

## NANOPARTICLES AND NANOTECHNOLOGY: CLINICAL, TOXICOLOGICAL, SOCIAL, REGULATORY AND OTHER ASPECTS OF NANOTECHNOLOGY

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### ABSTRACT

In last few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules like nanoparticles. The continuing advancement of nanotechnology represents a tremendous opportunities of society because of the unique traits that nanoscale material possess but there are many clinical, toxicological, social, regulatory and other aspects of nanotechnology which are matter of concern. The United States Food and Drug Administration (FDA) and some other authorities ensures that the nanoparticle based products meet the regulatory standards for approval but like other new technologies there are many ethical issues and regulatory challenges associated with the products of nanotechnology. Before nanotechnology is largely used to enhance the quality of life, it must be made certain that health risks are taken in to the consideration, social and ethical issues are addressed, public opinions are gathered, and regulatory matters are assessed from all aspects.

**Keywords:** nanoparticles, nanotechnology, FDA, ethical issues, regulatory challenges.

### INTRODUCTION

In pharmaceuticals, almost 90% of all medicines, the active ingredient is in the form of solid particles. Now with the development in nanotechnology, it is now possible to produce drug nanoparticles that can be utilized in a variety of innovative ways. Nanotechnology is defined by the United States government as research and technology development at the atomic, molecular, or macromolecular levels using a length scale of approximately one to one hundred nanometers in any dimension<sup>1</sup>. Nanotechnology uses nanoparticles. Nanoparticles are the simplest form of structures with sizes in the nm range. In principle any collection of atoms bonded together with a structural radius of < 100 nm can be considered a nanoparticle. These can include fullerenes, metal clusters (agglomerates of metal atoms), large molecules for example proteins, and even hydrogen-bonded assemblies of water molecules, which exist in water at ambient temperatures. There are various methods of preparation of nanoparticles and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are the systems in which the drug is confined to a cavity surrounded by a unique polymer membrane and nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles have various types of applications for example biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ and as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides<sup>2,3,4,5</sup>. Nanoparticles are very commonplace in nature - for instance proteins exist in almost all biological systems, metal-oxide nanoparticles are easily produced. These innovative ways of new drug delivery pathways are now used that can increase drug efficacy and reduce side effects. For example in 2005, the U.S. Food and Drug

Administration approved intravenously administered 130-nm albumin nanoparticles loaded with paclitaxel (Abraxane) for cancer therapy, The new albumin/paclitaxel- nanoparticle formulation offers several advantages. In spite of all these advantages of nanotechnology and nanoparticles, the awareness of nanotechnologies is very low among the general public. In one survey, 51.8% of 1536 American respondents indicated that they had heard nothing about nanotechnology<sup>6</sup>. About 39.8% of the respondents believed that the benefits of nanotechnology outweigh the risks and 38.3% perceived that benefits equal risks, because nanotechnology have various kinds of Clinical, Toxicological, Social, Regulatory aspects that are of prime concern. The Nanotechnology must be consistent with the ethical principles stated in various guidelines<sup>7</sup>. The overall principle of human dignity is spelled out in these guidelines. Against this background some questions are very important like, how should the dignity of people participating in nanoparticle research trials be respected? How can we protect the fundamental rights of citizens that may be exposed to free nanoparticles in the environment? How can we promote responsible use of nanoparticles which protects both human health and the environment? And what are the clinical, ethical and regulatory issues of Nanotechnology. In other words, the socio-ethical issues associated with nanoparticles will necessarily include considerations of clinical, public health, environmental impact, and so on.

### CLINICAL ASPECTS

To begin with, following pre-clinical animal testing that demonstrated potential effectiveness, research ethics review (based on principles of safety, efficacy, informed consent, and so on) would be required before proceeding to Phase I and Phase 2 clinical trials on humans. Novel scientific or clinical developments do not necessarily bring novel ethical considerations. While there may well be

challenging applications of ethical precepts that warrant careful ethical consideration, new developments do not in general necessitate the articulation of entirely new ethical principles. Some new techniques such as tomography, nuclear magnetic resonance or ultrasound scanning have enormously expanded the classical use of X-rays in producing images of increasing quality of the human body that are widely used in various types of diagnosis, including analysis of functions of the human brain. Imaging includes also analysis of microscopic images of tissues used in pathology<sup>8</sup>. Nanotechnologies may allow a more precise diagnosis. For example, super-paramagnetic iron oxides, with a diameter of less than 50 nm, allow the imaging of organs and have been successfully evaluated for improved lymph node metastases detection in various clinical trials<sup>9</sup>. There are several Clinical issues related with the use of these new techniques. Several nanoparticle technologies are currently in clinical trials and a few have progressed to clinical use. NanoCrystal technology from Elan Pharmaceuticals International, Ltd. is one breakthrough technology that is being licensed to pharmaceutical companies for specialized drug delivery systems. Currently, there are some FDA approved drug products employing this technology but there are some clinical issues associated with it.

### TOXICOLOGICAL ASPECTS

Nanotechnologies are employed in a wide variety of applications. These technologies have health effects when they are dispersed in the environment. Safety issues of nanotechnology and nanoparticles have been addressed in several reports across the world. Various toxic effects of some nanoparticles have been already demonstrated in cells, tissues and small animal experiments. There are some materials which are used at nano scale can increase the probability of nanoparticles entering the body and circulating or being absorbed into specific organs. Nanoparticles can act in a different ways in tissues for example the respiratory organs etc. These can be catabolised in a different way by the organism and recycled differently by the environment, when compared with larger particles. On inhalation, Nanoparticles can deposit in the respiratory tract. There are currently very few evidences from skin penetration studies but only a few specific nanoparticles have been investigated in a limited number of test systems, and extrapolation of this data to other materials is not possible<sup>10</sup>. This is very important to monitor the possible adverse effects on health arising from the use of free new nanoparticles for diagnostic, therapeutic or cosmetic purposes and these may lead to adverse effects due to accumulation in tissues or organs like consequences on cellular metabolism of the organism involved, including potential protein conformational change, as well as to the possible promotion of tumour formation. Various toxicological methods have been implied but there are examples indicating that known and widely accepted toxicological methods are not sufficient to detect possible damaging effects of nanoparticles on human<sup>11</sup>. Possible risks are associated with nanoparticles and nanotechnology with regard to the ecological consequences of nanoparticles accumulating in the environment and human health. The issue of the safe and responsible use of nanoparticles and nanotechnology raises two concerns about the hazardousness of nanoparticles and

the exposure risk. The first concern is about the biological and chemical effects of nanoparticles on human bodies or natural ecosystems and the second concerns the issue of spillage, leakage, circulation, and concentration of nanoparticles that would cause a hazard to bodies or ecosystems<sup>12</sup>. Many concerns have also been raised about the potential health risks for individuals other than patients due to the spread of free nanoparticles in the environment. The recycling of free and bound nanoparticles, and the possibility that such particles may pollute various resources like water, air and soil, raise issues about safety, and how the interests of the industry, competing for market shares, are to be balanced against other interests<sup>13,14,15</sup>.

### SOCIAL ASPECTS

Though this new technology called nanotechnology has caused quite a stir in the scientific community, but a little has been done to learn the long-term effects of nanotechnology on the environment<sup>16</sup>. In these days sufficient knowledge regarding the environmental and societal effects of pharmaceutical nanoparticles does not exist. So various other measures are used like knowledge from the effects of other types of particles, e.g., air pollutants, can be helpful. Several air pollutants are in the nanosize range and they never fully settle. So, one can assume that therapeutic nanoparticles will accumulate in the air, water, and soil, resulting in lasting effects in biological systems. The advantageous surface area of these nanoparticles may pose an added risk of explosion and fire hazard because of enhanced reactivity. As particle size decreases, the propensity toward violent dust cloud explosions increases leaving those who work in such industries susceptible to endangerment<sup>17,18,19</sup>. Thus, it is exceedingly important that the environmental effects of nanoparticles be thoroughly considered. Following inhalation, besides exerting respiratory effects, nanoparticles might translocate from the highly vascular lungs into the systemic circulation, potentially resulting in cardiovascular effects. The most common route is inhalation for systemic entry of environmental nanoparticles in the human body<sup>20,21,22</sup>.

### REGULATORY ASPECTS

Nanoparticles containing items are currently regulated by a variety of Federal agencies, depending on their intended application. Nanotechnology is an element under evaluation in FDA's Critical Path Initiative. Regulatory aspects of nanoparticles are concerned with FDA and other guidance authorities. FDA has approved many products with particulate materials in the nanosize range<sup>22</sup>. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health, but the current regulatory framework concerning the manufacture and use of nanoparticles is inadequate to protect people from the potential threat posed by nanoparticles but still nanotechnology is an exciting new field with hopes for improvements in a wide variety of applications<sup>23</sup>. One of the main concern is that nanotechnology is new, and there is much research needed before sufficient regulation can be determined. That is why the regulation of nanotechnology products including

nanoparticles is nonspecific. There are various issues regarding this like, if not directly but indirectly nanomaterials may be a part or a consequence in several products approved by the FDA<sup>24</sup>. For instance every approved biodegradable device and dosage form potentially contributes nanoparticulates to the biological system during its degradation process. The regulation and approval by the FDA is on a product by-product basis, the overall regulation process falls into three stages: premarket approval, premarket acceptance, and post market surveillance. Apart from these, there are some important factors regarding the regulatory aspects of nanotechnology, like

- There is extensive regulation of areas where nanoparticles are used in products. Medicinal products and medical devices are subject to strict rules. Cosmetics are also subject to rules requiring inter alia risk assessment, but without verification of the manufacturer's risk evaluation.
- There is lack of a clear legal definition of nanoparticles.
- Some nanoparticle innovations may fall within several categories of regulation which may apply simultaneously. This may lead to risk of uncertainty as to which regulation is applicable. Uncertainty and overlap of regulatory guidelines may result in a situation where the manufacturer may have to apply different systems or can choose between different systems with different procedures and different risk evaluations and assessments.
- EMEA has created the Innovation Task Force (ITF) to ensure EMEA-wide coordination of scientific and regulatory competence in the field of emerging technologies, including nanotechnologies, and to provide a forum for an early dialogue with applicants on regulatory, scientific or other issues that may arise from the development.
- Risk assessment is included in virtually all product legislation relevant to nanoparticles and even if regulation includes provisions on risk assessment, this only provides adequate protection if the implementation includes sufficient scientific expertise and the risk actually can be assessed and managed. Specific efforts are needed to develop measures for implementing existing regulations that would respond to the implications of nanoparticles.
- Moreover, The FDA regulations are for products, not technologies. In addition, the FDA regulates only the claims made by the product sponsor. If the manufacturer makes no nanotechnology claims regarding the manufacture or performance of the product, the FDA may be unaware at the time that the product under review employed nanotechnology.

#### OTHER ASPECTS

The aim of the patent system is to encourage innovation by striking a balance between knowledge protection and

information dissemination. There is, however, a risk of excessively broad patents being granted and the risk that the research exemption and the exemption for diagnostic and therapeutic purposes can be challenged. These factors have made the present patent system less well adapted to present conditions and produced problems in knowledge protection and, on the other, information dissemination in the area of nanoparticles especially if combined with a liberal policy of granting patents. Patenting of biomaterial for medical use is a matter of for medical use is a matter of an ethical concern where and in so far as it may limit the provision of medical treatment on financial grounds. Patent law represents an attempt to strike a balance between several legitimate interests. It must be taken in account that researchers and companies should be able to protect their intellectual property rights and benefit financially from their investment, but it cannot be forget that regulation will be needed in order to protect patients also. European Patent law does not permit patenting of "methods for treatment of the human or animal body by surgery or therapy". So these type of issues will need to be subjected to ethical analyses, particularly when systems involving both tissues and nanomaterials are available for surgical procedures. Some questions have also arisen that there may be a conflict over patentability if a new product is both a pharmaceutical and a "diagnostic, therapeutic and surgical method" used for humans or animals. The European Patent Convention has specifically excluded patentability methods for "treatment of the human or animal body by surgery or therapy or diagnostic methods", but permits patents on products like substances or compositions used in these methods. It is possible that a nanoparticle may be patented even if it constitutes a method, given the wording of the Article. In addition, the TRIPS agreement (Article 27) permits the exclusion from patentability of "diagnostic, therapeutic and surgical methods for the treatment of humans or animals".

#### CONCLUSION

The new technologies always present choices and there are clinical, ethical and various other concerns are raised by the development in nanotechnology. In general, and in spite of a rapidly increasing number of scientific publications dealing with nanoscience and nanotechnology, there is insufficient knowledge and data concerning nanoparticle characterization and their effect on humans and environment. So detailed ethical analysis and social scientific critique will be needed for the practical application of the nanotechnology in the near future. The nanomedicines prepared by nanotechnology serves various applications. We need a combination of ethically thoughtful scientists and policy-developers, scientifically savvy academics in the social sciences and humanities, and a public with sufficient scientific literacy to participate, in an informed way, in what is sure to be an on-going set of debates about the role of science and technology in our individual and collective live.

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