All India Institute of Medical Sciences (AIIMS), Translational Health Science and Technology Institute (THSTI), Department of Biotechnology (DBT) and Indian Society of Nanomedicine (ISNM) have jointly prepared the document, titled ‘Guidelines for Evaluation of Nanopharmaceuticals in India’ under the leadership of Dr. (Prof.) Y. K. Gupta. This was done in consultation with scientists and experts working in this area and the Indian regulators.

The comments and suggestions from all are welcome.

GUIDELINES FOR EVALUATION OF NANOPHARMACEUTICALS IN INDIA

Jointly Prepared by:

Indian Society of Nanomedicine

Translational Health Science and Technology Institute

All India Institute of Medical Sciences

Guidelines for Evaluation of Nanopharmaceuticals in India

Jointly prepared by

Indian Society of Nanomedicine (ISNM)

Translational Health Science and Technology Institute (THSTI)

All India Institute of Medical Sciences (AIIMS)

EDITORS

YK Gupta, GN Singh, AK Dinda, AK Pradhan

AIIMS CDSCO AIIMS CDSCO

December, 2017

डॉ. हर्ष वर्धन
DR. HARSH VARDHAN

सत्यमेव जयते

मंत्री
विज्ञान और प्रौद्योगिकी एवं पृथ्वी विज्ञान;
पर्यावरण, वन और जलवायु परिवर्तन
भारत सरकार
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MINISTER
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Office of the Minister for S & T and ES
DY. No. 55/17
Dt. 4/12/17

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(Dr. Harsh Vardhan)

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आचार्य रणदीप गुलेरिया
निदेशक

Prof. Randeep Guleria
MD, DM (Pulmonary Medicine), FAMS, FIMSA
Director

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I am confident that this much-needed exercise shall meet the felt need and contribute to rational and safe introduction of nanopharmaceuticals.

(Randeep Guleria)

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Executive Director

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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)	Drug Controller General (India)
DLS	Dynamic Light Scattering
DLT	Dose Limiting Toxicity
EPR	Enhanced Permeability and Retention
FDA	United States Food and Drug Administration
FT-IR	Fourier Transform Infrared
GLP	Good Laboratory Practice
HED	Human Equivalent Dose
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
MTD	Maximum Tolerated Dose
NCE	New Chemical Entity
NMR	Nuclear Magnetic Resonance
OECD	Organization for Economic Cooperation and Development
OVI	Other Volatile Impurities
PEG	Polyethylene glycol
pH	pouvoir Hydrogene
PIM	Pulmonary Intravascular Macrophage
PK	Pharmacokinetics
PD	Pharmacodynamics
PLA	Polylactic acid
PLGA	Polylactic-co-glycolic acid
RES	Reticulo Endothelial System
SOP	Standard Operating Procedure
TEM	Transmission Electron Microscope

2. Introduction

Nanoscience is the study of materials which are in nanoscale range. Conversion of any material in nanoscale results in alteration of its various properties such as physicochemical, biological, mechanical, optical and electronic properties. These newly acquired (novel) properties of the materials due to conversion into a nanoscale can be utilized for different useful activities. Thus, the nanotechnology is 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.

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 nanopharmaceuticals. The nanocarriers/ nanopharmaceuticals have a higher tendency of tissue sequestration which alters the PK/PD of the conventional/traditional drugs that are loaded in the nanosystems. This

may lead to additional risk of tissue based toxicity with low serum concentration of the drug. However, 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.

Efforts have been made for developing regulatory guidelines for nanoparmaceuticals 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 for evaluation of quality, safety and efficacy of nanopharmaceuticals 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.

Considering the complexity of the nanomaterial behavior in the biological environment, certain degree of uncertainty may be inherent to such system. This document has the aim to provide guidance for ensuring 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 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 Active Pharmaceutical Ingredient (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 disease in humans.

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 therapies.

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 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, 1945 as amended from time to time, with certain specific 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 100 nm in atleast one dimension. However, if the particle size is >100 nm 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 the API.

The size distribution of the nanopharmaceutical: Not less than 1% beyond the nano particle range i.e. 1 to 1000 nm is permitted. Further, > 60% of 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 %. At no stage the percent particle size should fall < 50% of claimed label.

In special cases, the nanopharmaceutical containing atleast > 60 % of particles having size of < 1 nm maybe considered as nanopharmaceutical,

with a scientific justification and validation of safety with appropriate tests.

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 materials is that biodegradable items decompose or break down naturally. Non-biodegradable items do not.

1. Biodegradable nanoparticles

Biodegradable nanoparticles have been used frequently as drug delivery vehicles due to their 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 nanoparticles

Nonbiodegradable nanoparticles are relatively less used in pharmaceutical products (though these systems are more commonly used in cosmeceuticals).

Almost all non-biodegradable nanoparticles have the potential to cause cytotoxic effects 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. The nanoparticle may also be multicomponent.

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 thereby having increased bioavailability 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 (e.g. 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, 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. Nanocarriers

can deliver drugs to otherwise inaccessible sites in the body because of their small size. 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 the 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, cyclosporine, 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. Accordingly, the formulation may be put into one of the following four 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 an Investigational New Drug (IND) and the general requirement

for quality, safety and efficacy will be as specified in Schedule Y of Drugs & Cosmetics Rules, 1945.

2. The drug is a New Molecular Entity (NME) but the nanocarrier system is already used for some other nanopharmaceutical. Such formulation should be treated as Investigational New Drug (IND). The general requirement for quality, safety and efficacy of such formulation should be the 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 country. For this category of nanoformulation product, the entire data of safety and efficacy as specified in Schedule Y for Investigational New Drug (IND), may not be required. In such cases, a ‘case by case approach’ should be adopted for evidence of safety and efficacy of the product.

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. These should be decided on a ‘case by case approach’ basis.

Note: It is to be noted that the requirements for quality, safety and efficacy of any nanopharmaceutical should be decided on a 'case by case approach' basis which will depend 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.

6. Scientific Rationale 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 the 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.

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

- Basis of making the claim of improved safety or efficacy; reduction in toxicity profile; reduction in dose or frequency of administration of the nanopharmaceutical; improved patient compliance; lower cost or any other benefit over the 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 trials, 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. 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 standardized, 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 Required

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 anticancer 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 preclinical 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 at 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) pharmacokinetics are affected by repeat dosing. An effort should be made to separate the evaluation of pharmacokinetics/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 nanopharmaceuticals, special studies should be done to measure drug concentration in different parts of brain along with the API.

10. Animal Toxicology Data Required

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. 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 predictive 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, are 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 further escalate the dose. 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 toxicity of the drug, 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 Required

The general requirements of clinical data and guidelines as specified in Schedule Y of Drugs and Cosmetics Rules, 1945 apply to the nanopharmaceuticals also. However, a nanopharmaceutical 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 a 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. Summary of the Information Required for Evaluation of Nanopharmaceuticals

As already mentioned, the information required for nanopharmaceuticals should be decided on a '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 clause 5.2)

d. Justification for developing the nanopharmaceutical

B. Chemical and pharmaceutical information

a. Information on the ingredients

i. Drug information (Generic name, Chemical name, International nonproprietary name)

ii. Information on nanomaterial 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),
- Electron microscopy (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 physicochemical 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 (refer to 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 (*refer to 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 (*refer to 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 the following:

- Safety data from clinical development
- All the potential risks of the nanopharmaceutical
- Summary of anticipated risks
- Population at risk
- 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.

While drafting the guidelines, all the experts were aware of the fact that the nanoscience is a rapidly developing discipline. Every research paper brings out a new dimension. Thus, this guideline is a dynamic document.

The suggestions and comments of all experts in the discipline, pharmaceutical industry and any other stakeholder are welcome and will help in making a robust regulatory framework in India for nanopharmaceuticals.

15. 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