



# Regulatory And Toxicology Issues Surrounding Nanomedicines

1Dr.(Mrs) Shilpa Chaudhari, 2Rutuja Panchave

1Head of Department, 2Student

1Savitribai Phule Pune university,

2Savitribai Phule Pune university

## Abstract: -

In the last several decades, the application of nanomedicine for clinical purposes has received significant attention from academia, researchers, government, funding agencies, and regulatory bodies. Key issues related to the clinical development of nanoparticulate nanomedicines include biological challenges, biocompatibility and safety, large scale manufacturing, government regulations, intellectual property (IP), and overall cost-effectiveness in comparison to current therapies. This review focuses on the introduction of nanoparticles and various challenges face by these formulations, controversy associated with the basic concept related to the nano systems. Nanoparticles based formulations have ability to overcome biological barriers to effectively deliver them from biological sites, despite of their advantages only small number of nanoparticles-based formulations get approved for clinical use with numerous challenges and hurdle at different stages of development. The biocidal activity of Metal nanoparticles in general and silver nanoparticles (AgNPs) depends on several morphological and physicochemical characteristics of the particles. Many of the interactions of the AgNPs with the human body are still poorly understood; hence, the most desirable characteristics for the AgNPs are not yet well established. This shows that with the regulatory issues related to nanomedicines there are also several pharmacological and toxicological issues which have to consider during synthesis of nanomedicines. This review summarizes challenges likely to be encountered during the development and approval of nanoparticle-based therapeutics, and discusses potential strategies for drug developers and regulatory agencies to accelerate the growth of this important field.

**Key Words:** Nanomedicine, Regulatory issues, Toxicology issues, Silver nanopartilces

## Introduction: -

In recent years, there has been an exponential interest in the development of novel drug delivery systems using nanoparticles. Nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules (1) Particles 500-1000 nm in size theoretically beyond the realms of nano technology can penetrate and reach the lower levels of human skin, 128 and smaller particles are likely to deeper into the skin (2). Nanoparticles can enter the human body in several ways (i) via the lungs where a rapid translocation through the blood stream to vital organ is possible, including crossing the BBB and absorptions by (ii) the intestinal tract (iii) the skin (3). Lungs: Based on three particle types titanium dioxide (TiO<sub>2</sub>) carbon black and the diesel particles, hazards studies in rats, demonstrate that ultrafine nanoparticles administration to the lung produce more potent adverse effect in the form of inflammation and subsequent tumours compared with larger sized particles, of identical chemical composition at equivalent mass concentration. Surface properties

such as surface chemistry may play a significant role in nanoparticles toxicity (4). Intestinal Tract: The epithelium of the small and large intestine is in close contact with ingested material so that nutrients can be utilized. A mixture of disaccharides, peptides, fatty acids and monoglycerides generated but digestion in small intestine are further transformed and taken in the villi. The smaller the particles diameter the faster they could penetrate the mucus to reach the colonic eutocytes; 14 nm diameter permeated within 2 minutes; 415 nm particles took 30 minutes while 1000 nm particles were unable to translocate this barrier (5).

Advantages of Nanoparticles: -

- i. Increased bioavailability Dose proportionality.
- ii. Smaller dose form. Increased surface area results in a faster dissolution of the active agent in an aqueous environment, such as the human body.
- iii. Faster dissolution generally equates greater absorption and bioavailability.
- iv. Smaller drug doses less toxicity.
- v. Reduction in fed/ fasted variability.

### **Rationale behind the development of nanoparticles: -**

Nanoparticles have some unique physical and chemical properties at cellular, atomic and molecular levels which usually seen with the bulk material (6). Due to their high surface to volume ratio. In addition to that ability to create three-dimensional multi-component structures of nanoparticles also allows a great degree of flexibility to design drug delivery systems that may fulfil several desired properties such as the ability to overcome biological barriers, the ability to deliver hydrophobic, poorly water-soluble molecules and potential ability to selectively target these medicines to preferred site in the body.

#### **1. Biological barrier to drug delivery:**

Many biological barriers exist for drugs to reach their appropriate disease sites. It is necessary for oral drugs to have high stability in gastro-intestinal tract and the ability to permeate through intestinal epithelium to give high systemic bioavailability (7).

Similarly, skin, nasal and pulmonary drug delivery needs efficient transport of drug across epithelium. While most new drug development for small molecules is focused on oral delivery with drug chemistry directed towards good oral absorption, intravenous (IV) for efficient delivery of drugs like peptides, proteins, larger molecules and polynucleotides. Drug in blood circulation needs to reduce several barriers to reach to their targets. The blood brain barrier restricts the diffusion of hydrophobic molecules into the CSF and major obstacle for CNS and brain disorders. Many novel based nanoparticulate systems are under development like liposomes, nanosphere and cationic albumin nanoparticles are under development to cross blood brain barrier (8)

#### **2. Delivery of hydrophobic substances**

The safe and efficient delivery of hydrophobic therapeutic compounds was always found to be serious hurdle in the pharmaceutical industry. The formulation of hydrophobic drugs requires toxic surfactants and solvent such as Tween and cremophor, which then impairs drug distribution and side effects associated with it. Example, Taxol is the conventional formulation of hydrophobic drug paclitaxel contains high concentration of Cremophor-EL, a solvent associated with significant toxicities with hypersensitivity, anaphylactic reaction and peripheral neuropathy (9,10). Cremophor can also sequester paclitaxel in micelles which prolongs systemic exposure and increase in drug toxicity (11). Polysorbate is another commonly used solvent for hydrophobic drugs which can induce hypersensitivity reaction.

#### **3. Desire for targeting**

Structures of nanoparticles allow the incorporation of various targeting moieties to increase drug delivery to the target sites to low off-target organ toxicities and to accelerate cellular uptake of therapeutic agents (12). Most active targeting moieties of nanoparticles are biologics including peptides, proteins, ligands for receptors and antibodies. The nanoparticles carrying ligands of monoclonal antibodies targeted to the surface receptor overexpressed by cancer cells such as transferrin receptors, the folate receptors and EGFR can increase cellular internalization of agents through endocytosis and improve efficacy of systemic anti-cancer therapy (13,14)

## challenges face by nanoparticles: -

### REGULATORY CHALLENGES: -

The complexity of nanoparticles as multi-component three dimensional constructs requires careful design and engineering, detailed orthogonal analysis methods, and reproducible scale-up and manufacturing process to achieve a consistent product with the intended physicochemical characteristics, biological behaviours, and pharmacological profiles. The safety and efficacy of nanomedicines can be influenced by minor variations in multiple parameters and need to be carefully examined in preclinical and clinical studies, particularly in context of the biodistribution, targeting to intended sites, and potential immune toxicities (15). Due to the complexity and large potential diversity of nanoparticle-based products, it may seem apparent that the regulatory pathway for nanomedicines may face several hurdles (16). Currently, the FDA, EMA, and other regulatory agencies examine each new nanoparticle-based drug on a product-by-product basis. There is generally a lack of standards in the examination of nanomedicines as a unique category of therapeutic agents (17,18). In the recently era of generic nanomedicines, both generic drug manufacturers and drug regulators will be faced with major challenges in defining the studies required to demonstrate that the generic nanomedicine is bioequivalent to the innovator and that the products have the same physicochemical properties and are safe and effective. For example, there have been several unsuccessful attempts in the marketplace to copy the nab-paclitaxel formulation. These attempted formulations which the manufacturers claimed were copies of approved nab-paclitaxel, when tested, failed to reproduce size distribution, stability, potency, or physicochemical characteristics of nab-paclitaxel, which could potentially lead to undesirable and unsafe effects. In one case, the claimed copy had high endotoxin and residual solvent levels greatly exceeding recognized safety limits (19). There was also a wide size distribution with a large portion of particles over 200 nm, resulting in significant drug loss after filtration through a 220-nm sterile filter. The reconstituted nanoparticles also displayed poor stability under accelerated conditions of 40°C and formed large precipitates and aggregates of several micrometres in size within 24 h, unlike nab-paclitaxel which was stable under these conditions. Such tests suggest that fundamental differences in the behaviour of these formulations result from differences in composition and manufacturing. These examples also illustrate how generic drug manufacturers and health authorities are going to face unique challenges in the development, regulation and approval of nanomedicines that claim to be equivalent to the innovator products. These issues will likely be no less challenging than the difficulties surrounding the development and regulation of biosimilar drug products (20). In the European Union, the nanomedicine market is composed by nanoparticles, liposomes, nanocrystals, nano emulsions, polymeric-protein conjugates, and nanocomplexes (21). Challenge is the development of a framework for the evaluation of the follow-on nanomedicines at the time of reference medicine patent expiration (22). Next-generation nanomedicines and nanosimilars:EU regulators' initiatives relating to the development and evaluation of nanomedicines. Nanomedicine 8, 849–856. FDA has recently started to consider relevant approval standards for generic copies of medicine. Several liposomal type products from novel category such as those containing drugs amphotericin and doxorubicin had gone off patent. The product should necessitate a different standards of “equivalence” testing what is required for standard drugs. In the absence of information related to composition, three-dimensional configuration of components and critical parameters which are essential for function of nanomedicine products they are at risk of “generic” version approved conventional controls, bioequivalence, chemistry and manufacturing for generic drug approvals might result in substandard products. Equivalence in formulation or bioequivalence not surely represent the function of the nanomedicine at the site of action as it was predicted for most standard formulation. Hence it is essential that complete physicochemical understanding of complex nanomedicine products and identification of critical parameters that effects their functions be conducted for potential nanomedicine in future. Certainly, the FDA has just now issued guidance for liposomal doxorubicin with approach (23). Nanomedicines are complicated multicomponent and multifunctional drug delivery system. It is necessary for regulatory agencies to develop lists of tests and approval process which will cover whole range of particle characterization, pharmacology and toxicology issues. The complete behaviour, PK and safety profile of nanoparticles is combined results of interplay of all nanoparticle components, parameters and spatial composition. There is no sufficient connection between nanoparticle physicochemical properties and its pharmacokinetics and safety. The conventional animal models were insufficient to correctly extrapolate and predict nanoparticle biotoxicity and toxicity in humans.

It is relevant when comparing novel nanoparticle-based drug with conventional formulations and when evaluating a generic version of an approved nanomedicine versus innovator product. The current regulatory framework has been proved to be enough until now. A first generation of nanomedicines got access to the market in a regulated environment, most of them before a real awareness existed about a number of issues related to safety concerns of nanomaterials and with demonstrative relative success in terms of clinical safety assessment and safe mainly in oncology area. This fact showed that how robust, flexible and safe the recent regulatory environment on comparison with innovative products. The materials such as phospholipids or biodegradable polymer are of completely different nature from anticipated for materials that will be produced in near future from the research pipeline. Carbon nanotubes, quantum dots and other non-biodegradable and potentially harmful materials should be given. As in already existing nano-pharmaceutical, when administered for same or new therapeutic formulations making use of different administration routes e.g pulmonary should not be waived of a full assessment of their differential toxicology impact, particularly in the pro-inflammatory area.

The way to move forward is not different from that regulator have done in past 15-20 years. Building new regulatory guidance with the consultation and participation of research institutes from academia and industry will promote a better regulatory environment in a stepwise transparent manner, as has been the case time and time again in Europe and USA. This can use a very successful European regulatory model now built into the genetic code of the European and national agencies for medicinal products, incorporating ICH-like approaches, closer and closer to a permanent global co-operation between the EU and USA, as well Japan and number of non-ICH associated.

## **PHARMACOLOGY AND SAFETY, TOXICOLOGICAL CHALLENGES OF NANOMEDICINES**

Because the pharmacological and safety profiles of nanomedicines are influenced by cumulative contribution of physicochemical characteristics, subtle changes in composition arising from all deviations in manufacturing process could result in substantial changes in pharmacology and toxicity of medicines.

### **PHARMACOLOGY ISSUES RELATED TO NANOMEDICINES**

It is important for a successful nanomedicine to obtain the desired pharmacological profile and PK profile suitable for the intended indication. However, several challenges are associated with trying to apply the standard criteria of small molecules PK to the PK of nanomedicines. Usually, only a small fraction of the administered drug reaches its intended location. Usually only a small fraction of administered drug reaches its intended location and because of this, the standard approach of determining PK in blood or plasma as a sole measure of in-vivo behaviour of nanoparticles may be inherently flawed. While small molecules of drugs may diffuse more readily through "biological barriers" and hence blood level may be somewhat in equilibrium and related to achievable target tissues levels, applying this logic for larger macromolecular complexes and nanomedicines cannot be assumed to be correct. It is well found, that very little compositional differences may affect the biodistribution of nanoparticles or nanomedicines.

The pharmacokinetics and biodistribution of active drug within the nanomedicine may be affected by different factors. Physicochemical properties of nanoparticle like size, shapes can alter the pharmacokinetic variation compared with conventional small molecules approaches. Nanomedicines may allow for novel routes of delivery including oral, pulmonary and dermal administration which requires high bioavailability through biological barriers. The pharmacokinetics of both nanomedicines as whole as compared with just "free" drug may be highly relevant (24,25,26).

### **TOXICOLOGICAL AND SAFETY ISSUES RELATED SILVER NANOMEDICINES:**

It is a general observation of the whole scientific community that reasonably less information is available about the hazard associated with their use. One of those studies include, 28-day systemic toxicity effect of 20–100 nm-sized AgNPs on rats using intravenous administration. The AgNPs showed the severe increase in the spleen size with increased population of T and B cells population. The histopathological study of the affected tissues showed the accumulation of AgNPs in spleen, liver, lymph nodes, and other organs. The clinical chemistry revealed increased phosphatase, alanine transaminase, and aspartate transaminase, which all signified the liver damage (27). AgNPs can enter in the body via ingestion and it get absorbed from

stomach duct and enters the portal vein. Later, it enters the liver and thus exerts the toxic effect on liver cells. To find the details of live damage, Xia et al. and Hussain et al. have attempted to find nanoparticles toxicity effects on mouse liver cells. In this they observed that the irregular cell shape and their cleavage because of the action of nanoparticles (28,29). Metal nanoparticles in general and AgNPs have also been used as antimicrobial coating to prevent the infection in bone implants. But it is also required to study whether the same nanoparticles are safe for patient's tissue where the bone is implanted. In this context, Pauksch et al. (109) investigated the influence of AgNPs on bone cell metabolism (30). For this study, they exposed the primary human mesenchymal stem cells (MSC) and osteoblasts (OB) with the AgNPs. The study concluded with the remarks that after 21-days exposure, the AgNPs cause time- and dose-dependent impairment of MSC and OB at the concentration of 10: g/g. Therefore, AgNPs below 10: g/g have the capacity to be used for therapeutic purposes but above this limit it will be cytotoxic to bone tissues (31). An interesting study conducted by Levard et al., revealed that the toxicity of AgNPs was shown to decrease by their sulfidation (32). The authors claimed that AgNPs readily reacts with sulfide to form Ag (0)/Ag<sub>2</sub>S core-shell particles. This sulfidation has shown to decrease nanotoxicity of AgNPs against four DOI 10.1002/jps.24001 Dos Santos et al., JOURNAL OF PHARMACEUTICAL SCIENCES 8 MINIREVIEW types of aquatic and terrestrial eukaryotic organisms, namely, zebrafish (*Danio rerio*), killifish (*Fundulus heteroclitus*), Nematode worm (*Caenorhabditis elegans*), and the aquatic plant "least duckweed" (*Lemna minuta*). The main reason for this decreased toxicity was claimed to be the decrease in Ag<sup>+</sup> concentration in the suspension medium. The lower release of Ag<sup>+</sup> was because of the lower solubility of Ag<sub>2</sub>S relative to Ag (Ag<sub>0</sub>). The study further concluded that even chloride ions in exposure medium can also affect the toxicity of AgNPs (33).

### Conclusions:

First generation nanomedicines got access to number of first-generation nanomedicines but there are number of safety concerns of nanomedicines. The regulatory environments robust, safe and flexible about the innovative product. It is necessary to give attention towards the safe and hazards regarding use of the nanomedicines such as nanoparticles. It is necessary to complete study the pharmacokinetics and toxicological study of such nanomedicines.

### References: -

1. Sovan Lal Pal, Utpal Jana, P. K. Manna, G. P. Mohanta, R. Manavalan Nanoparticle: An overview of preparation and characterization Journal of Applied Pharmaceutical Science 01 (06); 2011: 228-234.
2. Lademann J., Weigmann H., Rickmeyer C., Barthelmes H., Schaelmes H., Mueller G., Sterry W. Penetration of Titanium Dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacology and Applied Skin Physiology. 1999; 12: 247- 256).
3. Hett A. Nanotechnology: small matters, many unknown. 2004.
4. Lee KP., Kelly DP., Oneal FO., Kennedy GL. Lung response to ultrafine kertar aramid synthetic fibrils following 2-year inhalation exposure in rats. Findam Appl Toxicol. 1998;11:1-20.
5. Jani P., Halbert GW., Langridge J., Florence AT. Nanoparticles uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. J Pharm Pharmacol.1990;42(12) :812-826.
6. Emerich DF, Thanos CG. The pinpoint promise of nanoparticlebased drug delivery and molecular diagnosis. Biomol Eng. 2006;23(4):171-84.
7. Alonso MJ. Nanomedicines for overcoming biological barriers. Biomed Pharmacother Biomed Pharmacother. 2004;58(3):168-72.
8. Silva GA. Nanotechnology approaches to crossing the blood-brain barrier and drug delivery to the CNS. BMC Neurosci.2008;9 Suppl 3:S4.
9. Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer. 2001;37(13):1590-8.
10. Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, et al. Hypersensitivity reactions from taxol. J ClinOncol. 1990;8(7):1263-8.
11. Van Zuylen L, Verweij J, Sparreboom A. Role of formulation vehicles in taxane pharmacology. Invest New Drugs. 2001;19 (2):125-41.
12. Steele RH, Limaye S, Cleland B, Chow J, Suranyi MG. Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. Nephrology (Carlton).2005;10(3):317-20.

13. Gaumet M, Vargas A, Gurny R, Delie F. Nanoparticles for drug delivery: the need for precision in reporting particle size parameters. *Eur J Pharm Biopharm.* 2008;69(1):1–9.
14. Douglas SJ, Davis SS, Illum L. Nanoparticles in drug delivery. *Crit Rev Ther Drug Carrier Syst.* 1987;3(3):233–61.
15. Desai Neil, Challenges in Development of Nanoparticle-Based Therapeutics the AAPS Journal, Vol. 14, No. 2, June 2012.
16. FDA Nanotechnology Task Force. Nanotechnology Task Force Report 2007. 2007. <http://www.fda.gov/scienceresearch/specialtopics/nanotechnology/nanotechnologytaskforcereport2007/default.htm>.)
17. EMA. 1st International Workshop on Nanomedicines 2010 Summary Report. 2010. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/10/WC500098380.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500098380.pdf).
18. FDA. Draft Guidance: considering whether an FDA-Regulated product involves the application of nanotechnology.2011. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>).
19. Desai Neil, Challenges in Development of Nanoparticle-Based Therapeutics The AAPS Journal, Vol. 14, No. 2, June 2012,Page No.291)
20. FDA. Draft Guidance on Doxorubicin Hydrochloride. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>.)
21. Hafner, A., Lovrić, J., Lakoš, G. P., and Pepi'c, I. (2014). Nanotherapeutics in theEU: an overview on current state and future directions. *Int. J. Nanomed.* 9,1005–1023.
22. Ehmann, F., Sakai-Kato. K., Duncan, R., Hernán Pérez de la Ossa D., Pita, R.,Vidal, J. M., et al. (2013).
23. FDA. Draft Guidance on Doxorubicin Hydrochloride. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM199635.pdf>.
24. Emerich DF, Thanos CG. The pinpoint promise of nanoparticlebased drug delivery and molecular diagnosis. *Biomol Eng.*2006;23(4):171–84.
25. FDA. Draft Guidance on Doxorubicin Hydrochloride. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory>.
26. Zamboni WC. Concept and clinical evaluation of carrier-mediated anticancer agents. *Oncologist.* 2008;13(3):248–60.
27. De-Jong WH, Van Der Ven LTM, Sleijffers A, Park MVDZ, Jansen EHJM, Loveren HV, Vandebriel RJ. 2013. Systemic and immunotoxicity of silver nanoparticles in an intravenous 28 days repeated dose toxicity study in rats. *Biomaterials* 34:8333–8343.
28. Xia T, Kovochich M, Brant J, Hotze M, Sempf J, Oberley T, Sioutas C, Yeh JI, Wiesner MR, Nel AE. 2006. Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. *Nano Lett* 8:1794– 1807. 96.
29. Hussain SM, Javorina MK, Schrand AM, Duhart HM, Ali SF, Schlager JJ. 2006. The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. *Toxicol Sci* 92:456–463.
30. Pauksch L, Hartmann S, Rohnke M, Szalay G, Alt V, Schnettler R, Lips KS. 2014. Biocompatibility of silver nanoparticles and silver ions in primary human mesenchymal stem cells and osteoblasts. *Acta Biomaterialia* 10:439–449.
31. Silva T, Pokhrel LR, Dubey B, Tolaymat TM, Maier KJ, Liud X. 2014. Particle size, surface charge and concentration dependent ecotoxicity of three organo-coated silver nanoparticles: Comparison between general linear model-predicted and observed toxicity. *Sci Total Environ* 468–469:968–976.
32. Levard C, Hotze EM, Colman BP, Dale AL, Truong L, Yang XY, Bone AJ, Brown GE Jr, Tanguay RL, Di Giulio RT, Bernhardt ES, Meyer JN, Wiesner MR, Lowry GV. 2013. Sulfidation of silver nanoparticles: Natural antidote to their toxicity. *Environ Sci Technol* 47:13440– 13448.
33. Pokhrel LR, Dubey B, Scheuerman PR. 2013. Impacts of select organic ligands on the colloidal stability, dissolution dynamics, and toxicity of silver nanoparticles. *Environ Sci Technol* 47:12877– 12885.