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Souza, Pedro Borges de; Ramos, Daniela Fernandes; Gubert, Paulo Gilberto; Cigognini, Enir; Primo, Fabian Teixeira

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Nanodrug research and development: a bioethical approach

Pedro Borges de Souza [1], *Daniela Fernandes Ramos* [2], *Paulo Gilberto Gubert* [3], *Enir Cigognini* [3], *Fabian Teixeira Primo* [3]

1. Universidade Federal de Santa Catarina, Florianópolis/SC, Brasil. **2.** Universidade Federal do Rio Grande, Rio Grande/RS, Brasil.
3. Universidade Católica de Pelotas, Pelotas/RS, Brasil.

Abstract

Nanotechnology consist of using materials at the nanoscale, in which they acquire specific characteristics. Nanodrug research and development is one of the most promising fields today; however, these particles require particular evaluation. Moreover, studies lack consensus on which specific tests to follow, thus hindering the elaboration of legislation that ensure their safety and efficacy, as well as a more effective registration process. Thus, a bioethical approach to nanotechnology and its use in drug development is necessary to ensure scientific progress without irreversible impacts. Given this scenario, this article proposes a nanoethics discussion regarding nanodrug research and development by means of a qualitative, exploratory and descriptive analysis, based on literature review, documental analysis and quantitative data available.

Keywords: Bioethics. Nanotechnology. Toxicology. Regulatory frameworks for health.

Resumo

Pesquisa e desenvolvimento de nanomedicamentos: olhar bioético

Nanotecnologia é a utilização de materiais na escala nanométrica, em que estes adquirem características próprias. A área de pesquisa e desenvolvimento de novos nanomedicamentos é uma das mais promissoras atualmente, todavia essas partículas necessitam de avaliação particular e ainda não há consenso referente às testagens específicas a serem seguidas, o que dificulta a formação de uma legislação que garanta a segurança e eficácia destes medicamentos, além de um processo de registro mais eficaz. Assim, é necessária uma abordagem bioética da nanotecnologia e sua utilização em medicamentos, visando garantir que o progresso científico não acarrete impactos irreversíveis. Diante dessa problemática, busca-se promover uma discussão nanoética referente ao processo de pesquisa e desenvolvimento de nanomedicamentos, por meio de estudo qualitativo, exploratório-descritivo e de caráter analítico, utilizando revisão bibliográfica, análise documental e dados quantitativos disponíveis como técnicas de pesquisa.

Palavras-chave: Bioética. Nanotecnologia. Toxicologia. Marcos regulatórios em saúde.

Resumen

Investigación y desarrollo de nanomedicinas: desde la mirada bioética

La nanotecnología utiliza materiales nanométricos, en que estos adquieren características propias. El área de investigación y desarrollo de nuevas nanomedicinas es una de las más prometedoras en la actualidad, sin embargo, estas partículas requieren de una evaluación particular y aún no existe consenso en cuanto a las pruebas específicas que seguir, lo que dificulta establecer una legislación que garantice la seguridad y eficacia de estos medicamentos, además de un proceso de registro más efectivo. Por lo tanto, se necesita un enfoque bioético de la nanotecnología y su uso en medicamentos para garantizar que el avance científico no tenga impactos irreversibles. Ante esta problemática, se pretende promover el debate sobre la nanoética en el proceso de investigación y desarrollo de nanomedicinas a partir de un estudio cualitativo, exploratorio-descriptivo y analítico, que utiliza como técnicas de investigación la revisión bibliográfica, el análisis de documentos y los datos cuantitativos disponibles.

Palabras clave: Bioética. Nanotecnología. Toxicología. Marcos reguladores en salud.

The authors declare no conflict of interest.

Nanoparticles (NP) are materials located on the nanometric scale that present chemical, physical, biological and/or behavioral properties different from those found in the same materials in macroscales. One of the main fields of application of nanomaterials is the pharmaceutical sector, in which this technology enables new formulations of controlled releases using nanocarriers, generating a new class of drugs, called nanomedicines [1-3].

Pereira and Binsfeld [4] define nanomedicines as any substance or combination of substances with different physical-chemical properties used for prophylactic, healing, palliative, or diagnostic purposes. Nanomedicines are the *finished pharmaceutical form that contains a nanoscale medicine or associated with a nanoadjuvant with specific pharmacological action, aiming to modulate metabolic or physiological functions* [4].

The research and development (R&D) process of a new drug must ensure efficacy and safety. Scientific efforts and resources employed should thus meet the methodological rigor and principles involved in clinical research [5].

Considering sanitary legislation, clinical trials are divided into four stages. In the first stage, known as research stage, the molecular target of a given pathology is selected and a rational molecular design is drawn based on medicinal chemistry, in which its ligands present greater affinity with the chosen target; *in vitro* and *in vivo* pharmacological tests are then conducted, culminating in the discovery of a new prototype compound and its eventual optimization [6].

The development stage is next, being divided into an initial phase of pre-clinical trials with the prototype compound, covering toxicological tests, and a late phase, which comprises clinical studies in humans, divided into phase I, phase II, phase III and phase IV [6].

The pre-clinical stage aims to evaluate the candidate compound, including the methods and animals used in the study, the laboratory tests employed, and the data obtained regarding pharmacodynamics and pharmacokinetics characteristics, and therapeutic and toxicology margins. Finally, the relevance of these results is discussed, considering the desired therapeutic effects and possible adverse effects, then moving on to the clinical phase [7].

To assess toxicity in the pre-clinical phase, the Brazilian Health Regulatory Agency (Anvisa), in its *Guide for conducting non-clinical toxicology and pharmacological safety studies necessary for drug development*, lists the trials to which the new compounds must be submitted and, if approved, they can proceed to the other stages of R&D. However, the guide indicates no specific test for nanotechnology-based drugs. Anvisa also recommends the replacement of *in vivo* by *in vitro* tests, as long as validated and accepted internationally [8,9].

Finally, in the regulatory stage the new compound is registered by the regulatory body of each country, such as Anvisa, the Food and Drug Administration (FDA), or the European Medicines Agency (EMA). After registration, the prototype, now already a drug, enters its commercialization stage, with concomitant pharmacovigilance assessment (post-market surveillance) of the new medicine, in which the adverse effects (AE) from the use of this drug should be reported [6].

Nanomedicines aim to generate great benefits such as decreasing AE and the dose used, improving adherence to treatment [10,11], as well as the modified drug release [4,9]. Some characteristics make nanomaterials very attractive to R&D, though concern and mistrust may be raised, as their unknown intrinsic characteristics can irreversibly damage health and the environment [12,13].

Several studies indicate that NP may present health risks due to potential cytotoxic, genotoxic and teratogenic activity, which occur due to its metabolization in the body and permeation in cells, as well as its ability to interact with the organism's biomolecules, causing several types of reactions, depending on where it occurs. Moreover, these particles can produce reactive oxygen species and neurotoxicity, by crossing the blood-brain barrier, in addition to modulating the metabolism and modifying cell functions and structures [13-16].

Despite the great concern with the control of NP use and the various questions about its toxicity and peculiarities, the production

and standardization of toxicological tests is insufficient to evaluate the possible consequences that NP may cause in human beings and the environment [17].

Nanotoxicology is thus an answer to fill this gap, aiming to implement specific studies on the interaction between nanostructures and biological systems and to obtain a better toxicity assessment in preclinical studies in the development of new nanomedicines, ensuring greater patient safety [9,18].

Nanotoxicology

The impact of NP on humans depends on several factors and their properties—size, mass, chemical composition and surface, for example—and on how these NP aggregate. The way these particles penetrate the body (via the skin, inhalation, or orally) also generates several impacts [18-20].

The lack of standardization of tests to evaluate the safety of nanomedicines is one of the major problems of nanotechnology given their numerous differences when compared with macromolecules, for which several standardized tests already exist [8,21].

Nanotechnology science is still in development, being characterized by more uncertainties than concrete answers [22,23].

Other than the absence of answers about the toxicology of nanomaterials and the fact that they have applications in several areas, developing alternative research methods and tests is necessary to better assess the possible impacts of this technology. Given the numerous applications of nanotechnology, these tests should be able to evaluate the various properties of each NP, the toxicity of the routes of exposure and their elimination pathways. The individual and specific evaluation of each material is essential to determine the risk arising from its use [17].

Regarding the application of NPs in the pharmaceutical field, the risks presented by nanotechnology should be analyzed with caution and advance to avoid possible problems that may become irreversible for future generations [9,24].

New nanomedicines

Nanotoxicology applied to the research and development process

In the R&D of new nanomedicines, the interactions between nanostructures and biological systems are evaluated, seeking answers about the toxicity of such compounds in the pre-clinical phase of development, which ensures greater safety in using them in the different clinical phases [18,25].

After entering a biological system, the toxicity of NPs comes, mostly, from changes in physical-chemical properties after coming into contact with biological fluids, possibly causing affecting size, load and chemical surface, since the route of administration is also an important factor in these changes and one of the main problems related to NPs [26,27]. Moreover, comparisons comparison between NP with similar physical-chemical properties show significant discrepancies [1,2].

According to their intrinsic characteristics, NPs have a "synthetic identity" that describes their standard characteristics when manufactured, and acquire a "biological identity" when they enter a living organism. The lack of adequate methods and the complexity of this evaluation make it difficult to predict whether the nanomedicine will overcome the physical and physiological barriers of the organism and achieve its therapeutic target [26].

Studies conducted in the pre-clinical phase of a medicine's R&D process are necessary to advance the development of the new compound and justify research in humans. Nonetheless, due to the peculiarities presented by NPs, the exact behavior of a nanomedicine in a living system is not yet clearly understood [26,27].

Beyond the toxicological context, a bioethical approach is necessary, considering the animal testing policy of Russell and Burch [28], known as the 3Rs—replacement, reduction, and refinement—which seeks the better use of alternative models for testing the necessary effects in R&D. When developing tools for *in vitro*, *in silico* and *ex vivo* tests for NPs, the use of animal models is reduced and the results obtained are refined [8,27].

Simulations *in silico* are thus necessary to predict the NP uptake *in vitro*, deducing its intracellular distribution and *in vivo* behavior and efficiency when used as nanocarrier. These tests are essential because the ideal nanocarrier is designed from them, contemplating pharmacokinetics and toxicity characteristics and misdistribution within cells and tissues [2].

Several methods were developed to evaluate the pharmacokinetic properties of NP. However, the application of these methods is greatly complex [26].

Pharmacokinetics is characterized by the absorption, distribution, metabolism and excretion (ADME) processes in the body. Physical-chemical properties of NP, including particle size, composition, morphology, load, surface and stability can influence pharmacokinetics. The size of the therapeutic agent mainly influences pharmacokinetics, as it determines the amount of molecules and the absorption of the medicine on the surface of the nanoentity. Similarly, the chemical and physical-chemical composition of the particle controls the activity of the chemical substance, which, influences the pharmacokinetics of the medicine [1].

Several studies aim to evaluate and compare the kinetics and toxicity of NP using *in vitro* systems of cultivated cells, three-dimensional (3D) organoid cultures that imitate tissue structures or organs of different animal systems *in vivo*. However, despite presenting several advantages, important results, and a good correlation between 3D *in vitro* and *in vivo* models—as well as a considerable reduction in the use of laboratory animals, considering the ethical issues of animal testing—each system presents limitations [2,26].

The lack of patterns in the nanotechnology area causes problems in toxicity tests, as these include attempts to compare different NP types, different administration protocols—*in vivo* and *in vitro*—poor choice or differences in the chosen cell, resulting in differences in growth kinetics or endocytosis and frequent lack of nanomaterial stability tests or poor choice of methods—the two are fundamental aspects for any pharmaceutical product [1,2].

Faced with this issue, the European Union made nanotechnology research an essential point for occupational and environment safety and health. By using the little toxicological data available, the entity adopted a preventive approach to nanotechnologies due to possible exposure to them. In the United States, the National Institute for Occupational Safety and Health [29] recommended reducing the exposure of workers to NP until conclusive results were obtained [17].

The Brazilian scenario of toxicological tests of NP is similar to that of other countries: the document that indicates the toxicological evaluations to be made in the pre-clinical phase, provided by Anvisa, does not highlight any specific test for NP. The global lack of tests and specific regulations to evaluate the consequences of NP action for both humans and the environment is problematic because it adds to the issue of bioaccumulation in the disposal of these products, alerting to the need of developing studies that evaluate this impact in the long term [17].

Despite uncertainties about nanotoxicology, several medicines that use nanotechnology are already available in the Brazilian market. Such medicines were registered by Anvisa as similar medicines, however, according to the Collegiate Board Resolution (RDC) 60/2014 [30] of Anvisa, this registration would be incorrect because they should be registered as new medicines, since the bioavailability of nanomedicines can be changed when considering the reference medicine.

Pharmacovigilance is also impaired by the lack of information about the presence and/or type of nanotechnology used in the composition of medicines in packages and inserts, , which may hinder the control of possible AE [11,30].

Nanoethics

New technologies should be carefully analyzed when they arise, considering the impacts they can have on the quality of human, animal or plant life. This evaluation should be made by

observing and studying its relevance, priority, efficacy/effectiveness/efficiency, and scope, always aiming to ensure social justice and respect for human dignity [31].

Considering ethics, the didactic distinction proposed by Vázquez [32] is essential, for whom morality is a set of norms, whereas ethics is the science that has moral as its very object. In this sense, ethics does not hold normative character, as it can only assume this role in a second moment, and yet, it is limited to the confines of guiding, and not to casuistry.

Nanoethics must be based on the very principles of bioethics and, given the *status quaestionis*, the role to be played will be a questioning rather than normative one. Although bioethics evaluates and guides nanomedicines, it requires further investigations, demonstrating the applicability of its principles to specific procedures involving NP.

The principle of non-maleficence can and must be applied in the specific case of NPs, without stopping ongoing research efforts, and, at the same time, without endangering life in general and, especially, human life.

Given the great potential for applicability and profit in nanotechnology, the rate at which studies and applications in the area grow is overly high when considering the scientific knowledge available. This leads to a state of uncertainty about the impact in the future and to debates about the responsibility for regulating this technology, its management and the final destination of waste [33].

The literature is scarce on the classification of NPs, toxicological matters and trials to be followed. Thus, it is essential to develop a management plan for experiments to ensure greater efficacy in toxicity testing of nanoproducts [33].

Other than aiming to solve this lack of information about nanotechnologies, investment in R&D and public discussions on the subject are essential to create risk management methods for the use of therapeutic agents at nanometric scale [33]. A limit should be drawn, drafting different designs of risk-benefit analyses of the therapeutic agent, following four essential steps to the assessment of the traditional risk of hazardous materials: 1) hazard identification; 2) exposure assessment; 3) toxicity assessment; and 4) risk characterization.

Product development risk, performance risk and regulation should also be assessed [1].

When using the traditional risk assessment for nanometric therapeutic agents, estimating comprehensive toxicity of data acquisition, unintentional exposures, production of hazardous waste and contamination of water supply is necessary [1].

The context allows a bioethical analysis of people's use of nanotechnology, as this reflects impacts on the entire planet, no longer a solely human interest. The quantitative growth in experimentation results in the use of many laboratory animals and aiming beyond human health, that is, to meet the consumerist contribution of nanotechnological markets [33].

However, market interests should never come before life. The question of the universal dignity of human life thus comes into discussion. Human life is an inalienable and inviolable principle that must be above any other objective, as advocated by the *Universal Declaration of Human Rights*, in its art. 1: *All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood* [34].

The recognition of the universal equality of rights is seemingly simple. However, what is the principle that must guide human actions so that, in every-day life, the universal dignity of all cannot be set aside? Immanuel Kant, one of the greatest philosophers that humanity has known, formalized the following principle, which can serve as a guide: *so act that you use humanity, whether in your own person or in the person of any other, always at the same time as an end, never merely as a means*. In other words: people have value, and things, a price. This relationship should never be reversed.

Caution is thus required to prevent such scientific uncertainty from causing irreversible damage to humanity in the future, as Hans Jonas has already warned [36]. Therefore, the adoption of the precautionary principle becomes inevitable, since it aims to guarantee and/or preserve the basic rights, seeking

the preservation of life without interrupting technological development [9].

By adopting the precautionary principle, the assessment of the risks contained in the exposure to NPs is more detailed and rigorous, putting into question the entire scenario in which it is inserted. Legislation to regulate activities that use nanotechnology is necessary, minimizing risks to humans and the environment and, at certain times, delaying or prohibiting practices related to it that may cause irreversible damage in the future [37].

However, regulatory bodies around the world, responsible for the registration and monitoring of medicine, face difficulties related to insufficiency or uncertainty of scientific information. When adopting the precautionary principle policy in regulatory decision making in the health field, it is essential to control the use of nanomedicines until specific results are obtained proving their safety and evaluating the possible cost-benefit of their use to protect the patient and the environment. Risk levels must be reduced to acceptable standards, although they cannot be reduced to zero [11].

Final considerations

Nanotechnology is under development and, thus, many uncertainties about the long-term impacts on humans and the environment persist. Regarding the use of nanotechnology in the R&D of new nanomedicines, current scientific information is scarce to ensure its safe use and effectiveness. This lack of evidence hinders the creation of legislation that regulates production, defines the registration and indicates the pre-clinical and clinical evaluation processes to be conducted in the stages of development of a nanomedicine.

Such difficulties regarding the use and safety of NPs exist worldwide, raising great uncertainty about nanotechnology. Science is still unable to provide sufficient answers to ensure the integrity of humans and the environment, corroborating the need for a bioethical approach to the insertion of this technology in the R&D of nanomedicines, aiming to prevent possible irreversible deleterious effects on society.

From this observation, one can argue that we live in a risk society that requires the adoption of the precautionary principle to obtain a more rigorous and detailed analysis of the use of nanotechnology; thus, minimizing the risks linked to its use and aiming to guarantee and/or preserve the basic rights aimed at the preservation of life without interrupting technological development.

Despite being a promising area—especially when considering health and the development of new medicines—nanotechnology demands caution until science can uncover the gaps related to its peculiarities, which, sometimes, cause euphoria, since they present a wide range of use and/or innovation, given its unique characteristics; on the other hand, concern is also felt, as nanomaterials raise more doubts than answers.

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Pedro Borges de Souza – Master – pebsoza@gmail.com
0000-0003-4227-5865

Daniela Fernandes Ramos – PhD – daniferamos@gmail.com
0000-0001-6888-9553

Paulo Gilberto Gubert – PhD – gilbertogubert@gmail.com
0000-0002-6443-4479

Enir Cigognini – PhD – filoenir@gmail.com
0000-0002-0836-0778

Fabian Teixeira Primo – PhD – fabian.primo@ucpel.edu.br
0000-0002-2946-4920

Correspondence

Pedro Borges de Souza – Universidade Federal de Santa Catarina. Centro de Ciências Biológicas. Rua João Pio Duarte Silva, 241, sala 201, bloco F, Córrego Grande CEP 88037-000. Florianópolis/SC, Brasil.

Participation of the authors

Pedro Borges de Souza conducted the bibliographic research and was the main responsible for writing and reviewing the article. Daniela Fernandes Ramos, Paulo Gilberto Gubert, and Enir Cigognini carried out the critical review of the article according to their expertise. Fabian Teixeira Primo delimited the theme, assisted in the analysis of the material, and conducted a critical review of the study. All authors contributed to the writing of the article.

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