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Patents, Drug Delivery and Public Health Protection: Health Risk Management for Nanopharmaceuticals

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Abstract

The present article discusses the general risks associated with nanotechnology applications and the deficits of the risk management of engineered nanopharmaceutical particles. An evaluation of the possible health or environmental risks of nanoparticles must systematically be carried out and it is important to ensure that particle size and chemistry are taken into account when investigating possible adverse effects. It has been a goal subsidizes the policy-makers to adapt and modernize the regulatory framework on nanotechnology and risks involving health as a strategic area in the politics of Science. It is essential that health and environment be always directly or indirectly involved in various researches to understand the causes of affections and to develop control procedures in order to avoid them, providing results achievable, reliable and secure.

Keywords: nanopharmaceuticals development; risk management; public health; environment.

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Introduction

Hesitations in conventional quantitative risk assessment characteristically relate to values of parameters in risk models. For various environmental pollutants, there is a lack of appropriate information about multiple components of the risk valuation framework (Althaus, 2005; Borm, et al., 2006). In such cases, the use of default assumptions and extrapolations to fill in the data gaps is a common practice (Pidgeon, et al., 2011).

Nanoscience is characterized as the product of interdisciplinary collaboration among biotechnology, chemistry, physics, material sciences and engineering toward studying associations of atoms and molecules (Schulte, 2005; Salerno, et al., 2008). More than in other domains, nanotechnology requires the integration of many scientific, engineering and technical disciplines and competences (Antunes, et al., 2012; Pyrrho and Schramm, 2012). Applications of nanotechnology will penetrate nearly all sectors and spheres of life and will be accompanied by changes in the social, economic, ethical and ecological spheres (Schummer, 2004; Zanetti-Ramos and Creczynski-Pasa, 2008).

Nanotechnology refers to the development and application of materials, devices and systems with fundamentally new properties and functions because of their structures in the range of about 1-100 nanometres (Meyer and Persson, 1998; Cameron, 2006). It involves the manipulation and/or creation of material structures at the nanoscale, in the atomic, molecular and supramolecular realm (Schulte, 2005). Commonly these nanoparticles are natural products but their great commercial use has improved the artificial synthesis of these engineered nanoparticles (Lanone and Boczkowski, 2006; Mccomas and Besley, 2011). Accelerated production and use of these nanoparticles may cause their discharge in the environment and enable the frequent contacts with biotic and abiotic components of the ecosystems (Brar, et al., 2010). Regardless of notable commercial profits, their presences in the nature can origin harmful biological special effects. Consequently, detail understanding of their sources, relief contact with environment, and probable risk assessment would provide a basis for nontoxic use of engineered nanoparticles with negligible or no dangerous influence on environment (Kuempel, et al., 2012).

The human health impact of toxic substances and pollutants can be studied using frameworks of risk assessment developed over the past decades. Risk assessment in this context is a set of tools used to integrate exposure and health effect information for characterizing the potential for health hazards to humans (Marchant and Sylvester, 2006; Mccomas and Besley, 2011). Such methods typically use quantitative expectations of health impacts. However, qualitative risk assessments are also valuable when quantitative assessments are not possible (Montague, 2004). Even under the best of circumstances, risk assessment cannot estimate risk with absolute certainty. Modern quantitative risk assessment aims not to arrive at a single precise number, but to allow decision makers to face the possible consequences of a range of not undoubtedly incorrect responses and elect on the protective policies that are acceptable in light of the range of possible future outcomes of substitute policies (Cattaneo, et al., 2010; Bottini, et al., 2011). Thus, if there is uncertainty regarding exposures or dose in a population, one can either collect more data or use numerical models to estimate missing values or extrapolate values from other analogous populations (Fadeel and Garcia-Bennett, 2010).

Uncertainties about the health effects directly feed the risk-benefit discussions that increasingly make emergency responses for the regulation of new technologies (Choi, et al., 2009; Allarakhia and Wash, 2012). Although some applications of nanotechnology in pharmacology may be questioned, there is an area where the application of nanotechnology application is promising (Davies, 2006; Fadeel and Garcia-Bennett, 2010). Specifically, nanoformulations may eliminate the need for conditional administration of drugs, thereby promoting patient compliance and increasing therapeutic effects (Dorbeck-Jung, et al., 2011). However, like biotechnology before it, concerns about environmental and human health risks have already begun to have an effect on the societal debate around nanotechnology. Suspicions about risks of nanotechnology result from a basic enigma: the properties that make nanoparticles so promising, that they can perform very differently from bulk forms of the same material, and also make their health and environmental effects extremely difficult to predict (Ju-Nam and Lead, 2008). Some of the nanophamaceutical-based formulations are listed in Table I.

Nanoparticle risks posture a new form of risk assessment challenge. Besides a lack of data, there is deep scientific uncertainty regarding every aspect of the risk assessment framework: (a) particle characteristics that may affect toxicity; (b) their fate and transport through the environment; (c) the routes of exposure and the metrics by which exposure ought to be measured; (d) the mechanisms of translocation to different parts of the body; and (e) the mechanisms of toxicity and disease (Althaus, 2005; Borm, et al., 2006; Cattaneo, et al., 2010). In each of these areas, there are multiple and competing models and hypotheses.

Traditional risk assessment

Risk assessment is a complex process that involves the integration of information across a range of domains including source characterization, fate and transport, modelling,

Product	Company	Drug	Application
Doxil	Sequus Pharmaceutical	Doxorubicin	Kaposi sarcoma in AIDS
Amphocil	Sequus Pharmaceutical	Amphotericin B	Serious fungal infections
Ambisome	NeXstar Pharmaceutical	Amphotericin B	Serious fungal infectionS
DaunoXome	NeXstar Pharmaceutical	Daunorubicin citrate	Kaposi sarcoma in AIDS
Abelcet	The Liposome Company	Amphotericin B	Serious fungal infections
Rapamune	Wyeth/Elan	Sirolimus	Immunosuppressant in kidney transplant patients
Emend	Merck/Elan	Aprepitant, MK869	For chemotherapy patient to delayed nausea and vomiting
TriCor	Abbott	Fenofibrate	Primary hypercholesterolemiamixed lipidemia, hypertriglyceridemia
Megace ES	PAR Pharmaceutical	Megaestrol acetate	Treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of AIDS
Abraxane	American Biosciences	Paclitaxel	Metastatic breast cancer
Elestrin	BioSante	Estradiol	Treatment of moderate-to-severe vasomotor symptoms (hot flashes) in menopausal women

Table I. Some selected nanopharmaceutical products currently on the market.

exposure assessment, and dose–response characteristics (Mccomas and Besley, 2011; Pyrrho and Schramm, 2012). It uses well-defined quantitative models to describe the relationships between the various elements of the paradigm shown in Figure 1 explaining the general environmental health framework and its relationship to the risk assessment framework.

Exposure is defined as the intensity of contact between contaminant and the relevant biological sites of impact over a relevant time period (Siegrist and Keller, 2011). Exposure assessment includes assessing sources of pollutants and their strengths, measuring or modelling concentrations in environmental media, measuring or modelling human exposures through various pathways, and in some cases even biological monitoring to measure tissue burden and thereby estimate dose. The estimation of a biologically relevant dose from exposure information is, however, often very difficult and requires fairly detailed knowledge of the toxicokinetics of the pollutant in the human body (Shah and Khan, 2009; Pautler and Brenner, 2010).

Risk governance are important concepts for assessing and managing the implications of nanotechnology which looks set to become the next focus for heated debate about the relationship between new technologies, risk and sustainability (Dorbeck-Jung, et al., 2011). It includes the totality of actors, rules, conventions, processes, and mechanisms concerned with how relevant risk information is collected, analysed and communicated and management decisions are taken (Kosta and Bowman, 2010). Risk governance includes the processes, conventions and institutions that determine, some important questions, like as: How power is exercised in view of managing resources and interests? How important decisions are made and conflicts resolved? How various stakeholders are accorded participation in these processes? The flowchart in Figure 2 suggests that the main steps in the research and regulation of nanomaterial implications once released either in the environment or at the working place. The implications affect biosphere, surrounding infrastructure, and public health. The risk governance should ensure safety and the dynamic behaviour and multifunctionality of the nanostructure. The main argument is that nanotechnology represents a new class of processes and applications that

may threaten human identity; speed up the pace of modernization beyond the speed that human societies can cope with; and transform our environment into directions that nobody can realistically predict.

Translocation and health effect endpoints

A critical difference between nanoparticles and particles of larger size is the ability to nanoparticles to move or translocate to different parts of the body (Rediguieri, 2009; Kosta and Bowman, 2010). There is evidence for the translocation of inhaled nanoparticles from the alveolar spaces into the interstitial, to local and regional lymph nodes, and into the circulatory system.

Translocation into the blood stream may also affect the ability of blood to coagulate (Robinson, 2009). There is considerable uncertainty regarding the extent of translocation, which may depend on the surface and chemical characteristics of the particles. More recently, a growing body of evidence suggests that nanoparticles may translocate along the neuronal pathways into the central nervous system and the brain (Rossi-Bergmann, 2008). However, the exact mechanisms of transport have not been elucidated and there may yet be other pathways in addition to neuronal transport.

The small size facilitates uptake into cells and transport across epithelial and endothelial cells into the blood and lymph circulation, which may carry nanoparticles to potentially sensitive target sites such as bone marrow, lymph nodes, spleen, and heart (Youns, et al., 2011). The ability to reach new regions, unhindered by natural blocking mechanisms of the body is, not surprisingly, the reason that nanoparticles may be useful in medical applications.

The fate and transport of larger particles is well understood and inhalation is the exposure route (Schulte, 2005; Salerno, et al., 2008). The preceding discussion shows that for nanoparticles, several exposures routes are possible. This is summarized in Figure 3, which illustrates that there are several pathways and potential endpoints for assessing the adverse health effects of nanoparticles in the body. In the case of

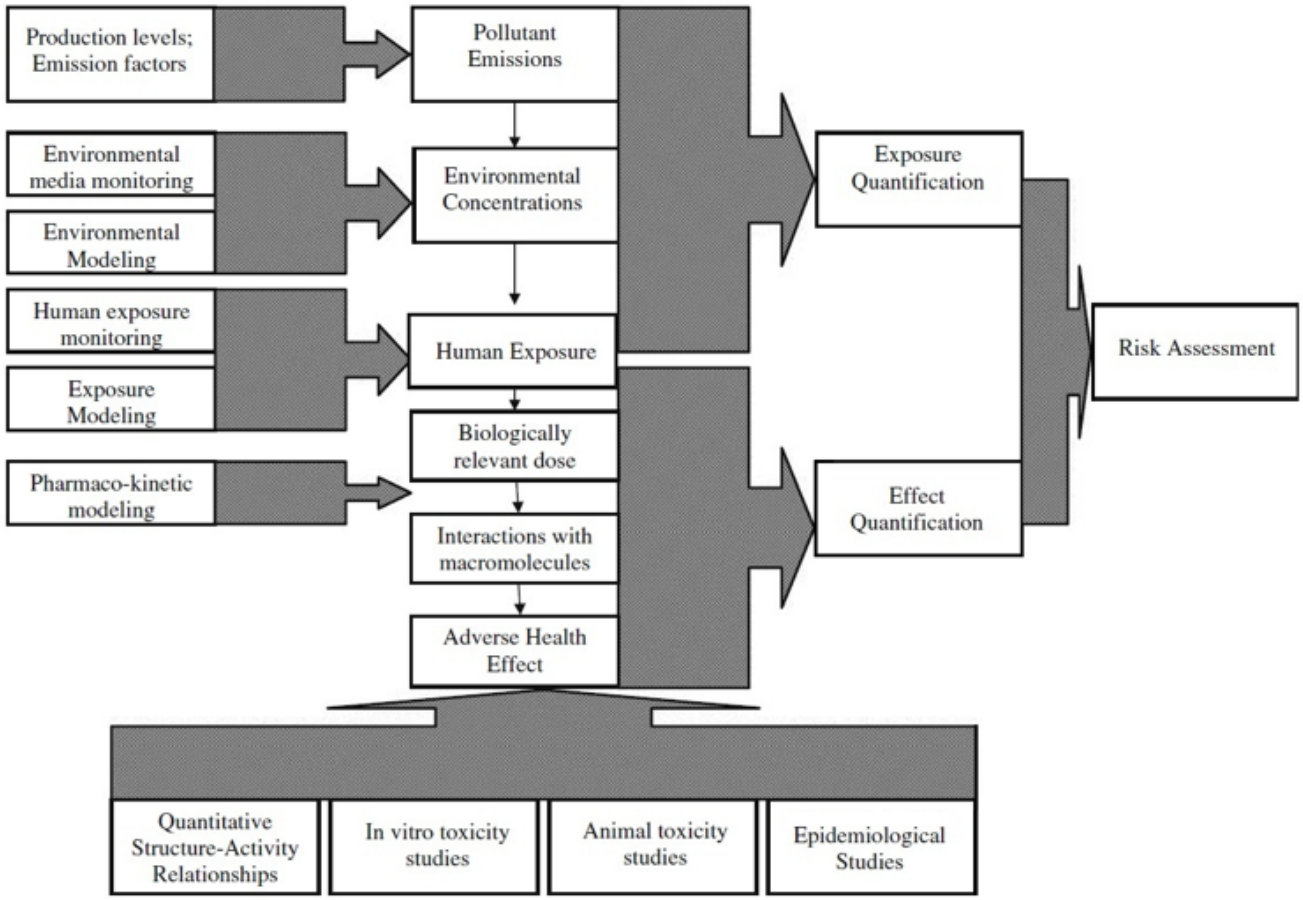
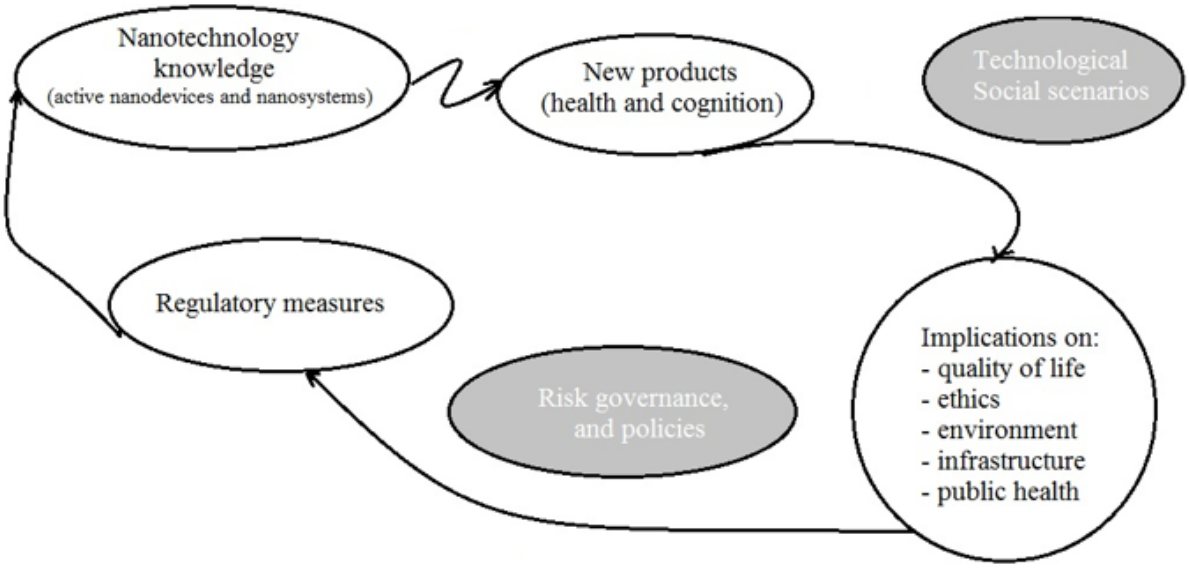


Figure 1. General environmental health framework for risk assessment.

Figure 2. Risk governance and policies for active nanostructures and nanosystems.



inhalation, larger particulates are deposited in the lungs and can cause localized health effects within the pulmonary system (Davies, 2006; Fadeel and Garcia-Bennett, 2010).
Nanoparticles, on the other hand, could have multiple health endpoints (Ju-Nam and Lead, 2008). For example, inhaled nanoparticles might translocate to the central nervous system either through neural pathways in the olfactory system or through the body's circulatory systems after absorption in the lungs and consequent crossing of the blood-brain barrier (Lanone and Boczkowski, 2006). The ability of nanoparticles to translocate to parts of the body that are not accessible to larger particles in the particulate matter range or to most toxic chemicals and carcinogens make it harder to extrapolate known laboratory and epidemiological findings to nanoparticles. In other words, existing physiological models of exposure and movement of particles within the human body are not sufficient.

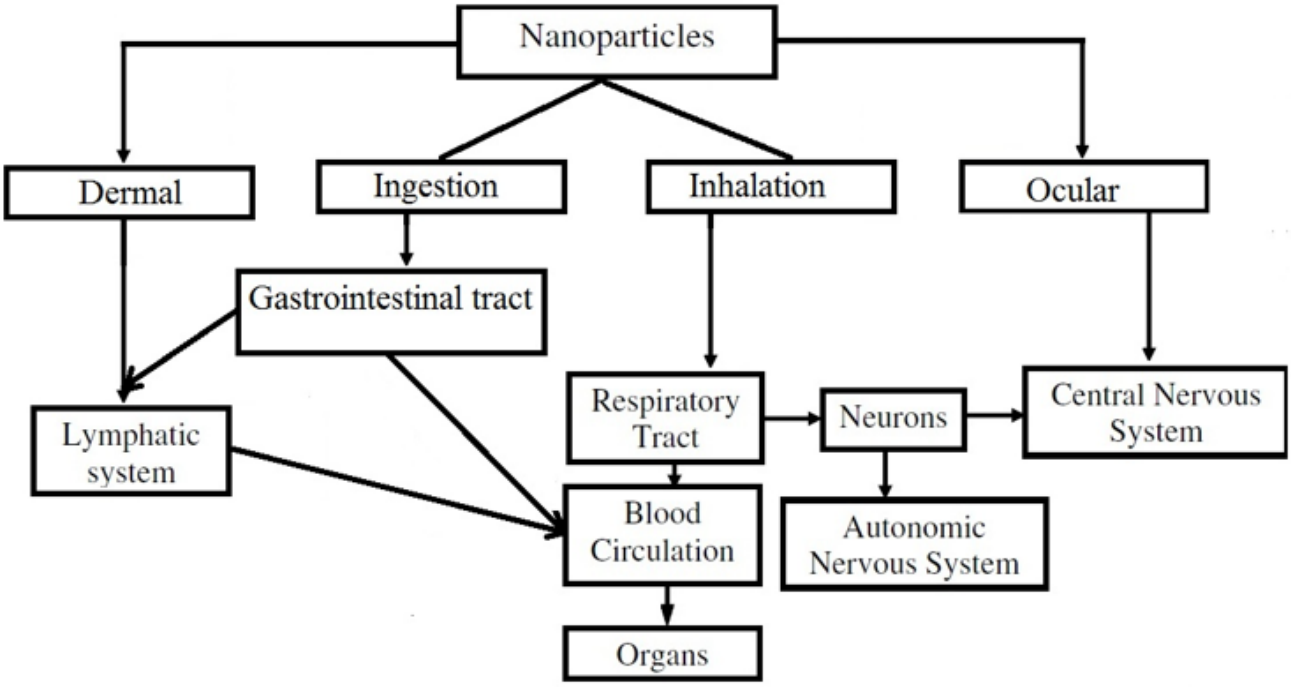
Keeping all these points in mind and after identifying the main characteristics and prospects of nanotechnology as an emerging technology upon various aspects, e.g. sources, different types, synthesis, interaction with environment, the present article discuss the general risks associated with nanotechnology applications and the deficits of the risk governance process today, aiming propose recommendations of possible strategies for risk management of engineered nanopharmaceutical particles, in detach to governments, industry, national organizations and other stakeholders.

Methodology

Initially an interdisciplinary analysis was executed to establish the type of therapeutic pertinent class, based on information of the Brazilian Sanitary Surveillance Agency (ANVISA). The therapeutic uses qualified in accordance with the Anatomical Therapeutic Chemical Classification System (ATC), which is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). This task demanded a considerable effort and included searches in international databases, since, in many cases, the released information was not indicating the generic name of the respective product or his possible therapeutic application.

To collect data on patents in Brazil was used the Brazilian National Institute of Industrial Property (INPI) database for the period of patent applications filed from 1991 to 2011. Our approach to developing a nanotechnology bibliometric search involved these steps: It was used a quantitative approach based on a bibliometric analysis of data obtained at the base of INPI. Data were collected within the last Electronic Journal of Industrial Property (EJIP) (INPI/2011), using 18 terms related to nanotechnology. In addition to the terms proposed by INPI, others were included, based on articles that deal with search strategies or bibliometrics analyses on nanotechnology (Coatrieux, et al., 2004; Porter and Cunningham, 2005; Daim, et al., 2006; He and Loh, 2010; Wang, et al., 2012). The terms were truncated in order to optimize and maximize results and are as follows: Dendrimer*, Nanod*, Nanom*, Fio* Quantic*, Nanoe*, Nanonet*, Fuleren*, Nanof*, Nanop*, Grafen*, Nanog*, Nanos*, Nanoh*, Nanob*, Nanot*, Nanoc*, Nanoi*, and Ponto* Quantic* (Feldman and Sanger, 2007).

Figure 3. Pathways for nanoparticle exposure and translocation.



To make this survey were selected patent documents (patents, utility models and certificates of addition to invention), containing in its title and / or abstract, at least one of the 18 terms listed above. Utility models were also included because they are susceptible for industrial application, and certificates of addition which are complementary inventions ever made, were also included in the study, totaling 1352 patent applications.

As data regarding to the legal process, the following fields were collected: (i) filing date, (ii) application title given by the inventor to his invention, (iii) name of the depository – patent holder or organization, (iv) notification - stage of the patenting process, (v) EJIP issue which published the notification, (vi) date of EJIP publication, (vii) applicant's country origin, and (viii) IPC main application. It was evaluated the typology of depositors, detaching their peculiarities: (a) legal entity non-resident; (b) legal entity resident; (c) individual non-resident; (d) individual resident; (e) Scientific & Technologic Institution non-resident; and (f) Scientific & Technologic Institution resident.

For patent mining, in analysis of observational data sets to find unsuspected relationships and to summarize the data in novel ways that are both understandable and useful, as well as to generate reports for analyzing the results in more consistently manner, was used the automated data mining tool, the software VantagePoint 7.1, Search Technology, Inc.

Results

Profile of the Brazilian Pharmaceutical Patents

Most of the patents granted (116, 31.69 %) belongs to companies that possess his counterfoil in the United States. Secondly it belongs to Brazilian companies, with a participation of 27.87 %. The remaining percentage (40.44 %) is distributed in 23 countries, which go from 7.97 % to 0.27 %, being demonstrated appears in the Table 2.

The main result of the research was to generate a database of pharmaceutical patents granted, one of whose main purposes is to provide information for decision-making, particularly in relation to products and ways to acquire more efficient procurement. This database yielded the results described below. In Figure 4 is demonstrated an analysis comparing quantitative data of pharmaceutical patents with nanotechnology patents observed from 1990 to 2011.

It was evaluated the typology of depositors, detaching in percentage: (a) legal entity non-resident; (b) legal entity resident; (c) individual non-resident; (d) individual resident; (e) Scientific & Technologic Institution non-resident; and (f) Scientific & Technologic Institution resident, as showed in Figure 5. It´s observed that, for the period studied (1990-2011), 85% of Nanotechnologic patents deposited and 59.5% of Pharmaceuticals patents are related to legal entity non-resident in

Nationality	Quantity of Patents	Percentage
United States	116	31.69
Brazil	102	27.87
Germany	29	7.92
France	26	7.1
Switzerland	19	5.19
Italy	9	2.46
United Kingdom	8	2.19
Australia	7	1.92
Canada	7	1.92
Ireland	7	1.92
South Korea	5	1.36
Spain	5	1.36
Holland	4	1.09
India	4	1.09
Finland	3	0.82
Belgium	2	0.55
Norway	2	0.55
Russia	2	0.55
Sweden	2	0.55
Venezuela	2	0.55
Argentina	1	0.27
Austria	1	0.27
China	1	0.27
Israel	1	0.27
Japan	1	0.27
Total	**366**	**100**

Table 2. Relative participation pharmaceuticals patents deposited in the period of 1990-2011, according to intellectual author.

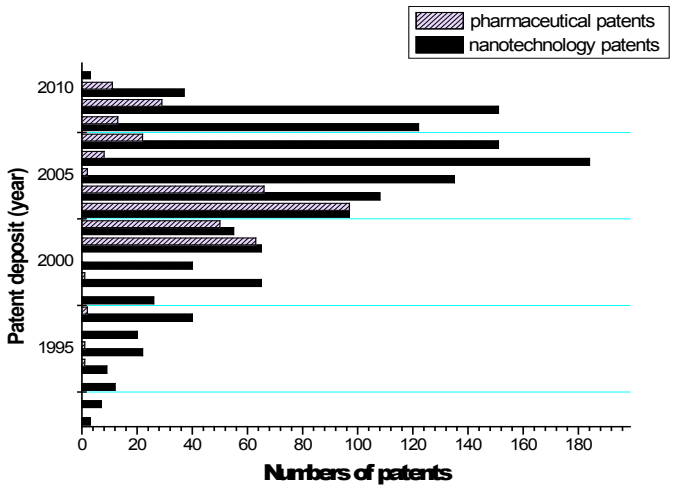


Figure 4. Comparative quantitative data of pharmaceutical and nanotechnology patents, according to the study period (1990-2011)

Brazil, in sequence it were found, 21% and 6.5% for legal entity resident, 5% and 4% for individual depositor non-resident, 23% and 6.6% for individual depositor resident, 8.5% and 6.6% for depositor from Scientific and Technologic Institutions non-resident, and a promising result of 42.5% and 12% for depositor from Scientific and Technologic Institutions resident.

Discussion

Due to serious environmental and health risk posed by the release of nanoparticles in the environment, it becomes essential to set specific standards for the manufacture, use, and disposal of nanoparticles (Choi, et al., 2009). There are many fail reports about legislations do not mention or define nanoparticles (Chamas, 2008). However, a number of organizations have evolved development, description and usage-associated standards for nanoparticles. The potential hazard by nanoparticles and the subsequent protection of environment and human health should consider these standards. Therefore, some nanoparticles by-pass the testing and safety evaluations as their concentration seldom reach this limit.

Nanotechnology holds out the promise of immense improvements in economic growth, health and manufacturing technologies; and especially pharmaceuticals products (Fernandes and Filgueiras, 2008). Both the nanotechnology industries and governments are now seriously considering the possibility of unforeseen risks for human health and environmental degradation as a result of this novel technology. The environmental science community also needs to embrace this positive approach, and devise appropriate testing protocols and predictive tools for addressing the crucial issue of risk management.

Another interesting point to be noted is that some nanoparticles have identical or similar chemical formula to an existing compound. This results in another by-pass of nanoparticles from chemical abstracting service which provides a series of unique identifying numbers for existing chemicals. Other than these non-specific rules, not only there are no specific regulations for nanoparticles, but also, the gaps in knowledge regarding their toxicological and exposure data prevail (Mcintyre, 2012). It is therefore an important matter of concern to build up specific legislations and guidelines for nanoparticles in order to avoid the risk imposed by nanoparticles on the environment.

Considering the wide application of nanoparticles and their entry into the environment, the study of their impact on the ecosystem, at biotic as well as abiotic level, has become mandatory (Paschoalino, et al., 2010). Only a limited number of areas have been covered as far as ecotoxicity tests and assessment of the hazardous effects of nanoparticles are concerned. Therefore, it is required to study their release, uptake, and mode of toxicity in the organisms. Furthermore, to understand the long-term effect of nanoparticles on the ecosystem, substantial information is required regarding their persistence and bioaccumulation. But it is a reasonably good surrogate that large-scale epidemiological studies have yielded remarkably consistent results (Rickerby, 2007).

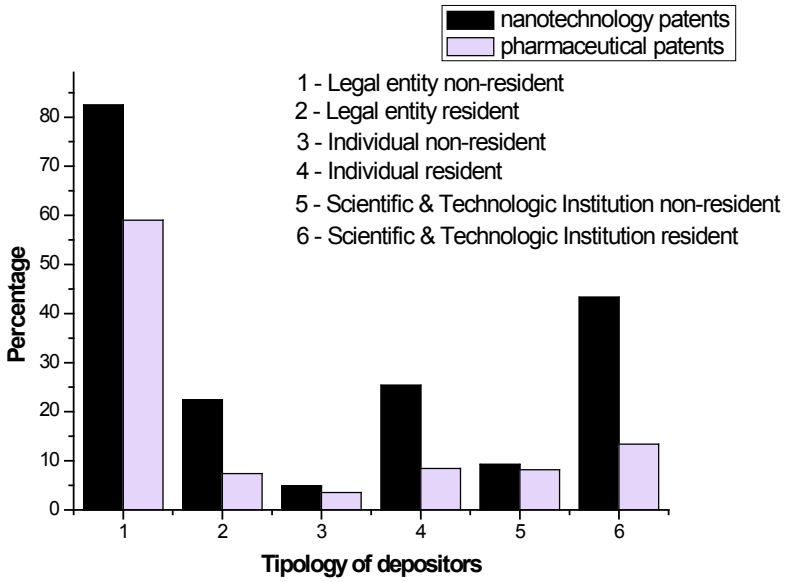


Figure 5. Distribution of pharmaceutical and nanotechnology patents deposited in Brazil by typology (1990-2011).

Indeed, the development of new molecules for pharmaceutical application may involve several levels of inventive techniques for the preparation of drugs in different forms and dosages are usually known (Poirot-Mazeres, 2011). Therefore, there is a limited range may be considered developments in this field genuinely inventive. The patent examiner should pay particular attention to the following cases of claims: (i) Formulations, compositions and processes for their preparation should be considered obvious in view of prior art, except in those cases in which obtaining a truly unexpected and surprising effect; (ii) Combinations: the combinations of known active ingredients should be regarded as devoid of inventiveness, with the exception of those cases where it is clearly established a new synergistic effect that is not obvious; (iii) Dosages / dose: the new dose for the same indication or for a different indication not constitute invention, particularly in countries like Brazil, where treatment methods are not patentable; (iv) Salts, ethers and esters, the salts, esters and other known pharmaceutical forms can generally be obtained through common procedures, and are not patentable, except in those cases where this is an unexpected advantage over the prior art; (v) Polymorphs: the polymorphism is an inherent property of matter in its solid state, the polymorphs not invention but are discovered as-they are not patentable as such. Moreover, the patenting of procedures for polymorphs should be considered only in cases that actually meets the requirements of novelty and inventive step; (vi) Individual enantiomers: patentable not be considered when the racemic mixture is disclosed (but it may be patentable processes for obtaining individual enantiomers, are novel and possess if inventive step); (vii) Active metabolites: patentable should not be considered separately from the active ingredient derived; (viii) Prodrugs: if granted, patents on prodrugs should be excluded from the claim to the active substance itself, if it has already been reported or is not patentable; (ix) Selections: the selection of a single item or small segment within a larger group known as the selected components have already been revealed, should not be patentable even if there are unexpected benefits; and (x) Procedures like: manufacturing procedures that are not in themselves novel and inventive to be considered unpatentable, beyond which the starting materials, intermediates and the final product is novel or inventive.

Conclusion

Innovative technologies and their resultant products demand new ways of thinking about pre-market risk analysis and post-market surveillance. A regulatory framework that is responsive to emerging knowledge about the hazards of novel technologies offers repeatable and transparent processes and remains economically and socially feasible. Nanopharmaceuticals and the nano-based technologies at their base are used by way of exemplar technologies that are currently taxing the ability of the regulatory system to provide adequate oversight. Uncertainties of definition, absence of a tracking system, and the scarcity of scientific evidence to support risk management efforts are among the findings of the study and need to be addressed as ameliorative steps toward an effective regulatory structure.

In many situations, there is a lack of sufficient information about multiple components of this risk framework. In such cases, agencies such as the United States Environmental Protection Agency (U.S.EPA) have resorted to the use of default assumptions and extrapolations to fill in the data gaps. In the case of nanoparticle health risks the uncertainties are so large as to obviate any simple extrapolations. Meanwhile, the technology is moving at a rapid pace, new nanoparticles are routinely manufactured and the social costs of getting it wrong are very high. In such a situation, there is a need for quantitative frameworks that help in risk assessment and expert judgment may be a valuable tool for doing this.

Health risks from nanoparticles share some features of risk calculations. The fundamental mechanisms for health risks from nanoparticles are largely unknown and extreme uncertainty prevails in almost every aspect of the exposure–response paradigm. No epidemiological data are available for engineered nanoparticle exposures, and it is unlikely that such data will be available in the near future in the absence of scientific consensus on the proper exposure metric and relevant health effect to be measured. This way, while comprehensive risk evaluation is far from feasible, even simple screening assessments are difficult due to the novelty of the materials and the lack of basic toxicity data.

Globally, healthcare costs have been increasing due to the costs associated with healthcare development in a heavily regulated environment and higher patient expectations. Cost-effective technologies and cutting-edge treatments, seeking early minimal intervention rather than invasive therapies, are therefore mandatory. Nanomedicine as a translational science has the goal to offer cost effective novel therapies and diagnostics using the expanding world of nanotechnology. To reach this goal the process of translating research results from academic laboratories to the clinic has becoming greatly enhanced.

Concerning nanomedication we can say that there is no sufficient consensus among the different actors that lets end the controversy, and this disagreement involves not only the discussions are subsidized by the interests of manufacturing new products, however they should be permeated between science, risk concerns, and public health. Otherwise, nanomedicine is currently a major scientific controversy, and there is no way of knowing when and how this controversy will end, but the fact is that in trying to build something

safe like nanomedicine, questions emerge, requiring necessity and urgent be enrolled a large number of actors, such as scientific articles, newspaper articles, scientists, regulatory agencies opinions and pharmaceutical industries.

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