Guidelines for Evaluation of Nanopharmaceuticals in India

Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India

सत्यमेव जयते
Department of Biotechnology
Ministry of Science & Technology
Government of India

Indian Council for Medical Research
Ministry of Health & Family Welfare
Government of India

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Guidelines For Evaluation Of Nanopharmaceuticals In India

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Central Drugs Standard Control Organization
Ministry of Health & Family Welfare

Department of Biotechnology
Ministry of Science & Technology

Indian Council for Medical Research
Ministry of Health & Family Welfare

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सबका साथ, सबका विकास, सबका विश्वास
Sabka Saath, Sabka Vikas, Sabka Vishwas

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स्वास्थ्य एवं परिवार कल्याण, विज्ञान और प्रौद्योगिकी
व पृथ्वी विज्ञान मंत्री, भारत सरकार
Union Minister for Health & Family Welfare, Science & Technology and Earth Sciences Government of India

MESSAGE

India is a developing country with a huge population burden. We also aspire to provide 'Affordable Health Care for All'. In this regard, development of cost effective quality enabled products is important which can be achieved through cutting edge technologies like nano-interventions. Nanocarrier based targeted drug delivery is an emerging field with introduction of nanopharmaceuticals in the market. These nanoformulations have higher efficacy, lower toxicity and are safer than the conventional drugs. I understand that the Indian researchers and the industry have made significant progress and capacity building for development and marketing of nanopharmaceuticals.

2. Keeping in mind the importance of the Nanopharmaceuticals the Department of Biotechnology, Ministry of Science and Technology, Indian Council of Medical Research and Central Drugs Standard Control Organization, Ministry of Health and Family Welfare have successfully coordinated with all relevant stakeholders and brought out an important document called 'Guidelines for Evaluation of Nanopharmaceuticals in India'.

3. These guidelines will pave the way for effective translational research towards development of novel nanoformulations and provide significant social and economic benefits to our country. It will also highlight our capability for newer product development using nano and emerging technologies in health care.

4. I convey my thanks to all the members of the team who have brought out this document.

(Dr. Harsh Vardhan)

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FOREWORD

Application of nanotechnology in medical therapeutics has the potential to revolutionize the current treatment strategies in near future. Nano pharmaceuticals can enable target specific delivery of drugs and therapeutic molecules minimizing off target effects and toxicity. There is a considerable scope of innovation in the area of nanoscience and Nano biotechnology which can develop new generations of nanomaterials with novel functions. We have made considerable progress in knowledge generation and innovation capabilities in this area. However, translation of these novel concepts to commercially viable products for clinical applications needs regulatory approvals assessing the quality, safety and efficacy of the formulations. In this respect, the present guidelines in this multidisciplinary complex domain will be of great help for the innovators and industries to optimize their research on developing the product based on the regulatory requirements.

I congratulate all the domain experts, representatives from industries and Industry Associations, regulators and concerned Govt. organizations for their participatory role which has led to development of this document on 'Guidelines for Evaluation of Nano pharmaceuticals in India'. I am sure these guidelines will enhance our capability to generate and commercialize Nano pharmaceuticals with a significant benefit to the end users. Also this document will initiate the activities for developing safety guidelines for other domains like agri-inputs and agri-products, cosmetics, implantable devices, etc where nanotechnology is being used.

(Renu Swarup)

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Foreword

Targeted drug delivery through nanotechnology intervention is emerging as a major player in the future era of precision medicine. Several new nanopharmaceuticals/ nanomedicine are being marketed every year. In cancer management the advantage of these nanoformulations are well recognized. India has a sizable pool of nonscientists generating large number of scientific publications in this domain. There is an urgent need for low cost high efficacy product development in India for health care considering rapidly expanding population burden. Nanotechnology based innovation may be an important solution. The regulatory approval is the most important factor for translating laboratory research to bedside medicine. In this regard, formulation of these 'Guidelines for Evaluation of Nanopharmaceuticals in India' is a very important step.

It will encourage innovators and industries to join hands for development of commercially viable products. The Indian pharmaceutical industry has a significant global market share in the area of vaccine and generic drugs. These guidelines can generate a lot of interest among these industries to develop next generation nanoenabled therapeutic agents.

I congratulate all the academic experts, industry representatives, regulators and Govt agencies for the collaborative effort to develop these guidelines.

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FOREWORD

Application of nanotechnology for targeted drug and biomolecular delivery to the disease site is an emerging filed. These nanopharmaceuticals or nanomedicines have shown their advantage in terms of higher efficacy and lower off target toxicity in many disease conditions specially cancer. Every year several nanopharmaceuticals are being marketed globally after successful clinical trials. The drug discovery has become a long time consuming and expensive process now. The nanotechnology can be used to enhance safety and efficacy of the existing drugs as well as in repurposing of the drugs. It has been projected that in near future nanopharmaceuticals will capture a sizable segment of current market. Indian pharmaceutical industry will be greatly benefited with these guidelines. They can utilize the strength of innovation of Indian scientists for development and commercialization of novel nanoformulations. In that process, the industry will attain a global leadership in the area of cutting edge medicine.

The nanomaterials have unique physical, chemical and biological properties which are very different from the bulk materials. The API when loaded in a Nano carrier is like to show a different Pk/Pd and bio distribution compared to pure compound. That is the root cause of complexity of evaluation of quality, safety and efficacy attributes of Nanopharmaceuticals. There are no universally acceptable guidelines in this domain. I congratulate DBT to take the leadership and develop these guidelines in collaboration with other Govt. agencies, academia, industry and other stake holders, which are recommendatory, dynamic and without prejudice to statutory provisions.

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Inter-ministerial Expert Committee

Inter-ministerial Expert Committee constituted by Department of Biotechnology vide OM. No. BT/Nano-Guidelines/Pharma/2018 dated 2nd May 2019 for the finalization of "Guidelines for Evaluation of Nanopharmaceuticals in India"

1.	Dr. Renu Swarup, Secretary, DBT	Chairperson
2.	Dr. S. Eswara Reddy, DCG(I), CDSCO	Co-Chair
3.	Dr. Y. K. Gupta, Former President, ISNM	Co-Chair
4.	Dr. Suchita Ninawe, Adviser, DBT	DBT Coordinator
5.	Representatives of CDSCO Shri A.K. Pradhan, DDC Shri R. Chandrashekhar, DDC	Member
6.	Representative of ICMR Dr. Geeta Jotwani, Scientist 'F'	Member
7.	Representatives of DST Dr. Milind Kulkarni, Scientist 'G' Dr. Namrata Pathak, Scientist 'F'	Member
8.	Representative of CSIR Dr. Alok Dhawan, Director, CSIR-IITR	Member
9.	Representative from FSSAI Dr. S. C. Khurana, Scientific Panel Coordinator	Member
10.	Representatives of CIB & RC Dr. S.K. Khurana, Secretary Dr. Sandhya Kulshreshtha, Consultant (Pharma)	Member
11.	Representative of ICAR Dr. Rajan, ADG	Member
12.	Dr. K. N. Ganesh, Director, IISER, Tirupati	Member
13.	Dr. A. K. Dinda, Professor, D/o Pathology, AIIMS, New Delhi	Member
14.	Dr. Shanti Nair, Director, Center for Nanosciences, AIMS, Kochi	Member
15.	Dr. Tapas Kundu Director, CDRI, Lucknow	Member
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17.	Dr. Anil Mishra, Scientist 'G', INMAS, Delhi	Member
18.	Dr. Alok Adholeya Director, TERI Deakin Nanobiotechnology Centre Gurugram	Member
19.	Dr. Vamsi Krishna Scientist 'E', DBT	Member Secretary

Preface

The 'Guidelines for Evaluation of Nanopharmaceuticals in India' are compiled with an aim of evaluation of the pharmaceutical preparations containing nanomaterials where the novel application of nanotechnology imparts the significant advantages over the existing active pharmaceutical ingredients (API) in terms of targeted delivery to disease site, higher efficacy and lower toxicity. The nanometer dimension of a material provides unique properties with a marked difference from its bulk counterpart. These unique properties of the nanoformulation can be utilized for targeted drug delivery and other applications. The properties of any nanomaterial depend on its physical and chemical characteristics. Variation of size and surface charge of the same material can show different functionalities. Thus, these nanopharmaceuticals need additional tests for ensuring uniform safety and efficacy. The general principle of regulatory guideline for API as mentioned in the New Drugs and Clinical Trial Rules 2019 issued by CDSCO has been followed. These guidelines are also aligned with ICH guidelines and international norms followed by other countries commercializing such products. The goal of these guidelines is to help the regulators to assess the quality, safety and efficacy of the nanoformulation/nanopharmaceuticals in a systematic manner. It will also guide the innovators and industries to generate the data according to the nanomaterial specific requirements. The current guidelines are applicable to nanopharmaceuticals and not for cosmetics and nanoenabled devices or implants.

The nanotechnology intervention has opened a new horizon for targeted delivery of approved drugs and repurposing of drugs. Every year several new nanopharmaceuticals/ nanomedicine are being introduced into the market globally. The rapid progress in this emerging field is expected to change the current therapeutic practice in near future. These guidelines will encourage the Indian innovators and industries to develop and commercialize new nanopharmaceuticals which will make our country a global leader in this area. With rapid advances in basic sciences, our understanding about the safety parameters of nanomaterials is continuously updated. The novel multifunctional nanomaterials may need additional new tests for safety assessment in future. So these first guidelines may need modification with new edition from time to time.

We sincerely hope this document will empower the Indian pharmaceutical industry to achieve a greater social and economic impact.

New Delhi, July 2019 ***Editors***

Acknowledgement

The development of first "Guidelines for Evaluation of Nanopharmaceuticals in India" was a great challenge considering the lack of such document in the public domain. The Task Force on Nanobiotechnology of Department of Biotechnology (DBT) had always emphasized on formulation of such required set of procedures for the use of researchers and industry. In this endeavor, Indian Society of Nanomedicine (ISNM) with active support from DBT organized a series of interactions and brain storming sessions involving the academia, regulators, industry representatives, international experts especially from USFDA and other stakeholders since 2016. Those sincere efforts led to compilation of the Draft Guidelines which was circulated to the participants during 2nd Annual Conference of the society at Kochi in December 2017. We sincerely acknowledge timely directions received from the Task Force and the efforts put in by ISNM towards framing the initial draft. Special thanks are due to Dr YK Gupta, Dr AK Dinda from AIIMS and Mr AK Pradhan, CDSCO and Dr. Dhananjay Tiwari, the then Program Officer, Nanobiotechnology, DBT. The earlier efforts of the ICMR Expert Group helped us to frame this document are also highly acknowledged.

Considering the need of such guidelines to promote commercialization of new innovations in this emerging field of Nanopharmaceuticals/ Nanomedicine, as a next step, DBT conducted extensive inter-ministerial consultations with active participation of domain experts, representatives from Govt. agencies (CDSCO, ICMR, DST, CSIR, ICAR, FSSAI and CIBRC), industry, Industry Associations and other stakeholders. CDSCO was always been extensively engaged in building up this document. We profusely thank contributions by each and every participant.

After necessary modifications in the document through initial inter-ministerial meeting, public consultation process was undertaken by DBT. More than 250 comments were received and considered. We are grateful to Industry Associations, pharmaceutical industries and academic experts for their constructive criticism and suggestions which helped us to modify the document further. The help of Dr. Manzoor Koyakutty, AIMS Kochi in preparing Action Taken Report on the Public Opinion is highly appreciable.

Incorporation of suggestions and comments through following meetings of Inter-ministerial Expert Committee chaired by Dr Renu Swarup, Secretary, DBT and Co-chaired by Dr. S. Eswara Reddy, DCGI and Dr. Y. K. Gupta, Former President, ISNM in the said document resulted in the final version. We are extremely grateful to Chair, Co-chairs and Members of the Inter-ministerial Expert Committee who contributed profusely.

Last but not the least, untiring effort and enthusiasm of the Editors led the zero draft to final version of the guidelines are put on record with high appreciation. The efforts of Dr Vamsi Krishna, Program Officer, Nanobiotechnology, DBT in the final stages of preparation of this document are appreciated. The hard work of supporting staff in DBT is acknowledged.

New Delhi, July 2019 ***Suchita Ninawe***

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
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
ND & CT Rules	New Drugs and Clinical Trials Rules, 2019
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
SEM	Scanning Electron Microscopy
SOPs	Standard Operating Procedures
TEM	Transmission Electron Microscopy
XPS	X-Ray photoelectron spectroscopy
XRD	X- Ray Diffraction

1. Introduction

Nanoscience is the study of materials, which are in nanoscale range. Conversion of any material in nanoscale results in alteration of its physiochemical, biological, mechanical, optical, electronic and other properties. These newly acquired (novel) properties of the materials due to conversion into nanoscale can be utilized for different useful activities. Thus, it is relevant for diverse sectors, such as health, energy, chemicals, consumer products, various other industries and environmental remediation.

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 and reduce toxicity due to improved (actively or passively targeted / sustained / controlled / triggered / enhanced / prolonged) delivery of the drugs. There may be a concurrent reduction of the dose of the drug with enhanced/sustained bioavailability and lowering of toxicity. Nanopharmaceutical is an emerging area that combines nanotechnology with biomedical and pharmaceutical science with the goal of improved/ targeted drug delivery. The concept of 5 R's: 'right target /efficacy', 'right tissue/exposure', 'right patients', 'right safety' and 'right commercial potential' may help in successful development of nanopharmaceuticals[1].

Development of a nano scale drug delivery system / nano API may 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, there is a need to formulate comprehensive guideline focusing on the quality, safety and efficacy of nanopharmaceuticals for their therapeutic use. These guidelines are intended to provide transparent, consistent and predictable regulatory pathways for nanopharmaceuticals in India. It is known that 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 nanocarrier such as size distribution, surface charge, single/multiphasic composition, stability during storage or in the biological environment, certain degree of uncertainty/variability may be inherent to the system which needs to be addressed by the regulators[2].

These guidelines have been prepared with an aim to ensure the quality, safety and efficacy of nanopharmaceuticals as well as to encourage the commercialization of nanotechnology based inventions by increasing their benefit-to-risk ratio.

There are no uniform internationally accepted guidelines for nanopharmaceuticals. The usual consensus 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 nanomaterial used and the product, route of administration, the indication for which the product is intended to be used and other related aspects.

2. Scope of the Guidelines

The 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 nano- scale dimensions, properties or phenomenon associated with the application of nanotechnology intended to be used for treatment, *in vivo* diagnosis, mitigation, cure or prevention of diseases and disorders 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

guidelines are also not applicable to medical devices, *in vitro* diagnostics, tissue engineered products using nanotechnology and nanoparticle modified cell based therapies.

These guidelines may serve as a useful document for manufacturers, importers of nanopharmaceuticals and other stakeholders involved in research and development of nanopharmaceuticals.

3. General Considerations of the Guidelines

Safety studies should be conducted as per general guidelines specified in Second Schedule of New Drugs and Clinical Trials Rules, 2019[3]. However, in case any specific study is not included in the general requirements of the said Schedule, the studies may be planned, designed and conducted as per the principles of USFDA[4], ICH guidelines for pharmaceuticals[5] or OECD guidelines for chemicals[6]. These guidelines are in conformity with the provisions of Drugs and Cosmetics Act, 1940 and New Drugs and Clinical Trials Rules, 2019, with certain specific aspects of quality, safety and efficacy applicable to nanopharmaceuticals.

These guidelines have evolved with considerations of the following documents:

- Schedule Y of D & C Rules, 1945 prevalent before 19 March of 2019 as well as the New Drugs and Clinical Trials Rules, 2019[3].
- Drug Products, Including Biological Products that Contain Nanomaterials Guidance for Industry [4].
- Second Regulatory Review on Nanopharmaceuticals, European Union, 2012, Nanomaterials: Commission proposes 'case by case approach' to assessment[7].
- Identification of regulatory needs for nanomedicines: 1st EU-NCL survey with the "Nanomedicine" working group of the international pharmaceutical regulators[8].
- Regulatory Aspects of the Nanopharmaceutical in the EU, 2017[9].

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

Specific scientific evidence required for approval of any nanopharmaceutical and the strategies for pharmacovigilance of such products have been incorporated in these guidelines. Each application should be considered on its own merit based on data submitted, using scientific judgment and logical argument.

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

4. Nanopharmaceuticals: Definition and Categorization

4.1 Definition

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

The nanomaterial is generally defined as material having particle size in the range of 1 to 100 nm in at least one dimension. However, if a material exhibits physical, chemical or biological phenomenon or activity which are attributable to its dimension beyond nanoscale range up to 1000 nm, the material should also be considered as nanomaterial. Therefore, any pharmaceutical containing such material should also be considered as nanopharmaceutical[4].

Particle size distribution of the nanopharmaceutical: The nano-size range should be declared in the product specification. Further, the particles should be within the claimed nano-size range in all given testing conditions during the claimed stability period and final product[4].

4.2 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 API form of the drug. Accordingly, nanopharmaceuticals are categorized as under:

4.2.1 According to degradability of nanomaterial:

The basic difference between biodegradable and non-biodegradable is that biodegradable materials decompose or break down naturally, while non-biodegradable materials do not. The details in this regard are given below.

Biodegradable: Nanoparticles fabricated with biodegradable material have been used frequently as vehicles for drug delivery due to their better encapsulation, controlled release, improved bioavailability and reduction of toxic potential. Examples of biodegradable nanoparticles are proteins, lipids, biopolymer such as PEG, PLA, PLGA, polycaprolactone and biomineral like calcium apatite, etc.

Non-biodegradable: Non-biodegradable nanoparticles are relatively less used in pharmaceutical products. However, these systems are more commonly used in cosmeceuticals. Non-biodegradable nanoparticles may have the potential to cause toxic effects, if not excreted quickly from the body. Prolonged retention, if any, of non-biodegradable nanoparticles is a concern. Some examples of non-biodegradable nanoparticles are those of metals such as gold, silver, platinum, etc.

4.2.2 According to nature of nanomaterial:

Nanomaterial may be organic or inorganic in nature depending on the method of synthesis/fabrication. Details in this regard are given below.

Organic Nanomaterials: These are the materials composed of carbon based organic compounds. They have been primarily developed for improved drug delivery and to reduce or overcome the risk of toxicity due to the intracellular and/or tissue sequestration leading to increased bioavailability at the site of action[10].

Examples of organic nanomaterials used in pharmaceutical formulations are polymers, lipids, carbohydrates, liposome, proteins, or their conjugates or composites. These nanomaterials are usually biodegradable which make them the most suitable systems for drug delivery and biomedical applications[11-12]. However, they may have limited chemical and mechanical stability. Non-biodegradable organic nanoparticles are carbon nanotubes, fullerene, graphene, etc.

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

Generally, inorganic nanomaterials are relatively more stable than organic nanostructures. Inorganic nanomaterials may have several advantages over organic ones. They are easier to prepare with a defined size and a very narrow size distribution. They may exhibit multiple useful functions, which can be applicable in heat generation, contrast function for imaging, etc. Most of the inorganic nanomaterials may not biodegrade with a potential for long term sequestration and toxicity[1-2-12]. However, there are biodegradable inorganic materials such as biominerals, etc.

Multi-component nanomaterials: These are the nanomaterials composed of two or more different materials. The integration of multiple materials in one structure offers opportunities for enhanced physico-chemical properties and multifunctionality. These materials can be used for targeted drug delivery along with imaging (theranostic) and many other useful functions[10-12]. However, stabilization of multiple materials within the nanostructure is challenging.

For example, magnetic liposomes containing an aqueous dispersion of iron oxide incorporated on lipid surface is a multi-component nanomaterial.

4.2.3 According to nanoform of the ingredient:

Nanocarriers loaded with Active Pharmaceutical Ingredient (API): A nano carrier 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), dendrimers, lipid-based carriers (micelles, liposomes), gold nanoparticles (nanoshells, nanocages) etc.[1,2,12].

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 (targeted delivery) to specific or otherwise in accessible sites within the body. In the area of cancer nanomedicine, the nanomaterials 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 off-target toxicity[10].

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

According to the approval status of drug and nanomaterial:

Based on the approval status of the drug and the nanomaterial, the requirements of quality, safety and efficacy data may vary. Broadly, all nanopharmaceutical preparations will be treated as New Drug which will be evaluated by CDCSO. They may be subjected to differential scrutiny according to the following four categories:

Category I – The drug is a new molecular entity and the nanocarrier is also new and not approved in any country. Such product would be treated as IND and the general requirements for quality, safety and efficacy as specified in the Second Schedule of the New Drugs and Clinical Trials Rules, 2019[3] shall be applicable.

Category II – The drug is a new molecular entity not approved in any country, but the nanocarrier is already used / approved for other nanopharmaceuticals. Such product should also be considered as an IND. The general requirements for quality, safety and efficacy will be same as specified in the Second Schedule of New Drugs and Clinical Trials Rules, 2019[3]. Independent studies for assessment of safety/performance of such carrier may not be required.

Category III – 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 any country. For this category of nanoformulation product, the entire requirements of safety and efficacy data as specified in the Second Schedule of New Drugs and Clinical Trials Rules, 2019 for IND[3], may not be required for the drug. However, adequate evidence of safety and efficacy of the nanomaterial and the final product should be provided.

Category IV – Conventional/ traditional form of the drug and the nanocarrier system both are approved as a specific formulation in well regulated countries, but yet not in India. It should be subjected to abbreviated/ bridging studies as per Second Schedule of New Drugs and Clinical Trials Rules, 2019[3].

Note: The requirements for quality, safety and efficacy of any nanopharmaceutical should be decided depending upon factors like physiochemical nature, biological nature, functions, bioavailability and biodistribution, possible interaction with biological and immune 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[2].

5. Scientific Rationality for Development of Nanopharmaceuticals

The rationality for development of a nanopharmaceutical should be clearly stated. The added advantage and possible disadvantage of the nanopharmaceuticals in comparison to conventional/traditional drug/API should

be demonstrated using in vitro and in vivo studies. Biodegradable nanomaterials with known toxicity profile are usually preferred as an option for development of nanopharmaceuticals. However, the nanocarriers (especially non-biodegradable) and its wasted disposal may have an adverse impact on the environment and ecosystem. Therefore, while justifying the rationality, the known and perceived adverse impact on environment by non-biodegradable engineered nanocarrier systems including the waste disposal should be described [4,14,15]. DST Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries15 as well as Guidance for Safe Handling of Nanomaterials16 may be consulted for waste disposal.

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, cost-benefit or any other benefit over conventional, traditional drug[3,4].

» Any issue arising out of significantly different pharmacokinetics (PK) and/or pharmaco-dynamics (PD) than that of the conventional/ traditional drug.

» The issue of specific adverse effect/ property, if any, of the nanoformulation compared to conventional/ traditional drug /API, in central nervous system (CNS), cardiovascular system including QTc prolongation, ophthalmic and immune system, etc. as well as its teratogenic potential should be addressed wherever applicable.

6. Specific Considerations for Evaluation of Nano-pharmaceuticals in the context of Second Schedule of the New Drugs and Clinical Trials Rules, 2019

These guidelines have been developed in line with the provisions of Schedule Y of Drugs and Cosmetics Rules, 1945 prevalent before 19 March, 2019, as well as Second Schedule of the New Drugs and Clinical Trials Rules, 2019 with specific requirements for nanopharmaceuticals wherever considered necessary. While Second Schedule of the New Drugs and Clinical Trials Rules, 2019 specifies the general requirements and guidelines for manufacture or import of new drugs or to undertake clinical trial, this document provides guidance for specific requirements of nanopharmaceuticals, their chemical and pharmaceutical information, non-clinical and clinical data relevant for any nanotechnology based pharmaceutical product. General requirements as specified in the Second Schedule of the New Drugs and Clinical Trials Rules, 2019 will be applicable for any nanopharmaceutical[3]. However, due to the inherent complexity in nanotechnology- based products, a 'case-by-case approach' should be adopted for evaluating their quality, safety and efficacy[7].

Considering the unique process conditions of nanoformulations, compared to traditional/ conventional drugs /APIs, the product description should include but not limited to detailed methods of manufacturing process, process controls and waste disposal methods as per the existent regulatory requirement[7-11]. The impact of nanomaterial waste disposal on environment should also be declared. In case of liposomal formulations, specific US-FDA guidelines for 'Liposomal Drug Products' of April 2018 may be consulted[17].

7. Stability Testing of Nanopharmaceuticals

The stability testing of nanopharmaceuticals should be done according to the general requirements specified in Clause 5 of the Second Schedule of New Drugs and Clinical Trials Rules, 2019[3] and ICH guidelines[18] .

Stability testing of developmental nanopharmaceuticals must be done extensively and systematically. When the drug is loaded in the nanocarrier, the stability of the drug in its active form should be confirmed from time to time under defined storage and transit conditions. It should focus on functionality, integrity, size range of nanopharmaceutical, carrier material stability, drug stability in encapsulated form, and degradation products.

The selected stability storage conditions should be relevant for the specific product and studies are done on proposed market packs[4,18]. In addition, parameters specific to nanomaterial-based systems need to be quantified at different time intervals for size and size distribution, surface characterization, drug loading, drug release kinetics, etc., using appropriate techniques[19].

In case of surface coating for example with PEG, the PEG layer thickness or quantity should be measured by appropriate analytical methods. 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. Properties specific to a sub-category of nanomaterial-based systems needs to be characterized. For example, lamellarity of liposomes can be evaluated using cryo-transmission electron microscope (cryo-TEM). Multiple analytical methods that complement each other to evaluate the same parameter may be used. For example, DLS, TEM, SEM, AFM can be used simultaneously for the measurement of particle size[20,21].

8. Animal Pharmacology Data

Knowledge of the activity and toxicity of the free API, the function of different delivery systems, observation of the influence of drug release rate on-target and off-target bioavailable concentrations of drug, selection of an suitable range of nanopharmaceuticals to test the overall principles of animal pharmacology should be according to the broad guidelines specified in Clause 3 of the Second Schedule of the New Drugs and Clinical Trials Rules, 2019[3].

To evaluate efficacy of a nanopharmaceutical, pre-clinical testing should generate data sets that evaluate the properties of product behaviour. Such properties include enhanced therapeutic efficacy, possible accumulation of the drug at the disease target site, for example, in case of cancer, the data for the preferential accumulation of nanopharmaceutical in tumor or enhanced overall bioavailability, circulation and biodistribution should be generated. In addition to the localized bioavailability, the contribution of the peripheral (or circulation) pharmacokinetics of the nanopharmaceutical should be assessed. It is likely that for any targeted delivery system, each of these features may be responsible for potential efficacy. Based on the study results, the dominant feature can help to choose the delivery system and desired release kinetics. Further, study of the off-target effects is as important as evaluating efficacy in development of nanopharmaceuticals. The pre-clinical testing with an aim to document the translational potential should provide detailed insight into the key parameters that influence nanopharmaceutical efficacy[21,22].

The informative and translatable data sets should consider characterizing the disease site specific retention and drug metabolism. It should differentiate between bioavailable drug and concentrations of drug at the site of action, wherever possible. For example, drug concentration in tumour vis-à-vis that in 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 (in case of targeted delivery, if applicable), pharmacokinetics is affected by repeat dosing. It is not necessary that the enhanced therapeutic efficacy is always due to higher dose at the site of action or enhanced target specificity. In such cases, the reasons for other mechanisms of enhanced effects should be established. The pre-clinical study should have a clear focus on the end clinical application of the nanopharmaceutical[23,24].

For brain-targeted nanopharmaceuticals, special studies should be done to measure drug concentration in different parts of the brain compared to that of the traditional / conventional drug /API.

9. Animal Toxicology Data

Generation of data in the area of animal toxicology for nanopharmaceuticals should follow the general guidelines according to the route of administration as specified in Clause 2 of the Second Schedule of the New Drugs and Clinical Trials Rules, 2019[3].

The toxicology studies should be conducted in the most clinically relevant animal model[11,12]. Toxicology studies should generally be performed in a rodent and non-rodent species, usually rats and dogs and in both sexes.

In certain cases, if specific animal species are known to be more susceptible of toxicity for certain drug classes (for example, primates for assessment of complement-mediated toxicity of phosphorothionate oligonucleotide therapies), it should be used for the study. In this context, it may be mentioned that due to species-specific target expression, in some cases primates are relevant for toxicology studies. There may be situations where there are no non-human target-expressing animals. In such situations, transgenic animals expressing the target or a surrogate ligand for a similar animal target can be used to assess toxicity profiles. For nanomaterials, uptake by the reticulo-endothelial system (RES) has been shown to be an important modulator of biodistribution. In the context of RES function, the most relevant species for evaluating nanomaterial toxicology or ADME may be used. The studies suggest that in laboratory animals (mice, rats, rabbits, guinea pigs and dog) and man, macrophages in spleen and Kupffer cells in liver are primarily responsible for sequestration of nanoparticles, where as in some of the larger animals (pig, sheep, goat and cat), pulmonary intravascular macrophage (PIM) are mainly involved in trapping/sequestration[12,23].

The determination of dosing regimen, duration and route of administration for repeat- dose toxicology studies are predicted by the proposed clinical administration route and regimen, which is, in turn, affected by the pharmacology of the nanopharmaceuticals[24,25].

The number of animals required for toxicology and safety studies depends upon the study length and statistical significance of the result, which in turn is dependent on variation of result[25].

There are some special issues that may be considered, while conducting toxicology studies for nanopharmaceuticals. The maximum dose used in preclinical toxicology studies is based upon several factors, including the toxicity of the nanopharmaceuticals and its solubility. It is usually not rational to dose a nanopharmaceutical over several g/kg, or 50 fold higher than the expected clinical exposure, based on area under the time– concentration curve (AUC). If toxicity is not detected at these high doses, then it may not be 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 nanopharmaceuticals), then the dose might 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 deficiency of toxicity profile characterization, and failure to identify a maximum tolerated dose (MTD) and dose limiting toxicities (DLT), either secondary to solubility limitations or instability at high concentrations complicates risk analysis or the determination of a first-in-man dose. The determination of the toxic doses is usually not difficult for cytotoxic chemotherapeutic agents. However, the biologics, which may not show toxicity in preclinical animal models at reasonable doses, are often dosed to pharmacologically appropriate blood concentration depending on receptor affinity or biomarker modulation, and not by MTD[24-27].

In case of new nanomaterial whose toxicity profile is not documented, it is important to include the drug-free (empty) nanoparticle in the toxicity studies. In case if API is a novel molecule, toxicity study of API should be presented with that of nanoformulation. This will allow identification of particle-dependent toxicities and particle-dependent shifts in the encapsulated drug toxicity.

The toxicity studies should be done with the norms of Good Laboratory Practices (GLP). These studies should be undertaken 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[28,29].

Safety studies of nanopharmaceutical 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. Data on ADME may be generated either as an integral component of the non-clinical toxicity studies or in specially designed

studies. Along with 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. Based on the unique biodistribution of the nanopharmaceutical, additional organ specific toxicity studies may be required[28].

An important benefit of some nanopharmaceuticals is the ability to formulate a drug without using dose-limiting toxic excipients present in already 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 nano particle 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 ingredient can be increased by avoiding the tolerability problems caused by the solubilizing surfactants[28,29].

In cases where the nanopharmaceutical does not show any clinically significant pharmacokinetic difference compared to, traditional / conventional drug / API and has no difference in biodistribution, exemption of some toxicity studies may be given on the basis of 'case-by-case approach'. Immunological safety study should also be conducted for nanoformulation for anaphylactic or other adverse reactions including complement activation.

10. Clinical Trial Data

The general requirements of clinical data and guidelines as specified in the New Drugs and Clinical Trials Rules, 2019 apply to the nanopharmaceuticals. However, nanopharmaceuticals should be demonstrated clinically through appropriate design, patient selection hypothesis and biomarkers to exploit the increased permeability and retention of drug (e.g. anti-cancer nanopharmaceuticals). This is due to modification in pharmacokinetics and tissue distribution of the nanopharmaceutical to improve its delivery/ performance. 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. 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 ADME, 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 API, whether it is a new chemical entity (NCE) or an approved drug molecule and the nanocarrier, clinical trial of appropriate phase may be conducted on a 'case-by-case approach' basis.

The selection of starting dose for clinical trial for nanopharmaceutical should be estimated in a similar fashion to conventional / traditional drugs. The clinical starting dose may be calculated 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 anticancer drugs is usually determined by surface area (/m^2) scaling of the rodent MTD, or the non-rodent MTD if 1/10 the rodent MTD is observed to be toxic to the non-rodent species. In nanopharmaceuticals, there may be variation in safety limits[27,29].

11. 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.

11.1 Introduction

» A brief description of the nanopharmaceutical

» Indication for which it is intended to be used

» Category to which it belongs (refer to clause 4.2)

» Justification for developing nanopharmaceutical

11.2 Chemical and Pharmaceutical Information

11.2.1 Information on the ingredients

» Drug information (Chemical Name, Generic Name, International non-proprietary name)

» Information on nanomaterial used, excipient/ inactive ingredients

» Brief description and rationality of the nanopharmaceutical (Refer to clause 5)

11.2.2 Physiochemical characterization data of nanopharmaceuticals

» Complete description of Individual component(s) [e.g. API, Nanocarrier material (single/multiphase) surface functional groups, contrast agents (theranostic), excipients, targeting ligands, etc]

» Chemical name, structure, crystal structure of drug and nanomaterial(s)

» Empirical formula (drug and nanomaterials)

» Molecular weight (drug and nanomaterials)

» Description of the product with

- Nano-size range by number and/ or intensity distribution, average size and polydispersion index, percentage of particle under each distribution with standard deviation
- Shape, surface texture information
- Surface charge with standard deviation (zeta potential)
- Percentage of drug loading with standard deviation
- Encapsulation efficiency, loaded versus free drug content, with standard deviation
- Osmolality (wherever applicable)
- Solubility / dispersion information (for injectable product)
- Colloidal stability information for injections (06 batches)
- State of drug(API) in nanomaterial (chemically conjugated/loaded/complexed with the nanocarrier)
- Scalable GMP process description of the nanopharmaceutical preparation
- Average pH (wherever applicable)
- Viscosity (wherever applicable)
- Mechanical integrity/Properties (as applicable)
- Endotoxin/microbial load level for parental nanoformulations
- Residual solvent content as per ICH guidelines
- Sterilization protocols/methods/stability post sterilization (as applicable)
- Waste disposal method

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, process controls and waste disposal methods should be provided.

11.2.3 Analytical data (nanocarrier/ API/ nanopharmaceutical):

» Size (DLS, TEM, AFM, SEM, etc.)

» Quantitative Elemental analysis (AAS, ICP, XRF, etc.)

» Mass spectrum analysis

» NMR spectra (state of the API as encapsulated or chemically bonded, or intercalated may be identified and specified)

» FT-IR spectra

» Fluorescence spectra

» Ramanspectra

» UV-VIS spectra

» XRD, XPS

» Polymorphic changes identification (during the shelf-life of the product)

Note: Data to be generated using appropriate scientifically validated analytical methods not limited to the ones mentioned above for a particular nanopharmaceutical depending upon the claim of novelty.

11.2.4 Complete monograph specification for the nanopharmaceutical

» Defined criteria for unique identification of nanopharmaceutical

» Identity and quantification of impurities

» *In vitro/ in vivo* release kinetics of the drug/active ingredient (as applicable)

» *In vitro/ in vivo* degradation kinetics of nanopharmaceutical in various simulated media

» Stability data

11.2.5 Analytical method validations for nanopharmaceutical

» Assay method

» Impurity estimation method

» Residual solvent/other volatile impurities (OVI) estimation method

» Dissolution test method

11.2.6 Stability studies of nanopharmaceuticals *(refer to clause 7)*

11.2.7 Data on nanopharmaceutical formulation

» Dosage form

» Route of administration

» Composition

» Details about loading process, chemical bonding/ conjugation between active ingredient and carrier, surface coating/ modification and functionalization

» In process quality control check

» Finished product specification

» Excipient compatibility study

» Validation of the analytical method

11.2.8 Comparative evaluation of innovator product or approved Indian product, if applicable

» Container and closure system

» Content uniformity

» Impurities

» pH

11.2.9 Stability evaluation in market intended pack at proposed storage conditions

11.2.10 Packing specifications

11.2.11 Process validation

11.3 Animal pharmacology *(refer to clause 8)*

» Summary

» Specific pharmacological actions

» General pharmacological actions

» Essential, follow-up and supplemental safety pharmacology studies

» Pharmacokinetics: absorption, distribution, metabolism, excretion (ADME)

11.4 Animal toxicology *(refer to clause 9)*

» General aspects

» Systemic toxicity studies

» Male fertility study

» Female reproduction and developmental toxicity studies

» Local toxicity

» Allergenicity / hypersensitivity

» Genotoxicity (as per regulatory requirement)

» Carcinogenicity (as per regulatory requirement)

11.5 Human / Clinical pharmacology (Phase I)

» Summary

» Specific pharmacological effects

» General pharmacological effects

» Pharmacokinetics - absorption, distribution, metabolism, excretion (ADME)

» Pharmacodynamics-early measurement of drug activity

11.6 Therapeutic exploratory trials (Phase II)

» Summary

» Study report (s)

11.7 Therapeutic confirmatory trials (Phase III)

» Summary

» Individual study reports with listing of sites and investigators.

11.8 Special studies

» Summary

» Bioavailability /bio-equivalence

» Other studies e.g. geriatrics, pediatrics, pregnant or nursing women

11.9 Regulatory status of the nanopharmaceutical in other countries

» Countries Marketed

» Approved

» Approved as IND

» Withdrawn, if any, with reasons

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

» Free sale certificate or certificate of analysis, as appropriate

» Prescribing information

- Proposed full prescribing information
- Drafts of labels and cartons

11.10 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.

11.11 Labeling information:

Proper labeling information indicating the nanoparticle content, composition to be included in the packaging.

12. Pharmacovigilance of Nanopharmaceuticals

Pharmacovigilance must be carried out throughout the lifecycle of the nanopharmaceutical. A detailed

pharmacovigilance plan alongwith marketing authorization application must be submitted by the product developer.

Pharmacovigilance plan must mention:

» 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 the particular claim proposed.

If any significant safety concerns arise during clinical trials which warrant studies in special population 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.

13. Conclusion

General requirements and guidelines specified for approval of manufacture/import of any new drug or to undertake clinical trial as specified in the New Drugs and Clinical Trials Rules, 2019 especially in Second Schedule of the said Rules 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 physiochemical and biological nature, and other aspects including the back ground data available on the API or nanocarrier, the regulatory status in other countries, etc., as enumerated in this document. Successful translation of nanopharmaceuticals from nonclinical proof of concept to clinics is challenging. Like development of any new drug, it requires effective integration of nanotechnology with chemistry, life sciences 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.

References

1. Harea JI, Lammers T, Ashford MB, Purie S, Barrya ST. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Advanced Drug Delivery Reviews. 2017;108:25–38
2. Fatehi L, Wolf SM, McCullough J et al. Recommendations for Nanomedicine Human Subjects Research Oversight: An Evolutionary Approach for an Emerging Field. J Law Med Ethics.2012 ; 40(4):716–750.
3. New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), Government of India Gazette Notification dated 19th March 2019.

   https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elemen ts/download_file_division.jsp?num_id=NDI2MQ _ assessed on 21st June 2019.
4. Drug Products, Including Biological, Products, that Contain, Nanomaterials Guidance for Industry (DRAFT GUIDANCE - This guidance document is being distributed for comment purposes only): U.S. Department of Health and Human Services
   Food and Drug Administration. December 2017.
   (https:// www.fda.gov/regulatory-information/search-fda-guidance-documents/drug- products-including-biologi-cal-products-contain-nanomaterials-guidance- industry)
5. Development and manufacturing of Drug substances (Chemical entities and Biotechnological and Biological entities) Version 23, 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Qua lity/Q11/Q11IWG_Step4_QA_2017_0823.pdf
6. OECD Guidelines for the Testing of Chemicals. 2018 (https://www.oecd- ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753)
7. Nanomaterials: Commission proposes 'case by case approach' to assessment. - Second Regulatory Review on Nanopharmaceuticals, European Union, 2012. (http://europa.eu/rapid/press-release_MEMO-12-732_en.htm)
8. Identification of regulatory needs for nanomedicines: 1st EU-NCL survey with the "Nanomedicine" working group of the international pharmaceutical regulators. 2016. (https://ec.europa.eu/jrc/en/publication/identification-regulatory-needs-nanomedicines-1st-eu-ncl-survey-nanomedicine-working- group)
9. Regulatory Aspects of the Nanopharmaceutical in the EU, 2017. (https://ec.europa.eu/jrc/en/publication/regulatory-aspects-nanomaterials-eu)
10. Ragelle H, Danhier F, Preat V et al. Nanoparticles-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opin Drug Deliv.2017Jul;14(7):851-864
11. Navya PN, Daima HK. Rational engineering of physiochemical properties of nanomaterials for biomedical applications with nanotoxicological perspectives. Nano Convergence:2016;3(1):1-14
12. Stern ST, Hall JB, YuLL et al. Translational considerations for cancer nanomedicine. Journal of Controlled Release. 2010;146:164–174
13. Flühmann B, Ntai I, Borchard G et al. Themagic bullets reaching their target? Eur J Pharm Sci. 2019; 128:73-80
14. Musazzi UM, Marini V, Casiraghi A. Is the European regulatory framework sufficient to as sure the safety of citizens using health products containing nanomaterials? Drug Discov Today. 2017; 22:870-882.
15. DST Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries

    http://nanomission.gov.in/What_new/Draft_Guidelines_and_Best_Practices.p df 2019.
16. Dhawan A, Shanker R, Das M and Gupta KC. Guidance for safe handling of nanomaterials. Journal of Biomedical Nanotechnology. 2011; 7 (1): 218–224.

17. Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation, Guidance for Industry: U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER): April 2018 Pharmaceutical Quality/CMC. (https://www.fda.gov/downloads/drugs/guidances/ucm070570.pdf)

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. ICH Guideline 2018.

    (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Q uality/Q1F/Stability_Guideline_WHO_2018.pdf)

19. AiJ, Biazar E, Jafarpour M, et al., Nanotoxicology and nanoparticle safety in biomedical designs. International Journal of Nanomedicine 2011; 6: 1117–1127

20. Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals. Version 1.0 May 2017

    (https://echa.europa.eu/documents/10162/23047722/appendix_r6-1_nano_draft_for_committees_en.pdf/cb821783-f534-38cd-0772- 87192799b958)

21. Sainz V, Conniot J, Matos AI et al. Regulatory aspects on nanomedicines. Biochemical and Biophysical Research Communications. 2015; 468: 504-510

22. Emily M, Ioanna N, Scott B and Beat F. Reflections on FDA Draft Guidance for Products Containing Nanomaterials: Is the Abbreviated New Drug Application (ANDA) a Suitable Pathway for Nanomedicines? AAPS J.2018; 20:92

23. Patel P and Shah J. Safety and Toxicological Considerations of Nanomedicines: The Future Directions. Curr Clin Pharmacol. 2017; 12:73-82.

24. Troiano G, Nolan J, Parsons D et al. A Quality by Design Approach to Developing and Manufacturing Polymeric Nanoparticle Drug Products. AAPS J. 2016; 18 : 1354-1365

25. Giannakou C, Park MV, de Jong WH, et al. A comparison of immunotoxic effects of nanomedicinal products with regulatory immunotoxicity testing requirements. Int J Nanomedicine. 2016;11: 2935-2952

26. Miernicki M, Hofmann T, Eisenberger I et al. Legal and practical challenges in classifying nanomaterials according to regulatory definitions. Nat Nanotechnol. 2019; 14: 208-216.

27. Soares S, Sousa J, Pais A and Vitorino C. Nanomedicine: Principles, Properties, and Regulatory Issues. Front Chem.2018; 6: 360

28. Tyner KM, Zheng N, Choi S, et al. How Has CDER Prepared for the Nano Revolution? A Review of Risk Assessment, Regulatory Research, and Guidance Activities. AAPSJ. 2017;19:1071-1083

29. Gkika DA, Nolan JW, Vansant EF et al: A framework for health-related nanomaterial grouping. Biochim Biophys Acta 2017; 1861:1478-1485.

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