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Nanotechnology-based medicines and regulatory affairs: where are we

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List of abbreviations

API: Active Pharmaceutical Ingredient

ASTM: American Society for Testing and Materials

CHMP: Committee for Medicinal Products for Human Use

EDQM: European Directorate for the Quality of Medicines

EMA: European Medicines Agency

EU: European Union

FDA: Food and Drug Administration

IM: Intramuscular

IV: Intravenous

NanoDDS: Nanoparticulate Drug Delivery System

NBCD: Non-biological Complex Drug

NCL: Nanotechnology Characterization Lab

NCI: National Cancer Institute

NIST: National Institute of Standards and Technology

NP: Nanoparticle

PEG: Polyethylene Glycol

RP: Reflection Paper

SDD: Solid Drug Dispersion

US: United States

Summary

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Abstract

The application of nanotechnology to pharmaceutical sciences is creating drug formulations with novel properties that can improve and innovate the therapeutic arsenal to treat, prevent and diagnose diseases with great benefits for the public health. These nanomedicines are complex in their nature and therefore difficult to correctly evaluate using old methodologies. Also, follow-on versions of current nanomedicines called nanosimilars need to be safely introduced into the market. This shows the importance that regulatory agencies have in evaluating their safety, efficacy and quality. We are going to discuss some of the different types of nanomedicine formulations available, while discussing the current regulatory approachs taken by the agencies and the current limitations to the commercialization of this type of products.

Keywords: Drug; nanotechnology; nanoparticle; nanosimilars; regulatory affairs; terminology;

1. Introduction

Nanotechnology probably was born in 1951 when Richard Feynman gave a lecture entitled "There's plenty of room at the bottom" at the American Physical society meeting at Caltech. This made nanotechnology an emerging science that expanded to various fields of medicine and pharmaceuticals such as drugs, therapeutics, diagnostics, surgery, imaging, tissue engineering and diverse medical specialties as oncology, immunology, osteopathy and urology (3).

Since then, in the pharmaceutical sciences, plenty of research has been carried out, such as development of nanoparticles (NPs) and nanoparticulate drug delivery systems (NanoDDS). Nanotechnology can be used to enhance the target delivery of drugs, or alter their solubility, dissolution rate, toxicity and biodistribution.

Even though first-generation nanomedicines (ones that already obtained market approval) have been considered safe and effective for many years, second-generation or follow-on versions are trying to get market approval.

The correct evaluation of these medicines is essential for confirming their safety, quality and effectiveness while giving consumers' confidence about new therapeutic or diagnostic technologies. Although, overevaluation can lead to some medicines never seeing the light of day while underevaluation can lead to potential harmful medicines in the market.

Thus, the role of regulatory agencies in the evolution of scientific knowledge is of high relevance, since if there are no advances in regulation in order to put new therapeutics into the market we might let escape better and more efficient health products for the consumers.

In this monograph we are going to briefly cover different types of nanomedicines, European Union (EU) and United States (US) regulators' initiatives in evaluating them and current limitations to their implementation into the market.

2. Nanomedicine

There isn't a consensus definition between the different scientific and international regulatory agencies about the definition of nanomaterial, as we can see in Table 1. Nanomedicine refers to any application of nanomaterials to medical purposes from diagnostics to therapeutics where at least one dimension of their size is in the nanometer range and exhibits properties dependent on its dimension (1).

This lack of consensus makes it harder for regulatory commissions to identify a pharmaceutical product as a nanomedicine or nanomaterial and correctly review it. Also, there is a limited standard nomenclature and reference material for these products.

Nanomedicine integrates knowledge from diverse areas of science such as physics, mathematics, materials, pharmaceutical science, chemistry, biology and engineering.

Table 1- FDA, Health Canada and the European Commission: different points of view on nanomaterial definition (1)

FDA	Health Canada	European Commission
Engineered materials or end products.	Manufactured substances or products, component materials, ingredients, devices or structures.	Natural, incidental or manufactured materials.
Has at least one dimension in the nanoscale range	It is in the nanoscale range in at least one external or internal dimension, or has a surface structure at the nanoscale.	Particles in unbound, aggregate or agglomerate states where more than 50% of the particles have at least one or more external dimensions in the nanoscale range
Exhibits properties that are attributable to its dimension, even if they fall outside the nanometer range up to one micrometer.	It is smaller or larger than the nanoscale in all dimensions and exhibits properties based on those dimensions.	The threshold of 50% may be replaced by between 1% and 50% when it concerns the environment, health, safety or competitiveness.

3. Classification of nanomedicines

Understanding the regulatory challenges that go in line with the market approval of nanotechnology based-medicines requires a deep understanding of their nature, knowing their different types and production methods, along with their unique and physicochemical attributes (3).

Therefore, the different types of nanotechnology-based medicines are discussed. There are two main formulations that differ in their main purpose of action which are drug nanoparticles, these are used to improve the dissolution rate and solubility of a drug molecule and nanoparticulate drug delivery systems are used to alter the pharmacokinetics and target drug delivery (3).

3.1. Drug Nanoparticles

Drug nanoparticles are often used to improve the dissolution rate and solubility of a drug. Many NCEs have low solubility so this is a promising technique in bypassing this since the use of nanoparticle versions of the API can alter their solubility and dissolution rates (3).

There are two types of drug NPs crystalline and amorphous depending on the state of the API.

3.1.1. Crystalline Drug Nanoparticles

These NPs have both the advantage of an increased dissolution rate and enhanced solubility of the drug. This is described by the Kelvin equation as we can see in Equation.1 (Eq.1). Drug's solubility is enhanced by the increase in surface energy by the small particles. The logarithmic nature of this equation shows that there's no substantial increase in solubility in particles on the micrometer range, making nano sized drugs a good alternative to solubility problems among NCEs (3).

$$\ln \frac{p}{p0} = \frac{2\gamma Vm}{rRT} \qquad \text{Eq.1}$$

Drug dissolution rate increases in accordance to the Noyes-Whitney equation (Eq. 2) since NP can increase surface area and solubility, which results in an increased dissolution rate.

Crystalline drug nanoparticles can be incorporated in solid drug dispersions enhancing their dissolution rate, which is attributable to the particle size effect and higher wettability due to the presence of the hydrophilic polymer at the drug particle surface. Since the drug particles are in the crystalline state normally they are more stable and offer greater storage stability than their amorphous counterparts, however they have a lower dissolution advantages, lower bioavailability and lower drug release compared to those.

$$\frac{dW}{dt} = \frac{DA(Cs-C)}{L} \qquad \text{Eq. 2}$$

3.1.2. Amorphous Drug Nanoparticles

These NPs can be incorporated in various formulations to enhance the solubility and dissolution of the API. They can be used in oral, dermal, ocular and pulmonary formulations whilst reducing the dose needed for the same pharmacological effect given by classical formulations. They also reduce the effect of gastric pH and food on drug bioavailability.

These NPs have some drawbacks such as: poor chemical and physical stability, hygroscopicity, isolation difficulties and tendency for the drug to crystallize due to high molecular mobility in the amorphous state (3).

Using SDDs allows obtaining amorphous drug dispersions, which are used to achieve higher solubility and/or dissolution rate of the drug. These contain a polymeric matrix where the drug is dispersed which contributes to the wettability and physical stability of the API (3).

The physical instability of these formulations often occurs due to high local drug concentrations, nucleation and crystallization in regional domains within the polymer matrix.

3.2. Different types of NanoDDS

They are generally used to alter the pharmacokinetics and target drug delivery into important tissues in the body. Micelles, liposomes and emulsions are often utilized as drug carriers. Drugs

are loaded into these systems during or after the manufacturing (3). In the next section we are going to briefly discuss them.

3.2.1. Emulsion and Micellar Polymerization

Through the use of drug-loaded micelles or emulsions, which use lipids or lipopolymers, NanoDDS can be formed. Lipidic excipients are often used in this formulations to favor their chemical compatibility, thermal, and rheological characteristics, hydrophilic/hydrophobic properties, regulatory acceptability, availability, cost, and scale-up issues (3).

They have regulatory concerns regarding the toxicity of the residual monomer, catalyst used in the reaction, and surface-active agent (used in the system to stabilize the disperse system before polymerization) (3). Another thing to note is that if the drug is loaded into the NP during polymerization it can lead to drug degradation and instability during storage (3). Based on these problems they have no current commercial application.

3.2.2. Liposomes

These are small molecules formed by a single or multiple bilayers of phospholipids that enclose one or more compartments. They have different pharmacokinetics and toxicodynamics from those of free drugs (ones not enclosed into a liposome). Hydrophilic drugs are localized in the aqueous compartment while hydrophobic ones move towards the lipid bilayer (3).

These formulations are often used as delivery vehicles for targeting drugs to specific biological sites through attaching antibodies to functionalized PEGylated lipid derivatives.

3.2.3. Micelles and Microemulsions

Drugs can be dissolved in micelles and microemulsions in order to overcome solubility limitations that arise from strong crystalline interactions and unfavorable free energy of solvation by water (3).

Upon mixing the drug solution with the dilution medium for injection or gastric fluid for oral ingestion it forms micelles with drug solubilized in the hydrophobic tail aggregates of the surfactant. To prepare the drug solution in the surfactant it is required to use organic solvents,

which is subsequently removed using reduced pressure to form the drug solution in the surfactant. It can also be dissolved in molten state surfactants that are solid at room temperature.

Self-microemulsifying drug delivery systems form a microemulsion upon dilution in the aqueous phase, before or after administration. They can also be incorporated into soft or hard gelatin capsules for oral administration (3).

3.2.4. Polymer-Drug Conjugates

These are used to improve the targeting, toxicity, duration of action, solubility bioavailability of the drug and to overcome drug resistance. These formulations can be either insoluble or soluble association colloids (3).

They use PEG, polyglutamate, dextran and N-2(2-hydroxypropyl)methacrylamide) copolymer being the first one the most commonly used. Also, they are prepared with protein or peptide drugs to alter their pharmacokinetics (3).

3.2.5. Superparamagnetic Iron Oxide Nanoparticles

These NP can also be coated with antibodies, fluorescent lipids and PEGylated lipids.

These have already been approved for other uses such as contrast agents for magnetic resonance imaging and treatment for iron deficiency aneamia.

They have been used for attachment of neoplastic drugs as a tumor-targeting strategy since these cells are more active in pinocytosis (3).

3.2.6. Advantages and Disadvantages of NanoDDS

The advantages and disadvantages of NanoDDS are displayed in table 2.

Table 2 - Advantages and disadvantages of NanoDDS (3)

NanoDDS	Advantages	Disadvantages
Emulsion and Micellar Polymerization	40 years of research	toxicity (residual monomer, catalyst, surface-active agent) drug degradation instability during storage

Liposomes	nontoxic nonantigenic biodegradable 50 years of research over 36,000 published articles	residual organic solvents scale-up chemical instability denaturation (heat/organic solvents) high price of phospholipids lack of in-house knowledge with this products confusion between the types of lipid products
Micelles	Research for more potent and safer solubilizers and surfactants	organic solvents large quantities of surfactant (hemolysis)
Microemulsions	reduction of inter and intrasubject variability enhance bioavailability of poor water soluble drugs	high concentration of emulsifier
Polymer-Drug Conjugates	improve targeting ability reduce toxicity increased duration of action increase bioavailability and solubility of the drug overcome drug resistance	considered NCEs
Superparamagnetic Iron Oxide	approved by agencies for other purposes uses in oncology	

4. Current approaches to regulation of nanotechnology products

As nanotechnology-based medicines become more and more complex and with novel properties regulators are challenged by the application of former regulations (1).

There is a huge gap between the rate at which nanotechnology-based medicines are developed and the rate at which data for policy and regulation is produced. As we know medicines aren't released into the market until safety testing is done, however regulations can't be developed until there is enough evidence and data to support them (1).

4.1. FDA's approved nanomedicines and approaches on regulation

The first FDA approved nanomedicine was Doxil® it was almost 20 years ago since then there has been 24 other market approvals, this shows a relatively higher rate of approval for this type of products compared to the EMA, which is going to get discussed in chapter 4.3. In Table 3 we show FDA's approved nanomedicines.

Table 3 – FDA's approved nanomedicines (1)

Brand Name (API)	Formulation	Delivery Route	Therapeutic Use
Doxil® (doxorubicin)	Liposome	IV	Oncology: Metastic ovarian or breast cancer Kaposi's sarcoma
Abraxane® (paclitaxel)	Albumin-bound nanoparticle	IV	Various cancers
AmBisome® (amphotericin B)	Liposome	IV	Fungal infections
Rapamune® (sirolimus)	Nano-scale particle of the API	Oral	Immunosuppressant for kidney transplants
TriCor® (fenofibrate)	Nano-scale particle of the API	Oral	Hypercholesterolemia Mixed lipidemia Hypertriglyceridemia
Emend® (aprepitant)	Nano-scale particle of the API	Oral IV	Anti-hemetic in chemotherapy
Diprivan® (propofol)	Liposome	IV	Anesthetic
Renagel® (sevelamer)	Cross-linked poly(allylamine) resin	Oral	Control of serum phosphorus concentrations (chronic kidney disease patiens on dialysis)
Triglide® (fenofibrate)	Nano-scale particle of the API	Oral	Lipid disorders
Myocet® (doxorubicin)	Liposome	IV	Late stage metastatic breast cancer (cardioprotective)
DepoCyt® (cytarabine)	Sustained release Liposome	IV	Lymphomatous meningitis
DaunoXome® (daunorubicin)	Encapsulated Liposome	IV	Kaposi's sarcoma
Estrasorb® (estradiol)	Micelles (emulsion)	Transdermal	Menopause, reduction of hot flushes and night sweats.
Macugen® (aptanib)	Polymer-aptamer conjugate	IV	Neovascular age-related macular degeneration
Abelcet® (amphotericin B)	Liposome	IV	Invasive fungal infections
Adagen® (pegademase bovine)	Polymer-protein conjugate	IV	Adenosine deaminse deffiency
PEGASYS® (peginterferon alfa-2a)	Polymer-protein conjugate	Subcutaneous	Chronic Hepatitis C infection
Somavert® (pegvisomant)	Polymer-protein conjugate	Subcutaneous	Acromegaly
Neulasta® (PEG-C-CSF)	Polymer-protein conjugate	Subcutaneous	Febrile neutropenia
Copaxone® (copolymeric mixture of L-glutamic acid, L-alanine, L-tyrosine and L-lysine)	Polypeptide colloidal suspension	Subcutaneous	Relapsing-remitting multiple sclerosis
Amphotec® (amphotericine B	Colloidal suspension of lipid-based API	Subcutaneous	Invasive aspergillosis
PEGINTRON® (peginterferon alfa-2a)	Polymer-protein conjugate	Subcutaneous	Chronic Hepatitis C infection in patients with compensated liver disease
Oncaspar® (PEG-L-asparginase)	Polymer-protein conjugate	Subcutaneous	Lymphoblastic anemia

Epaxal® (VIROHEP-A)	Hepatitis A vaccine adjuvanted with immunopotentiating reconstituted influenza virosomes	IM	Active immunization against Hepatitis A
Elistrin® (estradiol)	Gel incorporating calcium phosphate nanoparticles	Transdermal	Menopause – moderate to severe flashes

According to the FDA the application of nanotechnology may result in product attributes that differ from those of conventionally manufactured ones, so the evaluation of safety and effectiveness should take into account the unique properties and behaviours that nanomaterials may exhibit (4). The FDA doesn't categorically judge these products as intrinsically benign or harmful.

Taking that in mind the FDA's regulatory approach takes the following measures (4):

- Technical assessments are product specific in order to take into account their particular biological and mechanical effects
- It respects variations in legal standards for different product classes, drugs are evaluated not only by their risk profile but also their predicted benefit
- New drugs are subject to premarket review, applicants need to submit data to answer questions related to safety and efficacy. Also, the use of nanomaterials may need additional data on their safety and efficacy
- Dietary supplements, cosmetics and food are not subject to premarket review. Although, the FDA encourages applicants to consult with the agency before taking their products into the market. This helps the FDA advise companies, review safety information and design any post-market safety oversight
- Post-market monitoring of this products will be ensured
- The industry is responsible for ensuring that it's products meet all applicable legal requirements
- FDA collaborates with domestic and international counterparts on regulatory policy issues
- FDA offers technical advice and guidance to help industry meet their regulatory and statutory obligations

The FDA also elaborated a guideline for industries to help them consider if their products involve the application of nanotechnology or not. This guidance has been finalized and can be accessed through the FDA website (5).

4.2. Nanotechnology Characterization Laboratory - US

To get Market Authorization there is need to fully characterize the nanoparticle platform; this is getting more difficult as researchers develop techniques to create multifunctional conjugates (1). These are often attached with coatings, targeting molecules, drugs, prodrugs, tracking moieties and imaging agents.

Physicochemical properties of nanomedicines need to be characterized such as size, size distribution, state of agglomeration, particle shape, morphology, density, crystallinity, specific surface area, zeta potential, extent and nature of surface modification, so researchers need to develop methods to do so (3). Also, there is need to characterize their performance including protein binding, cellular uptake, drug release and metabolism (1).

To cover this characterization problem in the US the NCL was launched as a partnership between the NCI, the FDA and the NIST. Its main purpose is to accelerate the rate at which new nanomedicines for use in oncology get into clinic trials (1).

This laboratory has helped put seven nanomedicines into clinical trials over the course of nine years. It characterizes their physical attributes, their *in vitro* biological properties and their *in vivo* biocompability using animal models (1).

They have developed over fourty protocols to characterize nanoparticle physicochemical properties, as well as *in vitro* immunological and cytotoxic characteristics and absorption, distribution, metabolism, excretion and toxicity in animal models (1).

According to the NCL, to measure each physicochemical attribute various methods based on different principles should be used, this offers a more rigorous characterization since different methods are sensitive to different effects (1).

4.3. EU's regulatory agency (EMA) experience

The first-generation of nanomedicines have been considered safe and effective throughout the years. The EMA has evaluated eleven marketing authorizations for nanomedicines, only eight

of those have been granted market access. Their assessment reports are available at the EMA website (2). Six of the granted medicines are displayed in Table 4 even though eight granted medicines have been reported (2).

Table 4 - EMA approved nanomedicines (12)

Brand Name (API)	Year of Approval	Formulation	Delivery Route	Therapeutic Use
Caelyx® (doxorubicin)	1996	Liposome	IV	Oncology: metastatic breast cancer, advanced ovarian cancer, Kaposi's sarcoma, multiple myeloma
Mepact® (mifamurtide) Note: has orphan status	2009	Liposome	IV	Oncology: High grade non-metastatic osteosarcoma
Myocet® (doxorubicin)	2000	Liposome	IV	Oncology: Used in conjunction with cyclophosphamide for metastatic breast cancer
Abraxane® (paclitaxel)	2008	Nano-scale particle of the API	IV	Oncology: Metastatic breast cancer Metastatic pancreas adenocarcinoma
Emend® (aprepitant)	2003	Nano-scale particle of the API	Oral	Anti-hemetic for people undergoing chemotherapy or postoperative nausea and vomiting
Rapamune® (sirolimus)	2001	Nano-scale particle of the API	Oral	Prevent transplant rejection (most notable: kidneys)

Another thing to note is that the EMA has given orphan status to ten nanomedicines under development. Orphan status medicines are granted significant privileges such as access to the centralized authorization procedure, ten years marketing exclusivity, fee reductions and financial fundings (6). Fourty eight nanomedicines and nanoimaging agents have reached clinical trials while others are still in development in Europe (2).

In 2006 a cross-agency Nanomedicine Expert Group was created to assess potential needs for regulatory requirements for the evaluation and assessment of nanomedicines. In 2009 it was expanded via establishment of the International Regulators Subgroup on Nanomedicines, this was an initiative launched in conjunction with the FDA, the Ministry of Health, Labour and Welfare and Health Canada (2).

5. Nanosimilars

As we know generic drugs are compared to their reference products through their equivalent pharmaceutical properties and their bioequivalence measured in volunteers. This is the key for the market approval of a generic drug.

Over the last decades nanomedicines have been used without taking into account their nanoparticular structure or the resulting complexity of their mechanical, chemical and pharmacological properties. This is described as their *nano-character* which contributes to their safety, efficacy and quality (11).

NBCDs are very complex molecules where the pharmaceutical active ingredient is represented by the entire formulation. This non-homomolecular type of nanomedicines are hard to fully characterize by the typical physicochemical means described in pharmacopeial monographs as opposed to classical small-molecule drugs (1).

This makes it harder for nanosimilars to be compared to their reference product in order to make sure that their molecular structure is identical to the reference. Therefore, it's needed to evaluate the extent of similarity between the two. A case-by-case approach for their evaluation is necessary (2). It must be emphasized that the manufacturing process that largely contributes to the product properties: if the nanosimilar is obtained by a different production method from the reference one its physicochemical and therapeutic properties may change. Also, surface coatings are attached to these products in order to alter their body distribution, targeting them to specific tissues and changing their clearance. This emphasizes even more the need to fully control the manufacturing processes (1).

In the EU, the body issuing the European Pharmacopeia, EDQM established a specific working group to identify minor differences that are clinically relevant between a nanosimilar and the reference product. Also, the EDQM established a non-biological complex working party to elaborate European Pharmacopeia monographs on these complexes. These monographs ensure quality to the products that are prepared in accordance to them.

In 2011 the EMA main scientific committee, the CHMP, established a group on nanomedicines. Some reflection papers have been drafted for the evaluation of nanosimilars being developed in reference to first-generation nanomedicines (2). Nanomedicines should be regulated on a case-by-case scenario. The outcomes of this RPs are going to be briefly discussed next.

5.1. Intravenous lipossomal products developed in reference to an innovator product

It was identified that some physicochemical properties of intravenous liposomes are critical to their biological performance such as: particle size, membrane fluidity, surface charge and composition. These characteristics are sensitive to the production method, alterations in them can cause instability by rapid removal through the monocyte-phagocyte system and premature drug release from the liposome (2).

In this reflection paper it was concluded that differences in liposome characteristics might not be detectable by conventional bioequivalence tests, and additional studies are needed. These products require a similar regulatory approach as biosimilars, there's need for a stepwise comparability of quality, efficacy and safety between the innovator product and the nanosimilar (2).

Since the experience in this matter is limited, the assessment of pharmaceutical quality, clinical and nonclinical principles is done in reference to an innovator product. This RP encourages companies to seek specific scientific advice about their product regarding specific questions on the data requirement to demonstrate comparability (2)(7).

5.2. Nanosized colloidal iron-based preparations developed with reference to an innovator product

Colloidal iron-based preparations have been used to treat iron-deficiency anemia and have been developed as diagnostics. Since these products contain iron they can cause hypersensitivity, another thing to note is that unbound iron can be released causing short-term and chronic toxic effects due to oxidative stress (2). This shows the importance of the correct characterization of this products.

The pharmacokinetics and biodistribution and *in vivo* intracellular fate of this products is not fully understood, with this in mind the demonstration of bioequivalence between a follow-on and the innovator will not necessarily correlate with their therapeutic performance. Thus, we need to take into account the different production methods and composition of the products that can alter their safety and therapeutic performance (2).

The development of the nanosimilar should take into account the critical product attributes of the innovator while taking into account the evidence that supports its use when designing

the quality, clinical and nonclinical program. A challenge for this products is the scale of the clinical data required, which will depend on how accurately the physicochemical and non-clinical characterization can be used to predict differences that could influence the efficacy and safety of the product. Discussion in this matter is still ongoing (2) (8).

5.3. Joint Ministry of Health, Labour and Welfare/EMA reflection paper on the development of block copolymer micelles products

Block copolymer micelles can be used to improve the delivery of poorly soluble, highly toxic and/or unstable drugs. They are also used to improve tissue targeting and improving the cytosolic delivery of macromolecular drugs. There are several types of molecules that can be incorporated into these micelles such as low-molecular-weight chemical entities, nucleic acids, biological or biotechnological derived entities (peptides and proteins) (2).

This RP was released in July 2013 by the European and Japanese drug regulators, it discusses principles for the pharmaceutical development, non-clinical, and early clinical studies of block copolymer micelles (2) (9).

6. Limitations to the commercialization of nanomedicines

According to Raj Bawa (10) there are several bottlenecks that still limit the commercialization of nanomedicines such as: (1)

- Lack of standard "nano" nomenclature
- Lack of precise control over nanoparticle manufacturing parameters and control assays
- The currently used compounds and components for nanodrug synthesis pose problems for large scale good manufacturing practices
- Lack of quality control: difficult separation of undesired nanostructures during manufacturing (byproducts, catalysts, starting materials)
- High cost of fabrication
- Lack of pre-clinical characterization strategies via multiple techniques
- Lack of knowledge regarding the interaction between nanoparticles and biosurfaces/tissues

- Lack of consumer confidence, consumers are reluctant to embrace new technologies without clear safety or regulatory guidelines
- Lack of funding
- Ethical issues and societal issues are hyped by the media
- Big Pharma's reluctance to invest in nanomedicine
- Patent review delays, patent thickets, and issuance of invalid patents

Some recommendations have been given to FDA regarding their current regulation on nanomedicines in five major regulatory aspects, which are: safety and risk, data, standardization, tools, classification scheme (10). Those recommendations are as follows:

Safety and Risk

- Identify unique safety issues associated with nanomedicines on a case-by-case basis in conjunction with the industry
- Seek product safety data when pre-market review applies
- Incentivize industry to submit pre-market safety data when pre-market reviews don't apply
- Correlate physicochemical properties with *in vivo* biological behavior and therapeutic outcome
- Research strategies involving pharmacokinetic studies
- Toxicological tests and physicochemical characterization studies for nanomedicines
- Understand mass transport across membranes and body compartments
- Determine accurate biodistribution profiles after systemic administration
- Correlate the biodistribution with safety/efficacy by using parameters such as size, surface charge, stability, surface characteristics, solubility, crystallinity and density
- Creation of a databank relating to the interaction between nanomaterials and biological systems

Data

- Develop guidelines that provide specifics on what data is needed for the industry
- Share data in an international harmonized environment

Standardization

- Create reference classes for nanomaterials

- Testing protocols to provide benchmarks for the creation of nanoscale materials classes
- Uniform standards for defining nanomaterials
- Refine the definition of nanomaterial, nanotechnology, nanoscale, and nanomedicine
- Explore international harmonization efforts
- Involve standard setting organizations such as International Organization for Standardization and ASTM international.
- Consult and collaborate with other federal agencies

Tools

- Help develop new tools and techniques to characterize nanomaterials
- Develop imaging modalities for visualizing biodistribution
- Develop mathematical and computer models to evaluate risk/benefit
- Monitor quality, safety, product liability, effectiveness

Classification Scheme

- Reevaluate the current FDA classification scheme
- Develop a classification scheme based on function or risk of potential harm

7. Conclusion

Nanomedicines offer great technological advantages compared to conventional technologies ranging from increased solubility, dissolution rate, and lower toxicity to targeting molecules into tissues of interest in the organism and altering the pharmacokinetics of drugs.

Nanomedicines shouldn't be considered as inherently harmful since they can be used to put into the market old molecules that didn't pass clinical trials, due to low solubility reasons for example and thus offer new possible effective therapeutics for the benefit of patients. Also, it gives the pharmaceutical industry the opportunity to extend the economic life of their proprietary drugs and create additional revenue streams through reformulations via nanotechnology.

Regulatory agencies are reviewing products on a case-by-case scenario as recommended by reflection papers published by the EMA. Furthermore, regulatory agencies are working in conjunction in order to correctly evaluate nanomedicines, although the academia, pharmaceutical industry and regulatory agencies should work in conjunction to accelerate the

process of regulation. The industry needs to contact with the agencies early in order to ensure the quality, safety and efficacy of their products for the benefit of the consumers.

Follow-on versions of established nanomedicines can't be approved by regulatory agencies by only accessing the bioequivalence in volunteers, there's the need to fully characterize the nanoparticle platform and their specific attributes.

Finally, there's need for the standardization of the nanotechnology-based medicines nomenclature which at the moment is not well defined.

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