GUIDELINES FOR EVALUATION OF NANOPHARMACEUTICALS IN INDIA

Jointly Prepared by:
Department of Biotechnology, GoI
Indian Society of Nanomedicine

Guidelines for Evaluation of Nanopharmaceuticals in India

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Indian Society of Nanomedicine (ISNM)

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1. Abbreviations

ADME: Absorption, Distribution, Metabolism, Excretion

API: Active Pharmaceutical Ingredient

AUC: Area Under Curve

CDSCO: Central Drug Standard Control Organization

D & C Act: Drugs and Cosmetics Act, 1940

D & C Rules: Drugs and Cosmetics Rules, 1945

DCG(I): Drugs Controller General (India)

DLS: Dynamic Light Scattering

DLT: Dose Limiting Toxicities

EU: European Union

FDA: United States Food and Drug Administration

GLP: Good Laboratory Practice

HED: Human Equivalent Dose

ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IND: Investigational New Drug

MTD: Maximum Tolerated Dose

NCE: New Chemical Entity

OECD: Organization for Economic Co-operation and Development

PEG: Polyethylene glycol

PIM: Pulmonary Intravascular Macrophage

PK/PD: Pharmacokinetics/ Pharmacodynamics

PLA: Polylactic acid

PLGA: Poly lactic-co-glycolic acid

RES: Reticulo-Endothelial System

SoPs: Standard Operating procedures

2. Introduction

Nanoscience is the study of materials which are in nanoscale range. Conversion of any material in nanoscale results in alteration of its physicochemical, biological, mechanical, optical, electronic, etc. properties. These newly acquired (novel) properties of the materials due to conversion into a nanoscale can be utilized for different useful activities. Thus, it is an enabling technology, relevant for diverse sectors, such as chemicals, consumer products, health, energy, various other industries and the environment. The use of this technology is increasing exponentially in the pharmaceutical sector.

Nanopharmaceutical is an emerging field that combines nanotechnology with pharmaceutical and biomedical science with the goal of targeted drug delivery which may improve efficacy and safety profile. The concept of 5Rs: 'right target/efficacy', 'right tissue/exposure', 'right patients', 'right safety', and 'right commercial potential' as postulated by Cook D et al (2014) may help in successful development of nanopharmaceuticals.

Alteration of the substance into nanoscale associated with drug delivery may also significantly alter the pharmacokinetic, biodistribution and toxicokinetic parameters of the conventional/traditional drugs raising various concerns related to quality, safety and efficacy of the nanopharmaceutical products.

Efforts have been made for developing regulatory guidelines for nanopharmaceuticals in different countries. Since, there are no specific guidelines for development and evaluation of nanopharmaceuticals in India, it has been felt necessary to formulate comprehensive guidelines focusing on the quality, safety and efficacy of nanopharmaceutical for therapeutic use. These guidelines are intended to provide transparent, consistent and predictable regulatory pathways for nanopharmaceuticals in India.

Nanotechnology is an enabling technology for various incremental and disruptive innovations. Application of this technology has tremendous potential in pharmaceutical industry where it can improve the therapeutic efficacy with targeted delivery of the drug to the site of disease. There may be a concurrent reduction of the dose of the drug with lowering of toxicity.

However, the nanocarriers/ nanopharmaceuticals have a higher tendency of tissue sequestration which alters the PK/PD of the conventional/traditional drug which is loaded in the nanosystems. This may lead to additional risk of tissue based toxicity with low serum concentration.

Considering the complexity of the nanomaterial behavior in the biological environment certain degree of uncertainty may be inherent to such system.

These guidelines have the aim to ensure the quality, safety and efficacy as well as encourage the commercialization of nanotechnology based innovation with high benefit and low risk ratio.

There are no uniform internationally acceptable guidelines for nanopharmaceuticals.. The usual concensus for evaluation of quality, safety and efficacy of nanotechnology based products is to have a ‘case by case approach’ taking into consideration of the physical, chemical and biological characteristics of the nanoparticle used and the product, route of administration, the indication for which the product is intended to be used and other related aspects.

3. Scope of the Guidelines

These guidelines apply to the nanopharmaceuticals in the form of finished formulation as well as API of a new molecule or an already approved molecule with altered dimensions, properties or phenomenon associated with the application of nanotechnology intended to be used for diagnosis, treatment, mitigation or prevention of diseases in human.

These guidelines do not apply to the conventional drug with incidental presence of nanoparticles or drug products containing microorganisms or proteins which are naturally present in the nanoscale range.

These are also not applicable to medical devices, *in-vitro* diagnostics, tissue engineered product using nanotechnology and nano particle modified cell based therapy.

4. General Considerations of the Guidelines

Safety studies should be conducted as per general guidelines specified in Schedule Y of Drugs and Cosmetics Rules, 1945. However, in case any specific study is not included in the Schedule Y, the principles of ICH guidelines for pharmaceuticals or OECD guidelines for chemicals may be followed. This document may also serve as useful guidelines for manufacturers, importers of nanopharmaceuticals and other stakeholders involved in research and development of nanopharmaceuticals.

These guidelines are in conformity with the provisions of Drugs and Cosmetics Act, 1940 and Rules,1945as amended from time to time, with certainspecific aspects of quality, safety and efficacy applicable to nanopharmaceuticals.

These guidelines have evolved with consideration of the following documents

Schedule Y of D & C Rules, 1945

Guidance for Industry Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, 2014

Second Regulatory Review on Nanopharmaceuticals, European Union, 2012

Regulatory Aspects of the Nanopharmaceutical in the EU, 2017

In these guidelines, the nanopharmaceuticals have been classified according to their degradability, organicity, function and status of approval. Accordingly, the safety and efficacy data requirements have been described.

Specific scientific evidence required for approval of any nanopharmaceutical and the strategies for pharmacovigilance of such products have also been incorporated in these guidelines.

Each application should be considered on its own merit of the data submitted using scientific judgement and logical argument.

For new generation of nanomaterials, development of methods for safety testing and risk assessment, and a better availability of quality data on nanomaterials for regulatory purposes are essential.

5 Nanopharmaceuticals: Definition and Categorization

5.1 Definition

A nanopharmaceutical is defined as a pharmaceutical preparation containing nanomaterials intended for internal or external application on the body for the purpose of therapeutics, diagnostics and any health benefit.

These are the products that contain materials in the size scale range of 1 to 100nm in at least in one dimension. However, if the particle size is >100nm and <1000 nm, it will also fall within the definition, provided it has altered or different pharmaceutical characteristics associated with application of nanotechnology compared with API[1,2].

The size distribution of the nanopharmaceutical: Not less than 1% beyond the nano particle range 1 to 1000 nm is permitted. Further, the particles should be in the claimed nano size range. At any time point during the claimed stability period, the particle size range should not decline/ alter >10 %.

5.2 Categorization

Nanopharmaceuticals may be categorized depending on the nature and functions of the nanomaterial as well as the approval status of the nanomaterial and the conventional non nano form of the drug. Accordingly, nanopharmaceuticals are categorized as under-

I According to degradability of nanomaterial

The basic difference between biodegradable and non-biodegradable is that biodegradable items decompose or break down naturally. Non-biodegradable items do not.

1. Biodegradable

   Biodegradable nanoparticles have been used frequently as drug delivery vehicles due to its improved bioavailability, better encapsulation, control release and reduction of toxic potential. Examples of biodegradable nanoparticles are PEG, albumin, PLA, PLGA, chitosan, gelatin, polycaprolactone, poly-alkyl-cyanoacrylates, etc.

2. Nonbiodegradable

   Nonbiodegradable nanoparticles are relatively less used in pharmaceutical products (though these systems are more commonly used in cosmeceuticals). Almost all non-biodegradable nanoparticles have potential to cause

cytotoxic effects of particle due to long sequestration without significant degradation and excretion. Some examples of non biodegradable nanoparticles are titanium oxide, iron oxide, and metals such as gold, silver, platinum, etc.

II According to nature of nanomaterial

Nanomaterial may be organic or inorganic in nature. The composition and fabrication methods will determine the properties of nanoparticles. It may also be multicomponent nanoparticle.

1. Organic Nanoparticles

   These are the nanomaterials or nanoparticles composed of organic compounds like lipids, proteins, carbohydrates. They have been primarily developed for drug delivery to reduce or overcome the risk of toxicity due to the intracellular and/or tissue sequestration there by increased bioavilability at the site of action.

   Examples of organic nanoparticles used in pharmaceutical formulations are liposome, albumin, polymer–protein, or polymer–drug conjugates. The molecules used for the fabrication of the organic nanoparticles are usually biodegradable which make them the most appealing systems for drug

delivery and biomedical applications. However, they may have limited chemical and mechanical stability.

2. Inorganic Nanoparticles

   The inorganic nanoparticles are generally composed of an inorganic component. Depending on the composition, shape, size, surface property and crystallinity, these nanoparticles may have a number of tunable physical properties, such as optical absorption (e.g., metallic nanoparticles), fluorescence (semiconductor quantum dots), and magnetism (e.g., iron oxides).

   Inorganic nanoparticles are more stable than organic nanostructures.

   Inorganic nanoparticles may have several advantages over organic ones. They are easier to prepare with a defined size and a very narrow size distribution. More interestingly, they often exhibit multiple useful functions, for example, as heat generation and contrast function for imaging. However, most of the inorganic nanoparticles may not be biodegradable with a potential for long term sequestration and toxicity.

3. Multicomponent nanoparticles

   These are the nanoparticles composed of two or more different materials. The integration of multiple materials in one structure offers opportunities for

enhanced physical and chemical properties and for targeting drug delivery along with many other useful functions within a single nanostructure. However, stabilization of multiple materials within the nanostructure is challenging. For example, magnetic liposomes containing an aqueous dispersion of iron oxide incorporated on the lipid surface.

III According to nanoform of the ingredient

1. Nanocarriers loaded with Active Pharmaceutical Ingredient (API)

   A nanocarrier is a nanomaterial being used as a transport module for another substance like a drug. Common examples include micelles, polymer conjugates, polymeric nanoparticles, carbon-based materials (carbon nanotubes), lipid-based carriers (liposomes, micelles), dendrimers, gold nanoparticles (nanoshells, nanocages), etc.

   Examples of drugs loaded with nanocarriers are liposomal amphotericin B, albumin bound paclitaxel, liposomal doxorubicin, etc.

   Because of their small size, nanocarriers can deliver drugs to otherwise inaccessible sites around the body. These also have the advantage of targeted drug delivery to specific sites. In the area of cancer nanomedicine the nanoparticles are designed to exploit the Enhanced Permeability and

Retention (EPR) effect in the tumor tissue which is particularly helpful in enhancing therapeutic index and lowering of off target toxicity.

2. APIs converted to nano form

   Some of the conventional/traditional drugs may be converted into nanocrystals, thereby increasing their potential for improved dissolution and bioavailability. Examples are sirolimus, tacrolimus, fenofibrate, cyclosporin, griseofulvin, etc.

IV According to the approval status of drug and nanomaterial

Based on the approval status of drug and the nanomaterial, the requirements of quality, safety and efficacy data may vary. All nanopharmaceutical preparations will be treated as Investigational New Drug (IND) permanently. They may be subject to differential scrutiny according to the following categories:

1. The drug is a new molecular entity and the nanocarrier is also new and not approved in the country. Such product would be treated as Investigational New Drug (IND) and the general requirement for quality, safety and efficacy will be required to be undertaken as specified in Schedule Y of Drugs &

Cosmetics Rules, 1945.

2. The drug is a New Molecular Entity but the nanocarrier system is already used for other nanopharmaceutical. Such product should be considered as an Investigational New Drug (IND). Such formulation would be treated as Investigational New Drug (IND) and the general requirement for quality, safety and efficacy will be same as specified in Schedule Y of D & C Rules, 1945. Independent studies for the carrier, in such cases, may not be required.
3. Conventional/ traditional form of the drug is approved in well regulated countries and/or India but the nanocarrier system is new and not approved in the any country. For this category of nanoformulation product, the entire requirements of safety and efficacy data as specified in Schedule Y for Investigational New Drug (IND), may not be required. However for evidence of safety and efficacy of the product should be documented.
4. Conventional/ traditional form of the drug and the nanocarrier system both are approved in well regulated countries and/or India. It should be subjected to abbreviated studies.

   Note: It is to be noted that the requirements for quality, safety and efficacy of any nanopharmaceutical should be decided depending upon factors like physicochemical nature, biological

nature, functions, bioavailability and biodistribution, possible interaction with biological system or exogenously administered medications, therapeutic indication for which the product is intended to be used, route of administration, intended duration of therapy, age of the patient, background data available on the Active Pharmaceutical Ingredient (API) and nanocarrier, the regulatory status in other countries, etc[3].

6 Scientific Rationality of making the Nanopharmaceutical preparation

The rationality of making a nanopharmaceutical should be specified with reference to its added advantage and possible disadvantage in comparison to conventional/traditional drug. The nanocarriers and its waste disposal may have adverse impact on the environment and ecosystem. While justifying the rationality, the known and perceived adverse impact on environment should also be taken into consideration[4].

The following aspects should be specifically addressed for justification of a nanopharmaceutical:

- Basis of making the claim of improved safety, efficacy, reduction in toxicity profile, reduction in dose, frequency of administration of the nanopharmaceutical, improved patient compliance, lower cost or any other benefit over conventional, traditional drug.
- Addressing any issue arising out of significantly different pharmacokinetics (PK) and/or pharmacodynamics (PD) than that of the conventional/ traditional drug.
- Addressing the issue of specific adverse effect/ property of the conventional/ traditional drug, if any, such as teratogenic potential,

Central Nervous System (CNS) side effects, cardiovascular side effects, QTc prolongation, ophthalmic side effects, etc.

7 Specific Considerations for Evaluation of Nanopharmaceuticals *in the context of Schedule Y of Drugs and Cosmetics Rules, 1945*

These guidelines have been developed in line with the provisions of Schedule Y of Drugs and Cosmetics Rules, 1945, with specific requirements for nanopharmaceuticals wherever considered necessary. While Schedule Y specifies the general requirements and guidelines for manufacture or import of new drugs or to undertake clinical trial, this document also provides guidance for specific requirements of chemical and pharmaceutical information, non clinical data and clinical data relevant for any product developed based on nanotechnology.General requirements as specified in Schedule Y will be applicable for any new drug whether nanotechnology based or not. However, because of inherent complexity involved in nanotechnology based products, a ‘case by case basis’ approach should be adopted for evaluating their quality, safety and efficacy.

8 Stability Testing of Nanopharmaceutical

The stability testing of nanopharmaceuticals should be done according to the general requirements specified in Appendix IX of Schedule Y of Drugs and Cosmetics Rules, 1945.

Stability testing of developmental nanopharmaceuticals must be done extensively, and systematically. As the drug is loaded in the nanocarrier, the stability of the drug in an active form should be tested from time to time. It should focus on functionality, integrity, size of nanoparticles, carrier material stability, drug stability, degradation products, etc. It should be ensured that the selected stability storage conditions are relevant for the specific product and studies are done in intended market packs[5]. In addition, parameters specific to nanoparticle-based systems need to be quantified at different time intervals such as size and size distribution commonly measured using Dynamic Light Scattering (DLS), surface characterization (zeta potential, functionality, surface chemistry). In case of surface coating for example with PEG, the PEG layer thickness should be measured by small-angle X-ray diffraction. The morphology of the nanoproduct should be determined by microscopy. The residual drug in the system with reference to initial drug loading and drug encapsulation should be assessed. Characteristics specific to a subcategory of nanoparticle-based systems may need to be characterized, for example lamellarity for liposomes,

which can be evaluated using cryo-Transmission Electron Microscope (cryo-TEM). It is advisable to use multiple analytical methods that complement each other to evaluate the same parameter, for example, DLS, X-ray Diffraction and cryo-TEM can be used in parallel for the measurement of particle size.

9 Animal Pharmacology Data

Knowledge of the activity and toxicities of the free drug, the behaviour of different delivery systems, and an understanding of the influence of drug release rate on target and off-target concentrations of bioavailable drug selection of an appropriate range of nanopharmaceuticals to test. The overall principle of animal pharmacology should be according to the broad guideline specified in *Appendix IV of Schedule Y of Drugs and Cosmetics Rule, 1945.*

To evaluate nanopharmaceutical or nanomedicine efficacy, pre-clinical research should generate data sets that evaluate the properties of product behavior. Such properties include- the accumulation of the drug at the disease site, for example in case of anti cancer product its high accumulation in tumor, intra- tumoural distribution, and tumoural retention of the system. In addition, the contribution of the peripheral pharmacokinetics (or circulation) of the nanopharmaceutical should be assessed. It is likely that for any targeted delivery system, each of these features may independently contribute to potential efficacy. Based on the study results, the dominant feature can influence the choice of delivery system and desired release kinetics. Further, understanding the off-target effects is as

important as evaluating efficacy when nanopharmaceutical is being developed. The pre-clinical testing with an aim to document the translational potential should provide detailed insight into the key parameters that influence nanopharmaceutical efficacy.

The informative and translatable data sets should consider to characterize the disease site specific retention, drug release rates, and drug metabolism. It should differentiate between bioavailable/released drug and total concentrations of drug in the site of action (where applicable, for example tumour), plasma, and other key organs (e.g., liver, kidney, bone marrow, etc.). The data should help to evaluate how the plasma, off-target tissue, and disease site (target if applicable) pharmaco- kinetics are affected by repeat dosing. An effort should be made to separate the evaluation of parmacokinetics/biodistribution from efficacy/mechanism of action using nanopaharmaceuticals. The preclinical study should have a clear focus on the end clinical application (such as combination with standard-of-care) of the nanopharmaceuticals

For Brain targeted nanopharmaceutical special studies should be done to measure drug concentration in different parts of brain along with API.

10 Animal Toxicology Data

Generation of data in the area of animal toxicology for nanopharmaceuticals should follow the general guidelines as specified in *Appendix III, Schedule Y of Drugs and Cosmetics Rules, 1945*.

The toxicology studies should be conducted in the most clinically relevant animal model[6]. Toxicology studies should generally be performed in both sexes, in a rodent and non-rodent species, usually rats and dogs. In certain cases, if specific animal species are historically more predicative of toxicity for

certain drug classes (for example, primates for predication of complement-mediated toxicity of phosphorothionate oligonucleotide therapies), it should be used for study. In this context, it may be mentioned that due to species-specific target expression, in some cases only primates are relevant for toxicology studies. There may be situations where there are no nonhuman target-expressing animals. In such cases, transgenic animals expressing the target or a surrogate ligand for a similar animal target can be used to characterize toxicity profiles. For nanoparticles, uptake by the reticulo-endothelial system (RES) has been demonstrated to be an important modulator of biodistribution. In this context, the most relevant species for evaluating nanomaterial toxicology or ADME, with

regard to Reticulo-Endothelial System (RES) function, is not clear. The studies suggest that in laboratory animals (rats, mice, guinea pigs, rabbits and dog) and man, splenic macrophages and liver Kupffer cells are primarily involved in sequestration of nanoparticles, while in some larger animals (sheep, goat, cat, and pig) Pulmonary Intravascular Macrophage (PIM) are primarily involved in trapping/ sequestration.

The dosing regimen and administration route for repeat-dose toxicology studies are dictated by the intended clinical administration route and regimen, which is in turn dictated by the pharmacology of the nanopharmaceuticals.

Toxicology studies should also include the intravenous route for nanoformulations where the primary clinical administration route is not intravenous, to allow for high exposure comparison. The duration of multi-dose toxicology study is dependent upon the intended clinical dosing duration. The number of animals required for toxicology and toxicokinetic studies depends upon the study length and statistical significance of the result which in turn is dependent on variation of result. For example, the studies of up to 4 weeks in duration, 5–10 rats or 3–4 dogs per each sex per dosage group are usually sufficient.

There are some special issues which may be considered for nanopharmaceuticals. The maximum dose used in preclinical toxicology studies depends upon several factors, including the toxicity of the nanoformulation and its solubility. It is usually not reasonable to dose a nanoformulation over several g/kg, or 50 fold greater than the expected clinical exposure, based on area under the time–concentration curve (AUC). If toxicity is not observed at these high doses, then it is not necessary to escalate further. Alternatively, if the drug is only soluble or stable at mg/mL concentrations in the optimum vehicle (as is sometimes the case for nanoformulations), then the dose would be limited by this solubility and by the maximum volume that can be administered to the animal model by the clinically relevant administration route and dosing regimen. The lack of toxicity profile characterization, and an inability to identify a maximum tolerated dose (MTD) and dose limiting toxicities (DLT), either due to solubility limitations or instability at high concentrations, complicates risk analysis and the selection of a first-in-man dose. The identification of the toxic doses is generally not difficult for cytotoxic chemotherapeutic agents. However, the biologics, on the other hand, which may not demonstrate toxicity in preclinical models at reasonable doses, are often dosed to pharmacologically appropriate blood concentration, based on receptor affinity or biomarker modulation, and not MTD.

It is important to include the drug-free (or empty) nanoparticle and free drug as control groups in toxicology studies, to allow identification of particle-dependent toxicities and particle-dependent shifts in the encapsulated drug's toxicity, respectively.

The toxicity studies should comply with the norms of Good Laboratory Practice (GLP). These studies should be performed by trained and qualified staff using calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard operating procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Nanopharmaceuticals (test substances) and test systems (in-vitro or in-vivo) should be characterized and standardized. All documents belonging to each study, including its protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of 5 years after marketing of the nanopharmaceutical.

Toxicokinetic studies of the nanopharmaceutical (generation of ADME data either as an integral component of the conduct of non-clinical toxicity studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include

obtaining data to relate the nanoparticle sequestration based organ exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in nonclinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies. Apart from the drug, the metabolism and excretion of the carrier should be evaluated in cases of nanopharmaceutical. If toxicity is observed with a nanopharmaceutical, analysis of results should indicate that the occurrence of toxicity is unrelated or correlated with API and/or nanocarrier.

An important benefit of some nanopharmaceutical is the ability to formulate a drug without using dose-limiting toxic excipients present in currently marketed formulations, thus improving tolerability and enabling administration of more drug to patients. For example, higher doses of paclitaxel can be administered to patients using nanoparticle based albumin bound paclitaxel because this formulation avoids the use of cremophor needed to formulate conventional paclitaxel formulation. While not considered to be the major focus for many nanopharmaceutical product development, such solubilization benefits can be considerably cost-effective. Moreover, by achieving the ‘right safety’ profile, this approach can make a significant difference to the patients and the clinical

outcome, as the maximum tolerated dose of the active agent can be increased by avoiding the tolerability problems caused by the solubilizing surfactants.

In cases where the nanopharmaceutical does not show any clinically significant pharmacokinetics difference than API and has no difference in biodistribution, exemption of some toxicity studies may be given on the basis of 'case by case approach'.

11 Clinical Trial Data

The general requirements of clinical data and guidelines as specified in Schedule Y of Drugs and Cosmetics Rules, 1945 apply to the nanopharmaceutical also. However, nanopharmaceuticals should be demonstrated clinically through appropriate design, patient selection hypothesis and biomarkers to exploit the increased permeability and retention of drug. This is due to modification in pharmacokinetics and tissue distribution of the nanopharmaceutical to improve its delivery to the site of action. Clinical development of a nanopharmaceutical using a well characterized drug delivery system will be successful if the development plan is designed based on clear understanding of parameters driving the efficacy of the free drug and the *in vivo* behavior of the delivery system. Majority of approved nanopharmaceuticals, especially oncology products, have been designed clinically to exploit the increased permeability and retention effect. Such effect may minimize the peak concentration of free drug while increasing the overall bioavailability of the drug, providing prolong exposure of the drug at the site of action. At times, the development of a nanopharmaceutical may fail to achieve the clinical end point in terms of lack of adequate level of efficacy or increased toxicity due to multiple reasons. Appropriate design of clinical trials based on proper understanding of accumulation, retention, toxicity and efficacy profile of the agent and correlation

between the *in vivo* behavior and the delivery system is of paramount importance for successful assessment of clinical profile of the drug. In general, clinical trials should be conducted in stages. However, depending on the status of the Active Pharmaceutical Ingredient (API), whether it is an New Chemical Entity (NCE) or an approved drug molecule and the nano carrier, clinical trial of appropriate phase may be conducted on a 'case by case approach' basis.

The selection of starting dose for clinical trial for nanotechnology based drug is estimated in a similar fashion to conventional/ traditional drugs. The clinical starting dose may be determined by dividing the estimated human equivalent dose (HED) of the rodent, maximum tolerated dose (MTD) by a predetermined safety factor. The HED for small molecule cancer drugs is typically determined by surface area (/m2) scaling of the rodent MTD, or the non-rodent MTD if 1/10th the rodent MTD is found to be toxic to the non-rodent species. In nanopharmaceuticals there may be variation in safety limits.

12 Information Required for Evaluation of Nanopharmaceuticals

As already mentioned, the information required for nanopharmaceuticals should be decided on 'case by case approach' basis. However, in general, the following data should be submitted to the regulatory authority along with the application to conduct clinical trials and manufacture of nanopharmaceuticals for marketing in India.

A. Introduction a. A brief description of the nanopharmaceutical b. Indication for which it is intended to be used c. Category to which it belongs (refer to cause 5.1) d. Justification for developing nanopharmaceutical
B. Chemical and pharmaceutical information a. Information on the ingredients i. Drug information (Generic Name, Chemical Name, INN) ii. Information on nanomaerial used, excipients/ inactive ingredients iii. Brief description and rationality of the nanopharmaceutical (Refer to clause 6)

b. Physicochemical characterization data of nanopharmaceuticals

i. Individual component (s) (e.g. API, Nanocarrier material)

ii. Chemical name and structure

iii. Empirical formula

iv. Molecular weight

v. Description of the product with

- Size distribution (poly dispersion index),
- Electronmicroscopy (for shape, size and surface texture)
- Surface charge (zeta potential)
- Process of drug loading in the nanocarrier
- Particle size
- pH (in case of liquid formulation)
- Viscosity (in case of liquid formulation)

Note: From the full list of the product's physico-chemical parameters, some of them need to be identified as critical quality attributes. They should be listed along with the product specifications to ensure quality and reproducibility from batch-to-batch. In addition, a detailed description of the manufacturing process and the process controls need to be provided.

c. Analytical data (nanocarrier/ API/ nanopharmaceutical) i. Elemental analysis ii. Mass spectrum iii. NMR spectra iv. FT-IR spectra v. UV spectra vi. Polymorphic identification
d. Complete monograph specification for the nanopharmaceutical i. Identification- defined criteria for unique identification of nanopharmaceutical ii. Identity/quantification of impurities iii. Assay iv. *In vitro/ ex vivo* release kinetics of the drug/active ingredient (as applicable) v. *In vitro/ ex vivo* degradation kinetics of nanopharmaceutical and void nanoparticle at various simulated medium
e. Analytical method validations For nanopharmaceutical

• Assay method • Impurity estimation method • Residual solvent/other volatile impurities (OVI) estimation method
f. Stability studies of nanopharmaceuticals (for details refer clause 8)
g. Data on nanopharmaceutical formulation i. Rationale (justification of the nano form) ii. Dosage form iii. Route of administration iv. Composition v. Details about loading process, chemical bonding/ conjugation between active ingredient and carrier, surface coating/ modification and functionalization vi. In process quality control check vii. Finished product specification viii. Excipient compatibility study ix. Validation of the analytical method h. Comparative evaluation of innovator product or approved Indian product, if applicable

i. Container and closure system ii. Assay iii. Content uniformity iv. Impurities v. pH i. Forced degradation stability evaluation in market intended pack at proposed storage conditions j. Packing specifications k. Process validation
C. Animal pharmacology (*for details refer clause 9*) a. Summary b. Specific pharmacological actions c. General pharmacological actions d. Essential, follow-up and supplemental safety pharmacology studies e. Pharmacokinetics: absorption, distribution; metabolism; excretion(ADME)
D. Animal toxicology (*for details refer clause 10)* a. General aspects

b. Systemic toxicity studies c. Male fertility study d. Female reproduction and developmental toxicity studies e. Local toxicity f. Allergenicity/ hypersensitivity g. Genotoxicity h. Carcinogenicity
E. Human / Clinical pharmacology (Phase I) a. Summary b. Specific pharmacological effects c. General pharmacological effects d. Pharmacokinetics- absorption, distribution, metabolism, excretion e. Pharmacodynamics-early measurement of drug activity
F. Therapeutic exploratory trials (Phase II) a. Summary b. Study report(s)
G. Therapeutic confirmatory trials (Phase III) a. Summary b. Individual study reports with listing of sites and investigators.

H. Special studies

a. Summary

b. Bio-availability / bio-equivalence.

c. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

I. Regulatory status in other countries

a. Countries where the nanopharmaceutical is

i. Marketed

ii. Approved

iii. Approved as IND

iv. Withdrawn, if any, with reasons

b.Restrictions on use, if any, in countries where marketed /approved

c. Free sale certificate or certificate of analysis, as appropriate

J. Prescribing information

a. Proposed full prescribing information

b. Drafts of labels and cartons

K. Samples and testing protocol/s

Samples of pure drug substance, nanocarrier material and finished product

(an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

13 Pharmacovigilance of Nanopharmaceuticals

Pharmacovigilance must be carried out throughout the life cycle of the nanopharmaceutical.

A detailed pharmacovigilance plan along with marketing authorization application must be submitted by the sponsors.

Pharmacovigilance plan must mention:

- Safety data from clinical development
- All the potential risks of the nanopharmaceutical
- Summary of anticipated risks
- Population at risk and
- Situations not adequately studied
- All the potential drug - drug and drug – food interactions of the nanopharmaceutical either as a separate document with pharmacovigilance plan or pharmacovigilance strategies or in the section referring to safety specifications of the document.

For nanopharmaceuticals of antimicrobials, monitoring of patterns of resistance will be an important component of pharmacovigilance. Hence, strategies for monitoring and prevention of the resistance should be mentioned in a separate

section of the document. For nanopharmaceuticals of antimicrobial agents, a signal will be generated if there is an alarming rise in the incidence of resistance to it for the particular claim proposed.

If any significant safety concerns arise during clinical trials which warrant studies in special populations such as children, elderly, pregnant women or in hepatic or renal failure patients, the protocol of such studies should be submitted along with the pharmacovigilance plan.

Protocols for comparative observational studies (cross sectional/ case control/ cohort), drug utilization study or any targeted clinical evaluation to be conducted as a part of pharmacovigilance plan should be the part of the document.

14 Conclusion

General requirements and guidelines specified for approval of manufacture/import of any new drug or to undertake clinical trial as specified in the Drugs and Cosmetics Rules, 1945 especially in Schedule Y and other applicable regulations apply to nanopharmaceuticals also. However, the requirement of special or additional tests for safety and efficacy evaluation of a particular nanopharmaceutical should be decided on a 'case by case approach' basis which will depend upon various factors such as physicochemical and biological nature, and other aspects including the background data available on the API or nanocarrier, the regulatory status in other countries, etc. Successful translation of nanopharmaceuticals from nonclinical proof of concept to clinic is challenging. Like development of any new drug, it requires effective integration of nanotechnology with chemistry, lifesciences and medicine. However, because of complexity in nanotechnology, the system necessitates a 'case by case approach' with involvement of varied expertise for successful development of nanopharmaceuticals.

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16 Glossary

✎ Biodegradable product

The product that is capable of being broken down or decomposed into innocuous products/components

✎ Nonbiodegradable product

The product that is not capable of being broken down or decomposed into innocuous products/components

✎ Organic nanomaterials

The nanomaterials that are related to or have been derived from living matter.

✎ Inorganic product

The product that is not derived from or related to living matter.

✎ Nanoscience

The study of nanomaterials

✎ Nanotechnology

The application of nanoscience to enable innovations

✎ Nanocarrier

Nanoparticle/nanomaterial carrying drug or other biomolecules