as the nanomedicine may be considered to be a mere reduction in size of particles used in the existing technology without actually changing the fundamental basis of the application itself

V. Nanomedicines may qualify as Hazardous Chemicals

Unlike chemicals present in drugs which have a set reaction and toxicology at a given dosage level, nanomedicines behave differently, wherein a lot is dependent on their particle morphology and quantity, while an individual nanoparticle may show toxicity at 1.4 nm size, they won't show the same at 15nm size or their bulk quantity.[43] Furthermore, drug delivery nanomaterials have shown such features whereby besides increasing drug delivery and bioavailability they have the capacity to direct the harmful component for destruction of diseased tissue, provided the healthy tissues remain unharmed.[44] Hence in nanomaterials, toxicity is way more complex to determine the normal mechanism of dosage and size.

A nanomedicine may be listed as a hazardous chemical under the Manufacture, Storage and Import of Hazardous Chemicals Rules, 1989[45] or if the CDSCO or MoHFW through gazette notification which lists such a drug as a banned drug under S.26A of DCA which provides powers to the Central Government to prohibit manufacture, etc. of drugs and cosmetics in public interest.[46] Therefore, nanomedicine as a drug or a medical device yielding toxic outputs may be banned under the legislations discussed herein and must be assessed during the clinical trial stages to prevent future disruptions in manufacturing or marketing stages.

VI. Prescription of Nanomedicine by Medical Practitioners

The Good Medical Practice Guidelines under Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002 (**"MCI Code"**), require that a physician can only refer to such methods of treatment which has attained a scientific basis[47]and which is consistent with the provisions of the various acts including the EPA.[48] Though there are no obligations on the Physician to opt for the best line of treatment under the principle of due care towards the patient such an obligation does arise. As held in the case of Maharaja Agrasen Hospital v. Rishabh Sharma[49], the duty of the medical professional is not to offer the best treatment method, but be aware of the method of treatment and harms associated and inform the patient about the same and exercise reasonable care. Thus, the hesitation with the referring of nanomedicine for the diagnosis, treatment or cure of a disease by medical practitioners must be backed by safety profiles of such technology and incentives or guidelines introduced by the relevant authorities in the country.

42. Section 3(d), Indian Patents Act, 1970.
43. Wolfram, J et. al. (2015). Safety of Nanoparticles in Medicine. Current drug targets, 16(14), 1671–1681. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4964712/. (Last accessed on July 4 , 2022).
44. Id.
45. Manufacture, Storage and Import of Hazardous Chemicals Rules, 1989 - Rule 2(e)
46. Drugs and Cosmetics Act 1940, Sec.26A
47. Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002, Reg. 1.2.1.
48. Environment Protection Act 1986, Reg. 1.9.
49. (2020) 6 SCC 501, P. 12.4.

VII. Labelling

Branding of drugs and medicines are an important element which is often linked with essential standards laid down under the DCA,[50] which seeks to prevent misbranding of drugs which may entail insufficient labelling or making a false claim through a misleading label. The schedule to the DCA[51] provides for the branding and labelling standards to be complied with for specific class of substances.

The challenge in terms of labelling of nanomedicines would occur between 1 and 2 of the Schedule, while class 1 covers patent or proprietary medicines, nanomedicines can also lead to toxic effects, so whether they would generally qualify as toxins or not would become a question of dispute. In that regard the labelling standards of class 1 and class 2 are different and therefore, clarification has to be issued regarding the labelling standards for nanomedicines. Due to the inherent unpredictability of reaction of nanomedicines, the labels of such medicines would have to clearly designated and no false claims of extra-ordinary treatment be made, as well as specific labelling for such nanomedicines is indeed required for the common man and physicians to distinguish. Therefore, a stronger vigilance for such compliances of nanomedicines is necessitated.

50. Drugs and Cosmetics Act, 1940, Sec. 9, 17.

51. Drugs and Cosmetics Act, 1940, Sch II, Para 8, 16.

7. Ethical Issues with Nanomedicine

In the absence of legal restrictions on the application and use of nanomedicine, the lacunae in the regulatory framework settling issues surrounding the use of nanotechnology poses several unaddressed ethical concerns. Although they do not pose a roadblock to innovation of nanomedicine, the use of such technologies may become a concern. Some of these ethical issues are stated below:

i. The risk of application of nanotechnology exists across industries owing to the lack of clarity of its complete efficacy and safety. Although there has been tremendous progress in the sub-field of nanomedicine, there is an inherent fear which subsists in the manufacturing and use of nanomedicine due to the absence of proven efficacy of the use of nanomaterials itself. Further, the full life cycle process of nanomaterial is not scientifically discovered yet, hence the long-term effects of its use are dubious.

ii. The size and components of nanoparticles have the potential to cause more harm than the therapeutic efficacy derived from it. Many of the artificially manufactured nanoparticles are made of non-biodegradable pollutants, such as carbon black and metals, and the long-term behaviour of such substances is not known.[52] Further, while the size of the nanoparticle is the perceived benefit, it has the potential to distribute across various areas inside of the body through several ports and internal barriers. These unwarranted passages through the body beyond intended target areas can pose different health risks in the future. Further, given its size the form of administration whether oral or topical is irrelevant in the context of safety since it has the capacity to pass through skin and biological barriers and enter the bloodstream at a faster pace than traditional drugs and has the capability of interfering with vital cell functions. In the absence of specific nanomedicine risk-management norms, these issues have been significantly overlooked and there is little to no data available on the actual net health effect other than the efficacy for the condition the nanomedicine was originally intended for.

iii. In addition to the dangers it poses to the human body, nanomaterials are often associated with safety and environmental hazards. The toxicity levels of nanomaterials in general as well as the procedures of manufacturing such products cause pollution. Research has also suggested that some forms of carbon nanotubes could be as harmful as asbestos.[53]

iv. Nanotechnology is based on techniques and methods of manipulating matter on a nanoscale. In applications involving biologics this procedure poses an ethical issue of whether the manipulation of a living organism or a biological derivative into nanoscale medical preparations permissible under the genetic engineering norms. Further, it is unclear as to what can be nano-scaled and what is restricted, therefore the lack of limits within which innovation must operate can poses an ethical issue. For instance, a drug containing either whole or derivation of nano-scaled living organisms which are not microorganisms can be ethically problematic.

v. A major ethical issue is whether prescription of nanomedicine which involves the use of nanoparticles is in line with the MCI Code which stipulates the ethical practices to be undertaken by healthcare practitioners. Health care practitioners have the duty to ensure utmost care towards patients. Hence, given the contentious nature of nanotechnology, if the use/prescription of nanomedicine will be in line with medical ethics is a question.

52. Seung-heon S, Mitikyung Y, Jeung-kyu K (2006) The effects of nanosilver on the proliferation and cytokine production in peripheral blood mononuclear cells. Jpn. J. Rhinol. 45: 269-273

53. Katherine Sanderson, Carbon nanotubes: the new asbestos?, https://www.nature.com/articles/news.2008.845 (Last accessed on July 4, 2022).

vi. In new technologies such as nanomedicine there exists an information gap at each level of distribution up until the end-user. In such circumstances, obtaining informed consent of the patient who has been recommended the use of nanomedicine is an ethical concern. In addition to the unknown risks, a patient may not be made fully aware of the working of a nanomedicine application and how it is different from a traditional drug or medical device. While nanomedicine may have sufficed the tests of safety and efficacy through clinical trials, the patient may prefer a traditional drug as opposed to nanomedicine if equipped with appropriate knowledge.

8. Considerations for the Future

The proposed solution to developing legislation surrounding nanomedicine in India is as follows:

I. International Harmonization

International harmonization through consultations between regulators to arrive at uniformity in regulation of important aspects of nanomedicine such as categorization and safety will provide guidance in the formation of domestic legislations. These need not necessarily be treaties or binding agreements, instead informal consultations[54] or guiding principles on regulation of nanomedicine will harmonize the treatment of these novel technologies. These outcomes will be beneficial for innovators and regulatory bodies alike.

II. Categorization of nanomedicine

Nanomedicine encompasses a broad range of applications. For the purpose of regulation, the applications must be categorized on the basis of nature and functions for the ease of regulation. Broadly it can be divided into nanopharmaceuticals and medical devices. Further categories can be defined in the following manner:

i. Nanopharmaceuticals- nanoparticle, nanocarrier, nanoform

ii. Nanotechnology based medical devices- in-vitro diagnostic devices, in-vivo medical devices, automated in-vivo devices

III. Special Regulations

Since nanomedicines are essentially the upgradation of existing drugs and techniques with the application of nanotechnology, it is important to determine whether these applications will continue to be regulated as their traditional counterparts or whether they will be considered to be independent inventions requiring additional legal safeguards. It is recommended that specific restrictions must be introduced over and above general applicable laws for nanotechnology applications in respect of manufacturing procedures, clinical trials, restrictions on retail etc.

Further, safe handling of biomedical nanomaterials is also not presently covered under the law. Proposed laws such as the Draft Bio-Medical Waste (Management and Handling) Rules, 2016 and Draft Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries, 2016 will need to be implemented.

IV. Labelling Requirements

Labelling of drugs enables the consumers to be informed about its use and be warned of potential dangers of consumption. In respect of nanotechnology, additional declarations on the packaging must be mandated to inform consumers of the use of nanomaterials because of the potential risks associated with it.

54. Gary E. Marchant, Douglas J. Sylvester, Kenneth W. Abbott & Tara Lynn Danforth, International Harmonization of Regulation of Nanomedicine, 3 Stud. Ethics L. & TECH.1 (2009).

V. Price Control

Presently the DPCO regulates only specified dosage forms and prescribes their MRP, and incremental innovations will not fall under price control unless they are explicitly specified in the First Schedule. In case of nanopharmaceuticals, they may either manipulate an API or act as a carrier. It also remains to be seen whether nanopharmaceutical products would fall within the ambit of incremental innovation as provided in the explanation to the Schedule appended to the DPCO which is revised from time to time, since DPCO encourages innovation by exempting such innovations from price control unless specified with a drug listed under the schedule.

Further, drugs with the same strength and route of administration, which do not have significant difference in terms of pharmacokinetics or pharmacodynamics or efficacy-safety profile over the dosage form mentioned in the Schedule are deemed to be scheduled formulations. However, this approach will prove to be disadvantageous in the evaluation of nanopharmaceuticals since the primary difference is the drug volume while all other factors such as dosage, route of administration etc. may remain identical to the traditional form of the drug. Therefore, it must be clarified in the DPCO whether nanopharmaceuticals would be exempt from price control.

VI. Consent

Specific consent prior to administration of nanomedicine must be mandated. In taking such consent, the patient must also be informed about the difference between nanomedicine and traditional drugs or medical devices, and also the potential risks associated with its use. Given the shift in the understanding of consent experienced in recent years, where a continued consent is being required prior to administration of medical aid to patients, the compliance with such requirement may act as a hurdle in the application of nanomedicine for treatment. This must be clarified by the responsible medical authorities.

VII. Smart nanotechnology applications

Due consideration must also be given to aspects of liability, data governance and control procedures for smart nanodevices.

9. Future Beckons

"*Nanotechnology in medicine is going to have a major impact on the survival of the human race*"

– Bernard Marcus, American Businessman and Philanthropist

While, it is impossible to predict the full potential of nanotechnology, legal preparedness is necessary. Nanotechnology is beginning to be understood and noticed by lawmakers with the assistance of researchers and innovators. Ideally, nano-regulations should be a myriad of regulations encompassing laws governing the economic, sociological, psychological, legal and environmental in the country to enhance and ensure public health, safety and welfare. Prospective laws must be developed taking into consideration the wide array of applications powered by nanotechnology and the intrinsic issues that may arise with respect to each branch of nanotechnology application.

Nanomedicine is a vital application of nanotechnology and has immense potential in revolutionizing healthcare systems. The impact of nanomedicine can be broken down into the following areas: legal, economic, sociological/ psychological and environmental. While the world partakes in the race for survival, it becomes important for legislatures and regulators to devote time and effort into identifying how these technologies can be leveraged for the benefit of public health and monitored.

India may propose to recognize nanomaterial products under an independent category thereby introducing specific rules and regulations regulating the products utilized in the pharmaceuticals and healthcare industry in the country. The gaps in the terms of guidelines for waste disposal and handling of nanomaterial need to be addressed by the relevant authorities.

It is important to balance the risks inherent in the application of nanomedicine to healthcare space with the possible benefits it may offer the industry by increasing efficacy and possibility of disease mitigation and prevention. India has initiated steps to characterize the regulatory landscape for nanotechnology and its application to nanomedicine.[55] Keeping in mind that the use of nanotechnology is ever-evolving it becomes pertinent to introduce soft-governance mechanisms to regulate nanomedicine. These may include certification for nanomaterial, introducing policy regulations, providing guidelines for each stage in the lifecycle of a nanoproduct i.e. research, implementation and post marketing use.

Nanomedicine is set to bring about a revolutionary change in the pharmaceutical and healthcare industry in India and is bound to enhance the efficacy of treatment options and variables presently utilized for disease treatment and mitigation in the country. The regulation of nanomedicine is yet to be crystallised in the nature of rules and regulations which cater to the growth of the industry although once notified, nanomedicine can be a boon to the citizens of our country.

55. Pooja Bhatia & Archana Chugh, A multilevel governance framework for regulation of nanomedicine in India, December 15, 2016, Nanotechnol Rev 2017; 6(4): 373–382.

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