Current Pharmaceutical Design, 2022, *28*, 165-177

REVIEW ARTICLE

Development of Nanomedicines and Nano-Similars: Recent Advances in Regulatory Landscape

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ARTICLE HISTORY

Received: May 03, 2021
Accepted: October 07, 2021

DOI:
10.2174/1381612827666211115170001

Abstract: ***Background*:** Nanopharmaceuticals serve as emerging forms of modern medicines, which include nanomedicines, nanosimilars, nanotheranostics, nanodevices, and many more. In the last two decades, a large number of nano-based products have reached the market and are being used clinically.

***Objectives*:** Unlike conventional pharmaceutical products, nanopharmaceuticals behave differently both *in vitro* and *in vivo*, and therefore, the development of their generic versions needs special attention to replicate the similar drug release pattern leading to an identical therapeutic outcome. Further, drug-device combinations and 3D products are the latest advancements in precision medicine delivery and development.

***Methods*:** The regulatory guidelines for these products are being framed at many stages by various regulatory agencies like USFDA/EMA and still are in infancy at the moment if we look at wider perspectives and applications of nanomedicine.

***Results*:** For a formulation scientist, it is much needed that well-explained and directive guidelines should be made available before leading to the development of the generic versions of these nano-cargos.

***Conclusion*:** Here, in this review, we have summarized the silent features of the regulatory perspectives related to nanotechnology based next generation therapeutics and diagnostics.

Keywords: Nanomedicine, nanosimilars, nanotheranostics, regulatory, pharmaceuticals, nanodevices, drug delivery.

1. INTRODUCTION

Next-generation therapeutics include precise delivery of therapeutic agents objectively being delivered to the desired location in the body. Nowadays, a combined approach of therapy and diagnosis is more popular, especially being utilized in nano-sized particles and is known as nano theranostics [1-3]. Nanopharmaceuticals are specialized drug delivery devices which due to their size based peculiar nature, could deliver the loaded agent to the specific bio-environment either at extracellular or intracellular locations [4-7]. A large number of biomaterials have been explored in order to develop a safe and effective nanomedicine for diverse routes of administration and for a variety of diseases. The different classes of therapeutics, including small molecules to biomacromolecules, a drug to diagnostic agent, medicinal to nutritional, synthetic drug to generic drug, have been successfully encapsulated into these nanopharmaceuticals for one or other reason as evidenced from the literature [8-11].

The question of the hour is that what parameters should be used to define the similarity between commercially available nanopharmaceuticals and generic versions of the same.The parameters like size, shape, polydispersity, surface charge, loading capacity are important ones that affect not only drug release or pharmacokinetics but also the therapeutic performance of nanopharmaceuticals at large. The nature of the biomaterial selected for the development of nanopharmaceuticals also affects the overall biological fate and the effectiveness of the nano-sized system [12]. The nanoparticles can be developed by both physical (top-down method) and physico-chemical methods (bottom-up approach) [13]. The selection of the methods highly influences the physicochemical characteristics and hence the targetability and bioavailability at the desired location.

After the clinically effective nanopharmaceuticals hit the market, our traditional knowledge of drug transport was tuned to modern therapeutics, and it generated hope that more advanced nanosystems would emerge in the coming era. Additionally, the patented nano pharmaceutical products are leading towards the development of their generic versions by the competitive pharmaceutical market once the patent is expired [14]. For the growth of the pharmaceutical industry in this direction, it is required that some clear regulatory guidelines should be provided by the regulatory agencies worldwide.

2. NANOPHARMACEUTICALS

Nanopharmaceuticals are nanodrugs or advanced drug delivery systems capable of sustained and controlled delivery of loaded

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1873-4286/22 $65.00+.00

Table 1. List of next generation therapeutics and their silent features.

Next Generation Technology	Salient Features
Nanopharmaceutics	• Product development for Precise and controlled drug delivery. • Use of biocompatible and biodegradable biomaterials. • Targeted drug delivery for wide range of applications.
Nanomedicine	• Nano-sized therapeutics or nano-sized drug delivery carriers. • Nano-scale features of materials are explored for the treatment of diseases. • Improved bioavailability and shelf life. • Better safety and efficacy. • Stimuli responsive drug release. • Achievement of EPR effect in tumor targeting.
Nanosimilars	• Generic versions of marketed nanoproducts. • Established therapeutic efficacy and safety of the nanotechnology driven product. • Less time consuming and cost effective nanotechnology based products.
Nanodevices	• Nanocargos for intracellular targeting and organelle specific drug delivery. • Delivery of drug/genetic material is possible. • Enables better understanding of cellular trafficking, internalization and mechanism of cell cytotoxicity. • Third level targeting which avoids undesirable side-effects.
Nanotheranostics	• Co-delivery of both drug and diagnostic agent in a single nanocarriers. • Precise and accurate imaging possible using one to one interaction. • Provide early detection and drug therapy on demand. • Facilitates personalized drug therapy or medicine.

bioactive molecules. A unique formulation science called nanopharmaceuticals applies the principle of nanotechnology in pharmaceutics [15]. These tiny sized delivery systems are prevalent due to their size, shape, bioavailability, biodistribution, and pharmacokinetics. Nanomedicine is an advanced form of nanopharmaceuticals that mostly includes the development of engineered nanostructure with surface modifications for drug delivery purposes. Both the efficacy and toxicity of nanopharmaceuticals are directly related to pharmacokinetics, *i.e*., ADME of the drug products [16]. Absorption and distribution play an important role in efficacy, while metabolism and elimination are major contributing factors for the toxicity of nanopharmaceuticals [17]. Recently, some drug delivery nanosystems have been developed, including carbon nanotubes, metallic nanoparticles, lipid based nanoparticles (liposomes, SLN and NLC), micelles, dendrimers, and quantum dots. However, more advanced targeted drug delivery systems are the interest of modern nanopharmaceuticals [18]. The establishment of a nanopharmaceutical formulation is required to analyze the type of drug and selection of nanomaterial (*e.g*., polymer, lipid, polysaccharides, proteins, metals) followed by the manufacturing process. Before launching the formulation onto the market, it should be evaluated for its scale-up possibilities with the production method and henceforth should have elements for compatibility and quality of products. The regulatory issues related to nanopharmaceuticals still require expertise for harmonizing legislation and knowing the clinical complaint of production methods. Table **1** enlists the recent next generation therapeutics and their salient features.

2.1. Nanomedicine

Nanomedicine, a word proposed by Robert Freitas Jr. in 1952 and Eric Drexler in 1955, can be defined as a multidisciplinary branch that deals with nanotechnology, molecular biotechnology, and other nanosciences [19]. The word "nanomedicine" also refers to nanomaterials that are used in disease management, diagnosis, and therapy, as well as in the monitoring of numerous biological markers and parameters. It is a continuously growing discipline and has been divided into different branches and sub-branches [19]. Nanomedicine is a clinical application of nanotechnology that helps doctors, researchers, and technicians develop nano products and meet the challenges faced by the health care industry. Nanomedicine provides better pharmacokinetic and pharmacodynamic effects than micro-sized or conventional drug products and provides opportunities for the development of personalized medicine [20, 21]. Recently, nanomedicine has been moved from the laboratory to clinics as suggested by regulatory approval of Abraxane® and other similar nanotechnologically derived products [22]. Fig. (**1**) represents various types of nano-sized drug delivery carriers that serve as nanomedicine.

2.2. Nanosimilars

The first generation nanomedicine products are approved now and have successfully entered clinical practices. Now, regulatory agencies are required to play an important role so that generic versions of nanomedicine products so called 'nanosimilars' can be introduced timely and safely in the market [23, 24]. The medicine regulatory agencies should provide clear guidelines not only for establishing the regulatory approval process but also to assure that the approved generic nanotechnology based products have quality, safety, efficacy, and consistency in the case of nanomedicines. This will further ensure the timely entry of nanosimilars in the market for the benefit of public health and the delivery of market competence [25]. Nanosimilars are characterized by specific criteria that include the particle size and size distribution, surface characteristics, fraction of unentrapped bioactives, storage and ready to use stability, and finally, fate in the body after administration [23]. Nanosimilars are the nanotechnologically derived system that claimed to be similar to the reference nanosystem. However, before making a claim, these systems should be therapeutically equivalent and safe as the originator product. They combine the characteristics of nanocarriers with generic drugs to produce a new medicinal product. Large numbers of generic drugs are available in markets replacing off-patent drugs [24]. Due to the complexity of nanomedicines based product, the approaches for assessing statistical identity or similarity are not considered as effective as for generic and biosimilar products. The fractional analysis could be a solution in the mapping process as it can bridge the gap between the complete characterizations of morphological characteristics [24-26]. This phenomenon can be understood by the example of a liposomal product development, where the drug-to-lipid ratio isconsidered a critical process parameter for the optimization of the product and its therapeutic efficacy. So in the development of nanosimilars of liposomal systems, drug-to-lipid ratio is an important element that mustbe included in the nanosimilar product description [27].

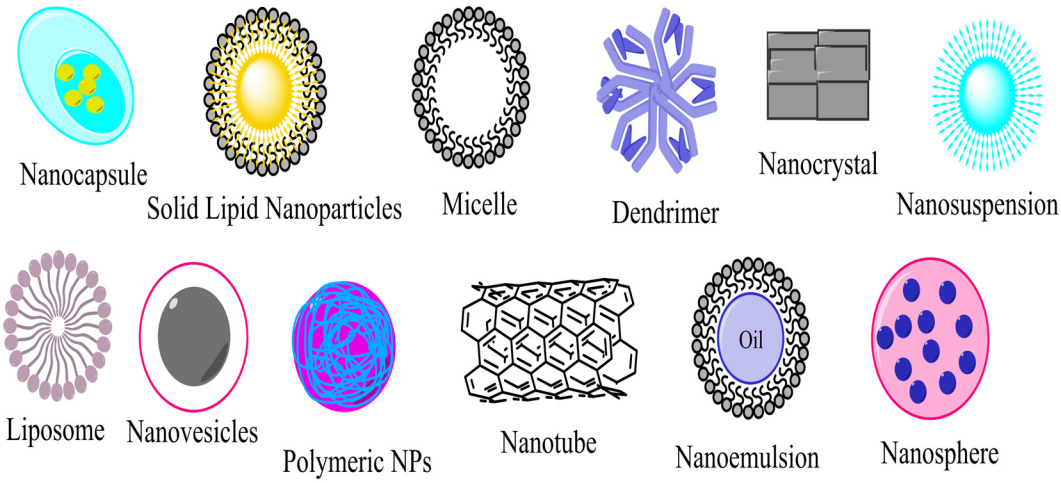

Fig. (1). Schematic diagrams for various nano-sized drug delivery carriers. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

2.3. Nanodevices

Nanodevices are attractive tools for the delivery of therapeutic molecules to target cells. These are surface functionalized or ligand anchored nanoparticles or environment responsive nanosystems especially capable of intracellular delivery of the target protein/gene/-drug for its treatment and diagnosis [28]. Usually, these nanodevices utilize the unlocking approach of the key features available at the target cell either in the form of over-expressed receptors or the specific presence of pH or enzymes in the microenvironment [29, 30]. Nanodevices are useful for imaging purposes. They have miniature imaging tools in them, which may be very helpful during early diagnosis and critical surgery [28, 31]. Metal based nano-architectures composed of gold, silica, iron oxide, carbon dots, fullerenes serve as a platform for these nanodevices.

2.4. Nanotheranostics

Nanotheranostics implies co-delivery of the diagnostic and therapeutic agent using a single delivery system [31]. Sometimes, biomaterials themselves serve as diagnostic/imaging agents such as gold, iron, fullerenes, *etc*. Targeted nanocarriers have been implied for this purpose using decorated fragments of monoclonal antibodies, folic acid, transferrin, estrogen, *etc*. [32, 33]. Nanocarriers like liposomes, dendrimers, polymeric micelles, and lipid nanoparticles have been explored for developing nanotheranostics. Smart nanotheranostics combine both active targeting as well as diagnosis of the targeted cell/tissue [34]. Magnetic resonance imaging (MRI) and Radio-diagnosis are relatively common approaches for achieving diagnosis with magnetic or radiolabelled nanoparticles.

3. DEVELOPMENT OF GENERIC NANOPHARMACEUTICALS

Nanotechnology is one of the most appealing technologies in the healthcare sector at the current time (Fig. **2**). Nanopharmaceuticals have been growing immensely in recent years, and USFDA approved more than 100 products based on their significant medicinal value [35] demonstrating the clinical worth of nanomedicine in various lethal disorders. Despite the success of nanomedicine, novel drug products remain out of reach for the majority of the population due to the complex and costly development of new products, as well as the undefined drug approval process for generic versions of such products. It is obvious that suitable documentary evidence and reference materials are the key elements of the drug regulatory approval process for any generic drug. These factors are very crucial to support the emerging sector of nanomedicine in the drug market, and the company needs to identify the relevant standards before the products enter into the regulatory approval process.

Moreover, the shortage of innovative drug products, particularly of the nano origin, is a challenging matter in USA, EU, and other drug markets, and this fact motivated the approval of generic nanodrugs at a fast pace. Also, the time frame of nanoformulation patent is slowly approaching, which paves the way for the manufacturers to introduce generic nanomedicine. Thus, drug manufacturers need a good understanding of the regulatory information that can be applied in particularities of nanomedicines. Some key issues for the development of innovative nanomedicine or introduction of generic nanomedicine include intellectual property, technical issues, development costs, and ethics and regulatory approval in respective markets. The primary concept of nanoparticles development and their approval required exhaustive characterization and documentation of each step in the development to improve the complexity in drug products as well as their approval.

The lack of formal regulatory guidelines, which is still shrouding the development of generics in ambiguity, is a major challenge to the launch of a generic version of nano drugs.When comparing nanomedicine to small molecule therapeutics (where the primary concern is API), it is important to note that nanomedicine involves several new formulation parameters, such as shape, size, and chemical composition, in addition to the API, and that they may be subject to more or different assessments than their innovative products [36]. Even two nanomedicine products need to be approved considering different strategies. For example, if the proposed product is for gene therapy application, the characterization parameters will be totally different if compared to the product for traditional synthetic small molecule drugs. For obvious reasons, the testing of such generic medicine will cost a higher amount and time to the drug manufacturer. There is also a huge gap in defining the innovative and generic nanomaterials' developments, *i.e*., the missing uniformity on drug loading methods and drug release methods, nanomaterials to immune system interaction, detection methods in tracking the nanomaterials in biological tissues, non-defined comparability between reference materials. The lack of suitable reference materials and standard methods to evaluate the suitability of nanomaterials is also a critical missing element [37].

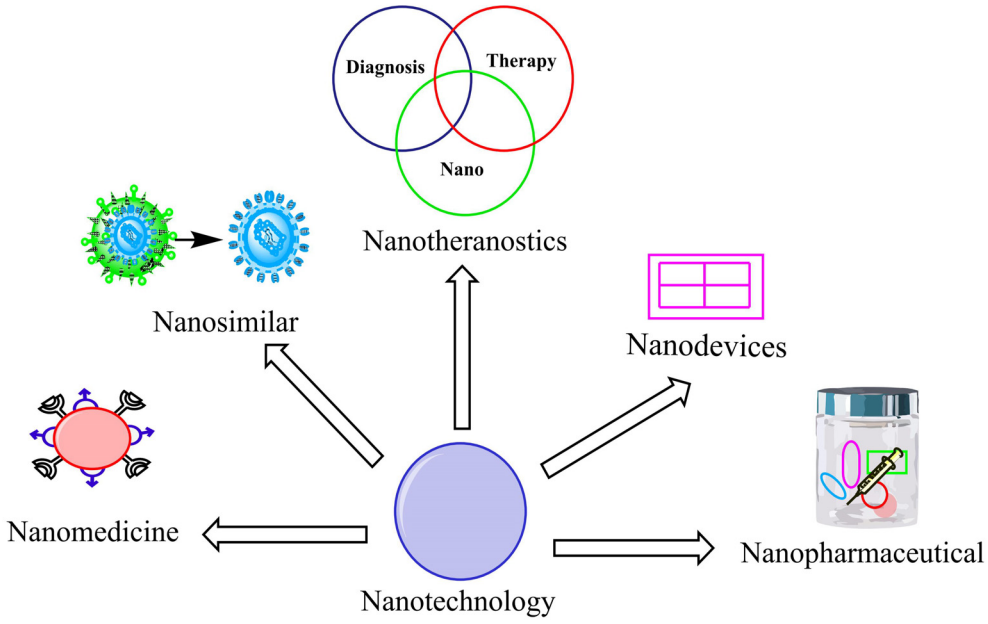

Fig. (2). Nanotechnology driven different classes of nanotherapeutics. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

In a similar way, the regulatory bodies will also need a more sophisticated approach to approve the nanomedicine. Even FDA does not have fully defined common parameters which can be applied to all nanomedicine. Thus, the agency has great flexibility to evaluate the generic application of potential nanodrugs as individual entities, and they recommend the approval case-to-case basis because each nano product is unique. However, the regulatory bodies suggested unique guidelines for the development consideration of such formulations. For example, the draft guidelines of USFDA (Section VI.B) suggest that generic formulation must show the bioequivalent to the reference listed drug and sufficient information about the API, conditions of use, route of administration, dosage form, API strength, as well as the labelling similar to the Reference Listed Drugs [38].

The USFDA developed guidance documents for drug manufacturers with regard to the application of nanotechnology in new products to be considered in the USA (2017). These guidelines recommend the purposeful manipulation and control of various dimensions to produce specific physicochemical properties in nanomaterials, which may further allow their evaluation with regards to safety, effectiveness, performance, as well as quality. In a similar way, EMA also suggested guidelines for the development of nanomaterials and suggested that they will evaluate any application on nanomedicine products primarily utilising the established principles of benefit/risk analysis rather than solely on the basis of the new technology before recommending drug approval. Thus, they were more interested in the overall benefit of patient's health, not in the technology itself (2006).

To avoid any danger associated with the production of complex nanomaterials, regulatory bodies advised drug manufacturers to examine chemical manufacturing and control parameters from the outset of such product development,*i.e.*, identification of the critical quality parameters to correlate the activity and safety, identification of suitable analytical characterization methods (physical, chemical, biological), identification of process parameters, evaluation of batch to batch variation, and scale up the process to ensure a successful reproducible manufacturing process. Manufacturers were also urged to contact regulatory agencies early in the product development process for scientific advice or an informal briefing in order to minimise additional hazards associated with the development process [39].

To summarize, the establishment of nanomedicine development protocol on a global level will accelerate the approval of much needed generic nano medicinal products, allowing them to reach the majority of patients suffering from lethal diseases. In the next section below, the regulatory requirements of various nanocarriers are being discussed, considering the example of one product in the market. Herein, the key factors of drug approval application required to grant market authorization are suggested in Table (**2**) based on the formulation development point. It is estimated that in the near future, many new nanomedicines will be approved based on earlier product development and regulatory strategies. Fig. (**3**) highlights the process and steps involved in the development, characterization, and regulatory approval of generic nanopharmaceuticals.

3.1. Marketed Formulations: Some Lead Examples and Regulatory Challenges

Successful marketed formulations pave the way for developing nanomedicine for next generations or nanosimilars. For the reader's benefit, a case by case discussion on different classes of marketed nanomedicines and their regulatory challenges has been presented in this section.

3.1.1. Doxil (Lipid based Vesicular Liposomal Nanocarriers)

Doxorubicin HCl liposome injection is an important part of cancer treatment among the several available cancer medicines. Doxorubicin HCl liposome injection was approved by FDA in 1995 and is currently marketed by Janssen as Doxil® in the United States/Japan and as Caelyx® in other parts of the world. The formulation is used for AIDS-related Kaposi's sarcoma, ovarian carcinoma, and multiple myeloma (in combination with bortezomib). In

Table 2. List of potential marketed nanopharmaceutical products, their components, target disease and critical development parameters.

Category	Formulation Name/Company	Components	Target Disease	Critical Development Parameters	Refs.
Liposomes	Doxil (Alza, Pakistan) also known as Caelyx®, Evacet® and Lipodox®	Doxorubicin, HSPC, cholesterol and MPEG-DSPE	Ovarian, breast cancer, Kaposi's sarcoma	Shelf life, vesicle size, size distribution, zeta potential, lipid phase transition, targeted accumulation, selection of lipids, release rate, surface chemistry, aggregation, osmolarity, thermodynamics.	[40]
	DaunoXome® (Galen, Craigavon, UK)	Dauborubicin, DSPC and Cholesterol,	AIDS-related Kaposi's sarcoma		[41]
	Onivyde® (Merrimack Pharmaceuticals, MA, USA)	Irinotecan, DSPC:MPEG-2000: DSPE	Combination therapy with fluorouracil and leucovorin in metastatic adeno-carcinoma of the pancreas		[41]
	DepoCyt® (Pacira Pharmaceuticals, NJ, USA)	Cytarabine/Ara-C, DOPC, DPPG, Cholesterol and Triolein	Neoplastic meningitis		[41]
	Marqibo® (Talon therapeutics, CA, USA; Fig. **4**)	Vincristine, SM, Cholesterol	Acute lymphoblastic leukaemia		[42]
	AmBisome® (NeXstar Pharmaceuticals, CA, USA)	Amphotericin, HSPC, DSPG, and Cholesterol	Presumed fungal infections		[41]
	Vyxeos® (Jazz Pharmaceutics, Dublin, Republic of Ireland)	Daunorubicin, Cytarabin DSPC, DSPG, and cholesterol	Secondary myeloid leukemia (sAML): therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)		[43]
	Abelcet (Defiante Farmaceutica, Funchal, Portugal)	Amphotericin B, DMPC and DMPG	Invasive severe fungal infections		[44]
	Visudyne® (QLT Phototherapeutics, Vancouver, Canada)	Verteporphin, DMPC and EPG	Choroidal neovascularisation		[44]
	Mepact® (Takeda Pharmaceutical Company Limited Cambridge, MA, USA)	Mifamurtide, DOPS, POPC, and MTP-PE	High-grade, resectable, non-metastatic osteosarcoma		[45]
	DepoDur® (SkyePharma, San Diego, CA, USA)	Morphine, DOPC, DPPG, Cholesterol and Triolein	Pain management		[43]
	Exparel® (acira Pharmaceuticals, Inc.)	Bupivacaine, DEPC, DPPG, Cholesterol and Tricaprylin	Pain management		[41]
Lipid based non liposomes nanocarriers	Abelcet®	Amphotericin B complex 1:1 with DMPC and DMPG (7:3	Antifungal and antibiotic for variety of serious fungal infections	Particle size, therapeutic cargo loading, intracellular delivery, endosomal escape, lipid fusogenicity, selection/ composition of ionizable lipid and helper lipids, stability, shelf life, zeta potential	[8]
	Visudyne® (CHEPLAPHARM Arzneimittel GmbH Germany)	Verteporfin, DMPC, ascorbyl palmitate, egg PC, egg PG, butylated hydroxytoluene (E321) and lactose monohydrate	Myopia, degenerative macular degeneration		
	Onpattro® (Alnylam Pharmaceuticals, Inc. USA)	SiRNA, DLin-MC3-DMA, PEG2000-C-DMG, DSPC and cholesterol	Polyneuropathy caused by an illness called hereditary ATTR (hATTR) amyloidosis		[46]
	BNT162b2 (BioNtech/Pfizer Germany / USA)	mRNA, ((4-hydroxybutyl)-azanediyl) bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, DSPC and cholesterol	COVID-19 viral SARS disease		[47]
	mRNA-1273 (Moderna USA)	mRNA, Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy)-hexyl)amino)octanoate,1,2-dimyristoyl-rac-glycero-3-methoxy-polyethylene glycol-2000, DSPC and cholesterol	COVID-19 viral SARS disease		[47]
Micelles	Estrasorb (Novovax, Columbia, MD USA)	Estradiol, soybean oil, water, polysorbate 80, and ethanol	Vasomotor symptoms in menopause	Colloidal stability, polymer concentration, balance in hydrophilic cornea and a hydrophobic core, target specificity, controlled release of drugs, biocompatibility, biodegradability	[48]
	GenexolPM (Samang Biopharm, Korea)	Paclitaxel,mPEG-PDLLA: monomethoxy-poly (ethylene glycol)-block-poly (D, L-lactide)	Metastatic Breast Cancer (MBC), Non-small cell lung cancer (NSCLC) and ovarian cancer		[49]
	Taxotere (Sanofi-aventis LLC, Bridgewater, NJ USA)	Docetaxel, polysorbate 80 (Tween 80) and dehydrated alcohol solution	Broad spectrum anticancer		[50]
Nanocrystals	Emend® (Merck & Co., Inc., NJ, USA)	Fosaprepitant dimeglumine (Aprepitant)	Prevention of delayed nausea and vomiting in adults receiving moderately emetogenic chemotherapy (MEC)	Controls of manufacturing critical steps *e.g.* milling process, mitigation, control of process-related impurities, stability of APIs, stability of polymorphic form(s), particle size distribution of drug substance, particle size distribution of nanocrystal colloidal dispersion, identification of polymorphic form (s)	[48]
	Ostim® (Osartis GmbH & Co. KG, Dieburg, Germany)	Nanocrystalline paste of calcium hydroxyapatite	Osteoinduction, used in orthopedic and dental surgery procedures.		[48]
	Ritalin® (Novartis, Switzerland, Basel)	Methylphenidate hydrochloride, lactose, magnesium stearate, starch, polyethylene glycol, sucrose, talc, and tragacanth FD & C Green No. 3	Attention deficit hyperactivity disorder (ADHD) and narcolepsy		[48]
	VitossR (Orthovita, Inc. PA, USA)	35% calcium, 15% phosphorous and 4.5% carbonate	Synthetic Cancellous Bone (Void Filler)		[48]
	TriCor® (Abbott Laboratories; generic name is fenofibrate, IL, USA)	Fenofibrate, hypromellose 2910 (3 cps), microcrystalline cellulose, sodium lauryl sulfate, docusate sodium, lactose monohydrate, sucrose, silicified crospovidone, and magnesium stearate	Primary hyperchole-sterolemia or mixed dyslipidemia, severe hypertriglyceridemia		[48, 51]
	Rapamune® (Wyeth Pharmaceuticals Hants, UK)	Sirolimus, sucrose, lactose, PEG 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, PEG 20,000, glyceryl monooleate, carnauba wax, *dl*-alpha tocopherol, yellow iron (ferric) oxide and brown iron (ferric) oxide	mTOR inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in renal transplant patients, and lymphangioleiomyomatosis		[48, 51]
	Zypadhera® (Eli Lilly Nederland B.V.The Netherlands)	Olanzapine pamoate, carmellose sodium, mannitol, polysorbate 80, water for injections, hydrochloric acid and sodium hydroxide	Maintain the improvement in symptoms in patients with schizophrenia		[52]
	MEGACE®ES (Breckenridge Pharmaceutical, Inc. BOCA RATON USA)	Megestrol acetate, alcohol artificial lime flavor, citric acid monohydrate, docusate sodium, hydroxypropyl methylcellulose, lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.	Treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of AIDS		[48]
	Triglide (SkyPharmaProduction SAS, France)	Fenofibrate, crospovidone, egg lecithin, monohydrate, mannitol, maltodextrin, carboxymethylcellulose sodium, lactose croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, and monobasic sodium phosphate	Treatment of Hypercholesterolemia, Treatment of Hypertriglyceridemia		[48]

(Table 2) Contd….

Category	Formulation Name/Company	Components	Target Disease	Critical Development Parameters	Refs.
Metal based nanocarriers for therapeutic or diagnostic purpose	Gastromark (Mallinckrodt Inc. St. Louis, USA	Ferumoxsil (poly [N-(2-aminoethyl)-3-aminopropyl] siloxane coated nonstoichio-metric magnetite (FeOx[C5H13N2SiO2]y)), sodium chloride, sorbitol, water, saccharin, carboxymethylcellulose, methylparaben, propylparaben, yellow dye #6, red dye #40, and flavoring	Magnetic resonance imaging	Particle size and size distribution, biodistribution, organ specificity, toxicity, pharmacokinetics, safety suspension stability, selection of suspending agents	[53]
	Resovist® (Bayer Healthcare, USA)	Ferucarbotran, iron oxide microparticles coated with carboxydextran	MRI contras agent in RES specially spleen and liver		[54]
	Feraheme®/ Rienso® (AMAG Pharmaceuticals, USA)	Ferumoxytol, Iron oxide particles surrounded by a carbohydrate coat, polyglucose, carboxymethylether (PSC), sorbitol sodium hydroxide, hydrochloric acid mannitol, and water	Iron deficiency in adult chronic kidney disease patients		[55, 56]
	Ferinject® (Vifor Pharma UK Limited, UK)	Ferric carboxymaltose, Sodium hydroxide, hydrochloric acid water	Iron deficiency		[56]
	Monofer® (Pharmacosmos UK Limited, UK)	Iron(III) isomaltoside, Sodium hydroxide, Hydrochloric acid and water	Iron deficiency (oral iron preparations are ineffective, or rapid iron delivery)		[56]
Emulsion based nanocarriers	Restasis® (Allergan USA)	Ciclosporine, oil-in-water nanoemulsion, contains CsA dissolved in castor oil with polysorbate 80	Increase tear production (patients with ocular inflammation)	Emulsion stability, composition and biocompatibility of emulsifying agents, droplets size and size distribution, temperature, pH, zeta potential, lipid content, viscosity, electrolyte, concentrations	[57]
	Ikervis®, Novasorb® platform Santen (Novagali)	Ciclosporine, medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide and water	Severe keratitis		[57]
	Oncaspar® (Sigma-tau Arzneimittel GmbH, Munich Germany)	Pegaspargase, sodium dihydrogen phosphate monohydrate, disodium phosphate heptahydrate, sodium chloride, and water	Acute lymphoblastic leukemia (ALL)		[58]
	Clinoleic® (Baxter Healthcare, Deerfield, IL, USA)	Olive oil (approximately 80%) and refined soybean oil (approximately 20%)	Source of calories and essential fatty acids for patients requiring parenteral nutrition		[56]
Antibody-drug / conjugates	Ozogamicin (Pfizer Limited, Sandwich, Kent UK)	Gemtuzumab mab targeting CD33 linkedto the cytotoxic derivative of calicheamicin (ozogamicin)	Acute myeloid leukemia	Target selectivity and specificity, blood stability, structural characterization, target antigens, selection, cytotoxic payload	[59]
	Polatuzumab vedotin-piiq (Genentech/Roche USA)	Monoclonal antibody (CD79b) covalently conjugated to the anti-mitotic cytotoxic agent monomethyl auristatin	Relapsed or refractory diffuse large B-cell lymphoma		[59]
	o-Trastuzumab emtansine (Genentech/ Roche)	Potent cytotoxic drug connected *via* a stable linker to the anti-HER2 antibody (trastuzumab)	HER2-positive breast cancer		[59]
	EDV™ nanocell (EnGeneIC, USA, Australia)	EGFR-targeted, doxorubicin-loaded EDV nanocells	Orphan drug for glioblastoma multiforme (GBM)		[60]
Protein based conjugates	Abraxane® (Abraxis BioScience, LLC., USA)	Paclitaxel, human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).	Metastatic breast cancer, metastatic pancreas adeno--carcinoma with Gemcitabine and non-small cell lung cancer with Carboplatin	Thermodynamic and kinetic factors (dissociation), encapsulation, carrier specificity and selectivity stability, pH, particle size distribution, zeta potential, osmolality, *in vitro* release, viscosity, identification of polymorphic form (s),API and protein ration, protein characterization and integrity	[61]
	Denileukin diftitox, known as Ontak® (Eisai, Japan)	Recombinant cytotoxic protein in sterile solution of citric acid (20 mM), EDTA (0.05 mM) and polysorbate 20 (< 1%) in water	Recurrent cutaneous T-cell lymphoma		[62]
	Rebinyn® (NovoNordisk, Bagsværd, Denmark)	Recombinant human Factor IX (rFIX) with a 40 kilodalton (kDa) polyethylene-glycol (PEG) conjugated to the protein	Hemophilia		[62]
	Somavert® (Pharmacia & Upjohn Co., Division of Pfizer Inc., NY)	Recombinant DNA origi protein covalently bound (Pegvisomant) to polyethylene glycol (PEG), other ingredients are glycine, mannitol, sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate	Acromegaly		[62]
	Cimzia™ (UCB Pharma SA, Belgium)	Recombinant, humanized antibody Fab' fragment (Certolizumab pegol), specific for human tumor necrosis factor alpha (TNFα), conjugated to 40kDa PEG (PEG2MAL40K), lactic acid, polysorbate, sucrose, sodium acetate sodium chloride water	Rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA)		[63]
PEG based polymeric nanocarriers	Adagen® (Enzon, Inc., NJ, USA)	PEG-pegademase bovine, Monobasic sodium phosphate, Dibasic sodium phosphate, sodium chloride and water	Immunodeficiency disease	Zeta potential and surface area, *in vitro* release kinetics, toxicological assessment, biocompatibility, biodegradability, blood retention, toxicity, PEG *vs.* polymer content, surfactant content and biocompatibility pH, stability, release kinetics, chemical composition, molar mass, chemistry	[53]
	Neulasta® (Amgen, Inc., CA, USA)	PEG-G-CSF, acetate, sorbitol 16, polysorbate 20, sodium, and water	Febrile neutropenia		[53]
	Oncaspar® (Enzon Pharmaceuticals Inc., NJ, USA)	PEG-asparaginase, ibasic sodium phosphate, monobasic sodium phosphate, sodium chloride and water	Leukemia		[53]
	Pegasys® (Hoffmann-La Roche Inc./ Genentech USA, Inc., CA, USA)	PEG-α-interferon 2a, acetic acid, benzyl alcohol, polysorbate 80, sodium acetate trihydrate, and sodium chloride	Hepatitis C		[53]
	Somavertt® (Pfizer Pharmaceuticals, CT, USA)	PEG-human growth hormone (HGH), glycine, mannitol (E421), sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate	Acromegaly		[53]
	Macugen® (EyeTech/ Pharmaceuticals Pfizer Inc. Florida USA)	Pegylated anti-VEGF aptamer (pegaptanib sodium), sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide	Age-related macular degeneration		[53]
	Mircera® or epoetin β (EPO)	Methoxy polyethylene glycol-epoetin beta, sodium dihydrogen phosphate monohydrate, mannitol (E421), methionine, sodium sulphate, poloxamer 188 and water	Symptomatic anaemia associated with chronic kidney disease (CKD)		[64]
	PEG-INTRON® (Schering Corporation/ Merck & Co., Inc. USA)	PEG-α-interferon 2b,dibasic sodium phosphate anhydrous, monobasic sodium phosphate dihydrate, sucrose, and polysorbate 80	Chronic hepatitis C		[53]
	Krystexxa® (Crealta Pharmaceuticals Ireland Limited, Dublin, Ireland)	Pegloticase, Disodium hydrogen phosphate dihydrate Sodium dihydrogen phosphate dihydrate Sodium chloride Water	Severe debilitating chronic tophaceous gout		[65]
Non-PEG based polymeric nanocarriers	Zilretta® (Flexion Therapeutics, MA, USA)	Triamcinolone acetonide, sodium carboxymethylcellulose (CMC), sodium chloride, and polysorbate80	Management of osteoarthritis pain	Particle size distribution, zeta potential, composition, toxicity, polymer composition, *in vitro* release kinetics, toxicological assessment, chemical composition, biocompatibility, biodegradability	[66]
	Renagel® (Genzyme Europe B.V. Amsterdam, The Netherlands)	Sevelamer hydrochloride, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid	Control of serum phosphorus in patients with chronic kidney disease (CKD)		[67]
	Zevalin® (Ceft Biopharma s.r.o. Czech Republic)	Ibritumomab tiuxetan, sodium chloride, water, sodium acetate vial, sodium acetate and formulation buffer vial	Consolidation therapy after remission induction, in rituximab relapsed / refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL)		[68, 69]
	Copaxone®, (Teva Neuroscience, Inc. USA)	Glatiramer acetate, mannitol COPPL-004	Immunomodulator, Multiple Sclerosis		[70]

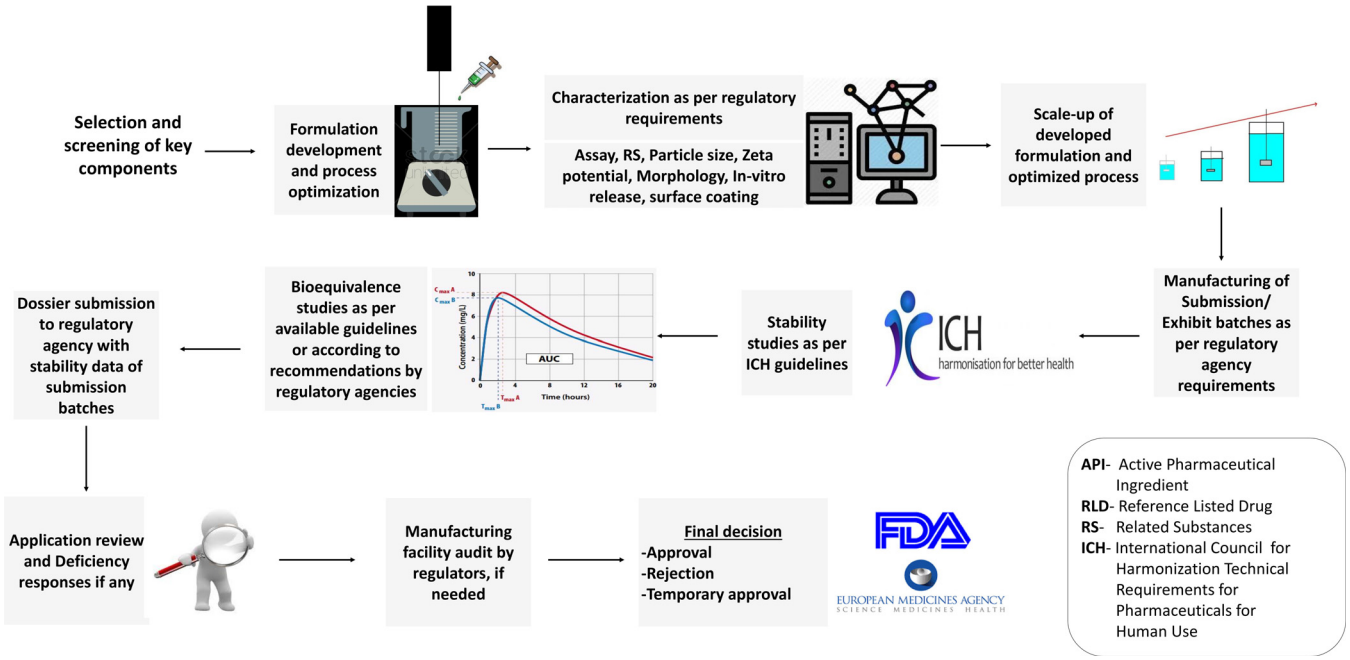

Fig. (3). Process and steps involved in the development, characterization and regulatory approval of a generic nanopharmaceutical product. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

European Union, it is also approved for breast carcinoma in patients at risk of anthracycline cardiotoxicity [70] in addition to the above categories. The antitumor efficacy and safety of doxorubicin HCl liposome injection developed by Sun Pharmaceutical Industry Ltd. were evaluated on syngeneic fibrosarcoma-bearing BALB/c mice. MX-1-bearing athymic nude mice suggested its efficacy at all doses tested in comparison to the reference drug Doxil. Furthermore, the pharmacokinetic parameters' rate and extent of doxorubicin absorption in mice were also similar between reference drug and generic products in fibrosarcoma-bearing BALB/c mice. Lately, Lipodox was launched as the first generic nanodrug of Doxil in the United States (2013) after the FDA observed that the generic version had the same quality and strength as the brand-name drug. In this case, clinical data was not required. Table **3** lists the comparison of parameters of the two marketed nano-based doxorubicin loaded liposome products, Doxil® and Caelyx®.

3.1.2. Abraxane (Protein-based Nanoparticles)

Abraxane (Abraxis BioScience) is Paclitaxel human serum albumin protein (HAS)-bound nanoparticles for various indications viz. metastatic breast cancer, non-small cell lung cancer (NSCLC), and pancreatic adenocarcinoma [71]. For the submission of ANDA application, FDA considered only bio-equivalence studies rather than full safety testing for the generic version of Abraxane [72]. In 2018, Panacea Biotec received ANDA on its filing for the generic version of Abraxane by USFDA. Later, Panacea Biotec and its partner Apotex Inc. and Apotex Corporation (Apotex) agreed with Abraxis Bioscience to develop and sell the generic version in the US market (2017c). Committee for Medicinal Products for Human Use (CHMP), a part of EMA, also adopted a positive opinion, recommending the marketing authorisation for the medicinal product Pazenir (Teva B.V.), a generic version of Abraxane. The EMA primarily considered the studies on the benefits and risks of the active substance in the authorised indication as well as the quality studies. Most importantly, in the case of Pazenir, a bioequivalence study was also not required because it is administered intravenously and the nanoparticles dissociate rapidly on injection. EMA approved Pazenir for first-line treatment of NSCLC in adult patients on which potentially curative surgery and/or radiation therapy is not adequate (2019). It is reported that the generic Pazenir has the same method and rate of administration, dosage form, API strength, and therapeutic indication.

3.1.3. Tricor (Nanocrystals; Crystalline Nanoparticles)

TriCor (Abbott Laboratories, Illinois, IL, USA) is based on nanocrystal technology having fenofibrate as an active ingredient useful for adjunctive therapy of severe hypertriglyceridemia [45]. In this formulation, the water-insoluble fenofibrate becomes more water-soluble by the application of Elan drug delivery nanocrystal technology, which allows this drug to be taken with or without food [73]. The formulation was introduced in the market in 1998 (Tricor 1) and faced the ANDA application by Novopharm, a generic drug manufacturer, in 2000. However, Abott immediately responded to this by filing patent infringement and further redeveloped the Tricor 2 formulation using a modified dose of fenofibrate 54 mg and 160 mg instead of 67 mg, 134 mg, and 200 mg of the original formulation. This approval was based solely upon bioequivalence studies comparing the new 54 mg and 160 mg tablets for the same pharmacologic properties as the original formulation. Nanocrystalline fenofibrate in Tricor is orally absorbed up to 35%, in addition to the reduced difference between fed/non-fed states [74]. Similarly, Abott introduced Tricor 3 version before the entry of the generic version of Tricor 1 and Tricor 2 (Teva 2007), to dominate the market in this area. Abott exclusively launched new Trilipix (API as fenofibric acid) delayed release capsules formulation 45 mg and 135 mg again on the basis of bioequivalence results [44] but considering NDA application. The approval was given on the basis of CMC data, non-clinical data, and comparing the clinical efficacy and pharmacology studies used in phase III data of Tricor [75]. Overall, their strategy to dominate the market has been quite

Table 3. Side by side comparison of parameters of the two marketed nano-based doxorubicin loaded liposome products Doxil® and Caelyx®.

Parameters	USFDA	EMA
Product	Doxil®	Caelyx®
Establishing comparability	Qualitatively (Q1) / Quantitatively (Q2) similar is needed.	The qualitative and quantitative composition of the developed product should be identical or closely match the reference product.
Description of lipidic components	Equivalent liposome characteristics including liposome composition should be comparable to the Reference Standard (RS).	Source and characterization, manufacture, assay, impurity profile, isomers and stability characteristics. Functionality-related characteristics as described in the pH. Eur. monograph 5.15 "Functionality-related characteristics of excipients" should be adequately addressed.
Drug loading process	Active liposome loading process with an ammonium sulfate gradient is recommended.	No specific loading process described in the guidance document.
Parameters for submission	• Liposome size distribution (D10, D50, D90; SPAN). • Population Bioequivalence (PBE) study needed. • Equivalent liposome composition needed to be evaluated. • Encapsulated drug to be in the form of doxorubicin sulfate crystal. • Comparison of Internal environment with the RS. • Lipid bilayer phase transition characterization. • Grafted PEG at the liposome surface: the PEG. thickness should be comparable to the RS. • Zeta potential to be comparable with the RS. • *In vitro* leakage testing under multiple conditions needed to be done.	• Liposomal integrity in plasma. • Lipid bilayer phase transition characterization. • Determination of particle size distribution and zeta potential. • Characterization of drug loaded inside the liposomes - Distribution of API within the liposomes. • Determination of pH of internal compartment for pH gradient loaded liposomes. • For PEGylated liposomes: chemistry of PEG-lipid linkage, quality, purity of PEG, disposition of PEG at the surface, molecular weight of PEG at surface and stability of conjugation. • *In vivo* studies to demonstrate any changes in physicochemical properties do not affect safety and efficacy of the product.
Clinical studies	Single-dose, two-way crossover *in vivo* study recommended to establish bioequivalence.	Comparative pharmacokinetic studies needed with the applicant's test product with reference product.
In vitro studies	*In vitro* dissolution studies needed to be done as per the FDA's recommendation.	No description about *In vitro* studies in the Reflection paper on requirements for i.v. liposomal products.
Non-clinical studies	No description about non-clinical studies in the Doxil® product specific guideline.	Non-clinical studies are not mandatory but recommended to understand pharmacodynamic, pharmacokinetic and toxicological aspects of developed product using suitable *in vitro* test.

successful even in the presence of several generic Tricor formulations by many competitors (Sun Pharmaceuticals, Alembic Pharms Ltd, Amneal Pharma, Valeant Pharms North, Prinston Inc, and Cipla Pharmaceuticals). Recently, several nanocrystal technology based nanomedicine products have been approved, *e.g.*, Megace® ES (Megestrol acetate), Gris-PEG® (Griseofulvin, Ultramicrosize), Grifulvin V (Griseofulvin, microsize), and Rapamune® (Sirolimus) [76].

3.1.4. Taxotere (Nanomicelles Technology)

Taxotere, a concentrate of Paclitaxel was developed using a mixture of Tween 80 and ethanol, showing significant improvement in antitumor activities up to 12-fold. The formulation has been used as broad spectrum anticancer agent against metastatic (gastric/ head and neck; 2006), non-small-cell lung (1999), and breast cancers (2004) [50]. Taxotere nano micelles concentrate produces favorable pharmacokinetics and maximizes efficacy with low adverse effects by enhancing the drug delivery to tumors by passive targeting. However, it is observed that the enhanced cellular uptake and cytotoxicity of Taxotere may be due to the nonspecific absorption of micelles by endocytosis and p-glycoprotein inhibition pathways [76]. There are several generic products in the market approved by US-FDA (innovative drug, 1994) and EU EMA (innovative drug, 1995) as the drug makers (Actavis Lic, Amneal Ltd, Mylan Labs Ltd, Dr. Reddys Labs Ltd, DFB Oncology Ltd, and many others). Since nanomicelles are not a very complex formulation and the final formulation is expected to be made shortly before administration, stability is not a difficult issue, and the availability of such a large number of generic Taxotere is expected. Other parameters, *e.g.*, stability of paclitaxel and other key ingredients (Tween 80 and ethanol) and cytotoxic issues, are not surprising due to the nature of drug activity. Moreover, the manufacturers bypass the rigorous clinical trials and testing as the innovative formulation and generic version can be proved "substantially similar" to a previously-approved one [77]. Also, the regulatory agencies were in agreement that the benefit to risk ratio is higher, and it is easier to grant approval *via* generic pathways, where bioequivalence is the primary issue in addition to quality data.

3.1.5. Feraheme® (Metal-based Nanoparticles for Imaging Purposes)

Ferumoxytol, an iron oxide particle coated with carbohydrate layer, is being explored as a potential imaging approach for evaluating lymph nodes and certain liver tumors. The feraheme nanoformulation was approved in 2009 for the treatment of iron deficiency anemia with chronic kidney disease [54]. Feraheme® was approved in the USA by AMAG Pharmaceuticals and as Rienso® in Europe. Ferumoxytol is uptaken by macrophages and consequently the reticuloendothelial system, which allows it to serve as a potential imaging approach to evaluate the lymph nodes and certain liver tumors [78]. Feridex® (ferumoxides), dextran-coated IONPs, was approved as an imaging contrast agent for the detection of liver lesions, however, discontinued in 2014 due to lack of clinical users. Another agent, Resovist®, is currently available in limited countries, *e.g.*, Japan (Resovist®; FUJIFILM RI Farma Co., Ltd., Kyobashi, Tokyo, Japan), Norway, (NC100150 Clariscan®, Nycomed) and Germany (VSOP C184, Ferropharm) [79]. It is important to note that Feraheme was withdrawn from the market in 2015. For the approval of metal-based particles, preclinical safety, toxicity, pharmacokinetics, and clinical safety and efficacy, are important considerations in addition to quality data.

3.1.6. Onpattro (Lipid-based Non-vesicular Nanocarriers)

Lipid nanoparticles (LNP) are spherical nanocarriers composed of ionizable lipids, which are positively charged at low pH (allows complexation) and neutral at physiological pH (reduce the toxic effects, as compared to positively charged lipids). Lipid nanoparti-

cles are quickly taken up by cells *via* endocytosis, and the ionization of the lipids at low pH enables endosomal escape to provoke the release of the cargo into the cytoplasm. LNPs are under development due to their aforementioned characteristics [80]. FDA allows the first small interfering ribonucleic acid (siRNA) based on Onpattro (patisiran; Alnylam Pharmaceuticals, Inc.) for the treatment of peripheral nerve disease (polyneuropathy), caused by Hereditary ATTR Amyloidosis (hATTR), a rare, debilitating and often fatal genetic disease [81]. Since the approval of Onpattro, several other LNP formulations have been under development and regulatory consideration, *e.g*., mRNA vaccine against Covid 19 (Moderna Pharmaceuticals USA and BioNTech GmbH Germany). This technology also enables the faster development of nanomedicine by providing effective loading, protection, and intracellular delivery of cargo for inducing the immune response in humans. In this type of formulation, additional factors for regulatory approval are endosomal escape, intracellular delivery, in addition to other factors, *e.g*., size, zeta potential, and nucleic acid complexation ability [47]. Onpattro has been approved by EMA's Committee for Medicinal Products for Human Use (CHMP) on the basis of ADME data, product shelf life, preclinical and clinical safety, and efficacy data provided by Alnylam (2018b). It is suggested in the case of gene therapy products, the specificity and efficacy of generic siRNA (or mRNA) are also very important aspects along with the performance of the nanoparticles.

3.1.7. Spritam® (3D Printed Drug Product)

3D printing has been introduced in drug formulation technology. When materials are deposited layer by layer to assemble a 3D object in 3D printing technology, it allows the local control of material composition as well as microstructure [82]. Aprecia Pharma, Inc. developed the first 3D-printed prescription drug Spritam, using "ZipDose" 3D printing technology. Its porous structure allows for high water solubility and rapid hydrolysis of the formulation, as well as ease of swallowing in epileptic patients [83]. However, there were several technical and regulatory challenges addressed before the product approval. Safety was a primary concern for the FDA team considering the complexities of the product. They observed the bioequivalence data and clinical pharmacology studies of the product and concluded that Spritam performed inconsistently with the known safety profile of Keppra (marketed drug levetiracetam). The CMC data also verified that the stability testing and manufacturing facilities for the approval of 250 and 500 mg tablets were both satisfactory [78]. Overall approval process was long due to the combined feature of the product (Hybrid pathway of a New Drug Application (NDA) due to involvement of new technology and Abbreviated New Drug Application (ANDA) for the BE comparison against Keppra).

3.1.8. Abilify Mycite (Drug-device Combination Product)

Abilify Mycite® (Otsuka Pharmaceutical Co., Ltd.) is a combination of aripiprazole tablets embedded with a sensor approved for the marketing by USFDA in December 2017 for the treatment of schizophrenia, bipolar I disorder associated manic and mixed episodes, and add-on treatment for depression. The associated sensor warns the patient if he/she missed taking the prescription through the patient's mobile phone [84]. However, as per the report published in BMJ journal, it is evidenced that the approval was given based on non-concrete data, and there was no actual benefit of medication compliance as well as any superior pharmacological effect than its traditional form. The product also could not qualify by EMA approval after a thorough investigation on application documents, and thus the company withdrew the marketing application in EU. Thus, the benefit *vs*. risk ratio was considered the most important factor before approval rather than newer technology. This example will further guide the sponsors for the development of nanomedicine wisely. It is, however, believed that the company will reapply the authorization with some additional data of efficacy. In this kind of hybrid product regulatory application, the company only can submit the quality data, as agencies believe that the benefits and risks data of the active substance are not needed and already have been carried out with the reference medicine [82].

3.2. Critical Formulation Factors for Nanopharmaceuticals

The ultimate objective of a nano pharmaceutical product is to achieve desired drug release pattern at the desired target site in order to ensure maximum therapeutic benefit with minimum side effects. The fate and biodistribution of nanopharmaceuticals depend upon many aspects, including the desired biodistribution after *in vivo* administration with specific control over the rate and extent of delivered drug/biomacromolecules. The formulation parameters that affect the overall performance and acceptance by the FDA include particle size, size distribution, surface charge, targetability, specificity, safety, and toxicity profile of biomaterial. When developing a generic nanopharmaceuticals product, the objective is to obtain as many silent properties as possible (preferably identical) in the generic version as in the FDA-approved product. The reproducibility and scale-up of nanomedicine have been a major challenge to the formulator where a large number of process and material related issues affect the final outcome of a nano pharmaceutical product.

3.3. Bioequivalence Issues

Unlike conventional pharmaceuticals such as a tablet, the setup of establishing a bioequivalence or procedure for the same in the case of nano similar to the existing approved nanomedicine product is not achieved yet. As discussed above, many factors like material, process, design and development, production, and intended use make them very different and complex compared to usual pharmaceuticals. For example, multilamellar liposomes show different release behaviour than unilamellar ones. Similarly, the composition of lipids in the case of SLNs also affects the digestion followed by absorption and hence different bioavailability upon oral administration. A lot of work is required to understand the *in vitro in vivo* correlation of these recent nanosystems before discussing bioequivalence. It is evident from the literature that every specific research design has adopted the drug release estimation as per the nature of the nanosystem or the as per reported literature. In the absence of proper design of the experiment or the procedure or official monographs, it is hard to control our understanding for the same.

4. REGULATORY GUIDELINES AND PRODUCT APPROVAL PROCESS FOR NANOPHARMACEUTICALS

4.1. US FDA Guidelines

Throughout the years, no guidelines have been published specifically for the nanomedicines by USFDA. In the year 2017, USFDA drafted guidance for drug products containing nanomaterials and biological products. The USFDA, in the past, evaluated nanotechnology-based products on a case-by-case basis. Materials exhibiting nanoscale range show different physicochemical properties and biological effects compared to the materials existing on a larger scale. This dimension-dependent phenomenon is utilized for improving the properties of pharmaceutical formulations. Various properties of formulations existing in the nanoscale range show increased bioavailability, reduced dose and dosing frequency because of the increased potency of the drug product, decreased toxicity profile of the drug product, and targeted delivery of the drug

molecules at the site of action. Till now, USFDA has not established the regulatory definitions of "nanotechnology", "nanomaterial", "nanoscale", or any terms related to nanoformulation based drug products. Currently, USFDA will inquire whether the drug product based on novel technology has at least one external dimension or a surface structure in the nanoscale range (approximately from 1 nm to 100 nm) and if the dimensions of the drug product fall outside the nanoscale range, up to one micrometer (1000 nm), USFDA will further question the effect of dimensions on the physicochemical properties of the product and its biological effect. These considerations will also apply when there are changes in manufacturing processes that result in altering the dimensions, properties, or any effect on the FDA regulated product [85]. The guidance on 'Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation Guidance for Industry' discusses what type of information the applicant should submit in the new drug application (NDA) or abbreviated new drug application (ANDA) application for a liposome drug product reviewed by the Center for Drug Evaluation and Research (CDER). The information should describe the drug substance and discuss in detail the information pertaining to the composition of the drug product like lipid, non-lipid, and non-liposome excipients (buffers), physicochemical parameters, manufacturing processes, and stability studies, along with the product specific guidelines. The human pharmacokinetics section of the document should include the clinical pharmacology studies, information related to drug release kinetics, and comparison of the liposome drug product with the non-liposome drug product to understand the various biopharmaceutical parameters of the novel formulation. A specific recommendation related to the information to be included in the labelling of liposome drug products is also mentioned in the guideline [86].

4.2. European Guidelines

European Medicines Agency (EMA) established an ad hoc expert group on nanomedicine in the year 2009 known as Committee for Medicinal Products for Human Use (CHMP). This ad hoc group issues recommendations on the approval or rejections of nanomedicines in the EU [87]. In 2011, the European Commission defined 'nanomaterial' as a product existing in one or more external dimensions in between the range of 1 nm to 100 nm. The CHMP help in drafting technical documents addressing the current regulatory experience on nanomedicines at EU level [88]. In the past, similar to USFDA, the EMA has considered reviewal and approval of nanomedicines on a case-by-case basis. Currently, EMA does not have any guidelines for nanomedicines and nanosimilars; though the agency has issued several reflection papers related to a specific nanomedicine product. A reflection paper is also developed by the agency to provide a framework for discussion and clarification in particular areas where scientific knowledge is growing and experience is relatively limited. Reflection papers cover the data requirements for the nanotechnology-based formulations such as intravenous iron-based nano-colloidal product [89], intravenous liposomal products [90], development of block co-polymer micelle medicinal products [91], and general issues related to surface coatings for consideration regarding parenteral administration of coated nanomedicine products [92].

4.3. Miscellaneous Guidelines

4.3.1. Japan

Medicines in Japan are regulated by the Ministry of Health, Labour and Welfare (MHLW) & Pharmaceuticals, and Medical Devices Agency (PMDA). The Japanese regulatory bodies are yet to come up with guidance and regulations for nanotechnology-based drug products [93]. By the collaborative working of MHLW and EMA, several reflection papers have been issued remarkably on the development of block copolymer micelle medicinal products. PMDA has considered reviewal and approval of nanomedicines on a case-by-case basis.

4.3.2. India

Drugs and medical devices are regulated by the Central Drugs Standard Control Organization (CDSCO) in India. The evaluation of nanopharmaceuticals for quality, safety, and efficacy is based on a case-by-case approach, taking into consideration the physicochemical properties of the nanomaterial used in the drug product. A guidance document- "Guidelines for Evaluation of Nanopharmaceuticals in India", was published in the year 2019. This guidance document was designed by the collaborative efforts of the Inter-ministerial Expert Committee constituted by the Department of Biotechnology comprising of experts from various departments of the Government of India. The definition of nanomaterial stated in this guideline is similar to the definition given by USFDA and EMA. According to the guideline, nanopharmaceuticals are categorized as follows:

(a) Degradability of nanomaterial: whether the nanomaterial is biodegradable or non-biodegradable.

(b) Nature of nanomaterial: depending on the synthesis, the material could be organic or inorganic and multi-component type (composed of two or more different materials, for example, magnetic liposomes).

(c) Nano form of the ingredient: this category comprised of either nanocarriers loaded with active pharmaceutical ingredients (API) like liposomes, polymeric nanoparticles, *etc*., or the API converted into the nanoparticulate or nanocrystal form.

According to the guideline and the aforementioned information, details about the scientific rationality of the development of nano pharmaceutical products should be stated in the application for reviewal. The guideline also discusses the requirements for data related to pre-clinical studies, clinical trials, stability data of the drug product, and information required for the evaluation of nanopharmaceuticals [94].

CONCLUSION AND FUTURE PERSPECTIVES

The success stories of commercially available nanopharmaceuticals have driven the force to develop the generic versions of these nanomedicines/nanosimilars. However, the complex nature and composition of these nanosystems develop a major challenge for generating nanosimilars. Currently, regulatory guidelines are available only for a specific product and not for the general term "nanomedicine". In our opinion, a detailed classification of nanomedicines on the basis of their unique composition or application type is required, like bionanomedicine, herbal nanomedicine, genetic nanomedicine, targeted nanomedicine, theragnostic nanomedicine, and long acting nanomedicine with sustained drug release, *etc*. For each class type, at least general guidelines should be developed and proposed in the future by the regulatory agencies to provide concrete objectives with specific needs of these future generic versions of upcoming nanopharmaceuticals. The information may be divided into various sub-classes not limited to but including a) material and composition, b) process of development, c) intended applications, d) product characteristics and target parameters, e) biodegradability and safety aspects. These specific areas may be prioritized in specific cases as well. The fulfilment of certain minimum similarities must be the basis of filling a generic ver-

sion of nanomedicine. Still, there is a long way to go in terms of laying out a roadmap for generic versions of nanopharmaceuticals. However, the way forward regulatory agencies have initiated this complex but much needed task, as evidenced by the guidelines available to them for some specific products. Herein, collaborative efforts from the pharmaceutical industry, regulatory agencies, and all the stakeholders of the health care team are required to fasten the process as more and more products are being generated every year, demanding rigorous work to regulate and facilitate the next generation nanopharmaceuticals.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study has been financially supported by the Department of Biotechnology, Ministry of Science and Technology, New Delhi, India (Grant no. BT/PR26950/NNT/28/1505/2017).

CONFLICT OF INTEREST

Dr. Rishi Paliwal is the editorial board member of the journal, Current Drug Therapy.

ACKNOWLEDGEMENTS

Declared none.

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