REVIEW
https://doi.org/10.22239/2317-269x.01765

# Nano drugs: regulation and quality control

## Nanomedicamentos: regulamentação e controle de qualidade

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Approved: 26 Aug 2020
Approved: 04 Jan 2021

## ABSTRACT

**Introduction:** The use of knowledge from nanotechnology in the pharmaceutical industry has led to the production of new drugs with their own therapeutic and toxicological characteristics. Controlled-release drugs that act directly on their action places, reducing their potential side effects, have been produced at the expense of this technology. With sizes comparable to those of biological entities and unique properties, this new class of drugs, the nanodrugs still presents some gaps that hinder its regulation. **Objective:** To evaluate these gaps, their impacts in the regulation and quality areas and the new regulation approaches under study. **Method:** A data survey was carried out in the electronic databases MEDLINE, PubMed and SCIELO, searching for original indexed articles, in Portuguese or in English, since 2002 until 2020. Relevant search terms in both languages were used ("Nanomedication", "nanomedicine regulation", "nanocarriers", "nanomedicine", "nanotechnology drugs", "quality and safety by the procedure" and "nanomedicine health surveillance"). **Results:** The selected works describe the current moment of regulation and quality control of these nanoproducts, as well as highlight the problems that still require greater understanding. **Conclusions:** Nanotechnology applied to the formulation and manufacture of drugs is undoubtedly a great advance for health. However, there are several points that still require further development and that impact the regulatory frameworks for the registration, effectiveness and safety of these products.

**KEYWORDS:** Drugs; Quality control; Nanotechnology; Health Surveillance

## RESUMO

**Introdução:** A utilização dos conhecimentos oriundos da nanotecnologia na indústria farmacêutica tem propiciado a produção de novos medicamentos com características terapêuticas e toxicológicas próprias. Medicamentos de liberação controlada e que atuam diretamente em seus locais de ação, reduzindo seus potenciais efeitos colaterais, têm sido produzidos às custas desta tecnologia. Com tamanhos comparáveis aos de entidades biológicas e propriedades únicas, esta nova classe de medicamentos, os nanomedicamentos, apesenta ainda algumas lacunas que dificultam sua regulação. **Objetivo:** Avaliar estas lacunas, seus impactos nas áreas de regulamentação e qualidade e as novas abordagens de regulamentação que estão em estudo. **Método:** Foi realizado um levantamento de dados nas bases de dados eletrônicas MEDLINE (PubMed) e SciELO, buscando artigos originais indexados, em português ou em inglês ou espanhol, a partir de 2002 até 2020. Foram utilizados termos de busca relevantes nas três línguas ("nanomedicamento", "regulação de nanomedicamentos", "nanocarreadores", "nanomedicina", "medicamentos com nanotecnologia", "qualidade e segurança pelo procedimento" e "vigilância sanitária de nanomedicamentos"). **Resultados:** Os trabalhos selecionados descrevem o atual momento da regulamentação e do controle da qualidade desses nanoprodutos, bem como evidenciam os problemas que ainda requerem maior compreensão. **Conclusões:** A nanotecnologia aplicada à formulação e à fabricação de medicamentos constitui indubitavelmente um grande avanço para a saúde. No entanto, existem vários pontos que ainda requerem maior desenvolvimento e que impactam os marcos regulatórios para o registro, a eficácia e a segurança desses produtos.

**PALAVRAS-CHAVE:** Medicamentos; Controle de qualidade; Nanotecnologia; Vigilância Sanitária

## INTRODUCTION

The pharmaceutical industry has sought to develop new pharmaceutical forms capable of directly reaching their biological targets and then promoting the controlled release of their active drug ingredients, since the release of the correct dose of the drug at the site of action would produce more effective, safer, and more effective drugs and with fewer side effects[1]. Therefore, the industry has been investing in technologies that favor the optimization of products that allow the transport of larger loads of drugs, increased drug circulation time in its entirety in the body, increased bioavailability of poorly water-soluble drugs, the targeting and release of the drug at the desired location, the ease of permeating various biological barriers, of interacting with selected biological targets and, consequently, minimizing side effects and increasing efficacy. In other words, an attempt is made to increase the drug's bioavailability by changing its pharmacokinetics[2,3,4,5].

For this, the technology that has been most widely used is the use of technologically controlled (or modified) nanoparticles produced using nanotechnology, that is, with the ability to measure, design, and manipulate materials at the atomic, molecular, or supramolecular levels with the objective of understanding, creating, and applying systems and structures with specific functions specific to their dimensions of approximately 1 to 100 nanometers[6]. Pharmaceutical products obtained using this technology, nano drugs, have physical, chemical and biological properties that differ from the same material on a usual scale[7]. In the case of the pharmaceutical industry, this definition is deficient, as it does not address important issues such as scientific, legal, environmental, regulatory and ethical implications as it is based only on particle size, ignoring the complexity of its interactions with the external environment and especially with living organisms[7].

In general, nano drugs are characterized by the reduction in the size of drug particles with low solubility to nanometric dimensions and subsequent conjugation with appropriate carriers that play a fundamental role in their therapeutic efficacy. In nano drugs, unlike usual drugs, the physicochemical and morphological properties of carriers interfere with the pharmacological characteristics of nanoproducts[8,9].

Nano drugs are defined as dosage forms that contain one or more drugs in the nanoscale or as pharmaceutical ingredients that are associated with an adjuvant in the nanoscale[2,9,10]. These have specific pharmacological action aiming to modulate metabolic and physiological functions and can be used with prophylactic, curative, palliative purposes or for diagnostic purposes[10]. Today it is known that more than 20 properties of nanomaterials are capable of influencing their effects on health and their environmental risks[11,12,13,14].

Therefore, the comprehensive knowledge of how nano drugs behave in a biological system requires the participation of several disciplines, among which: physiology, anatomy, pathology, genetics, biochemistry, physical chemistry, and nanotoxicology. In fact, the genetic and epigenetic characteristics and the existence of possible pathologies in the body, as well as the physical and physicochemical properties of nanomaterials, influence the interactions with cellular components (proteins, membranes, phospholipids, vesicles, and organelles) and consequently affect their pharmacokinetics and pharmacodynamics[4,7,10,15].

Currently, the search for guidelines for the regulation and quality of this new class of drugs involves a series of gaps and is a worldwide challenge, since the main international regulatory agencies, such as *Food and Drug Administration* (FDA), from the United States of America, and the *European Medicines Agency* (EMA), do not have a harmonized regulation for their registration and release[2,16].

Thus, this article intended to discuss the main gaps in current knowledge, as well as some guidelines that are being proposed by the regulatory bodies of the largest producers of nano drugs in the world.

## METHOD

### Databases consulted and search strategies

For this study, the electronic databases *Medical Literature Analysis and Retrieval System Online (MEDLINE), from PubMed, and Scientific Electronic Library Online* (SciELO) were consulted. All original scientific works indexed from 2002 to 2020, when the discussion on the use of nanotechnology in the health area began, were initially considered. The following search terms in Portuguese were used individually in all databases and their versions in English and Spanish: "nanomedicamento", "regulação de nanomedicamentos", "nanocarreadores", "nanomedicina", "medicamentos com nanotecnologia", "qualidade e segurança pelo procedimento" e "vigilância sanitária de nanomedicamentos" ("nano drug", "regulation of nano drugs", "nanocarriers", "nanomedicine", "drugs with nanotechnology", "quality and safety by procedure", and "health surveillance of nano drugs").

### Inclusion/exclusion criteria for articles

Scientific works focusing on technologies applied to drugs and those that pointed out the still existing scientific gaps were included. In addition to these, the applicable legislation and official documents from regulatory agencies that addressed guidelines and definitions on nano drugs and quality control that were still in force during the search period and available on their respective electronic portals were included in the analysis material of this work. The only restriction was in relation to the language of publication of the works, only those published in Portuguese, English, and Spanish being included.

Scientific papers without full *online* access and duplicated scientific papers were not considered. In addition, those that did not address concepts, those that presented only the synthetic route of nano drug, those that addressed a different theme

from the object of this study, and those that had inconsistent data, such as articles that lacked intellectual quality with reduced content and little depth, when compared to the rest of the literature.

### Review procedures

The survey of bibliographic data was carried out by two authors/researchers, based on the established inclusion criteria and, at a later time, in a confrontation of the findings, there was compatibility of the material found by both researchers. The first stage of selection of productions was carried out by reading and analyzing the titles and abstracts of all identified articles. After this initial screening, the selected studies were read in full, which allowed the exclusion of other texts for not addressing the subject of this review.

## RESULTS AND DISCUSSION

The bibliographic survey found 1,011 published scientific works. Of these, 546 were excluded for being present in more than one database, thus being registered in duplicate. When applying the other exclusion criteria listed above in the titles and abstracts, 238 were excluded, leaving only 227 scientific papers to be read in full by the researchers. After this second evaluation, only 108 works were selected and used as a theoretical basis for the elaboration of this work. All have been included in the references of this article.

Figure 1 presents the flowchart with the stages of identification, selection, and inclusion of scientific articles.

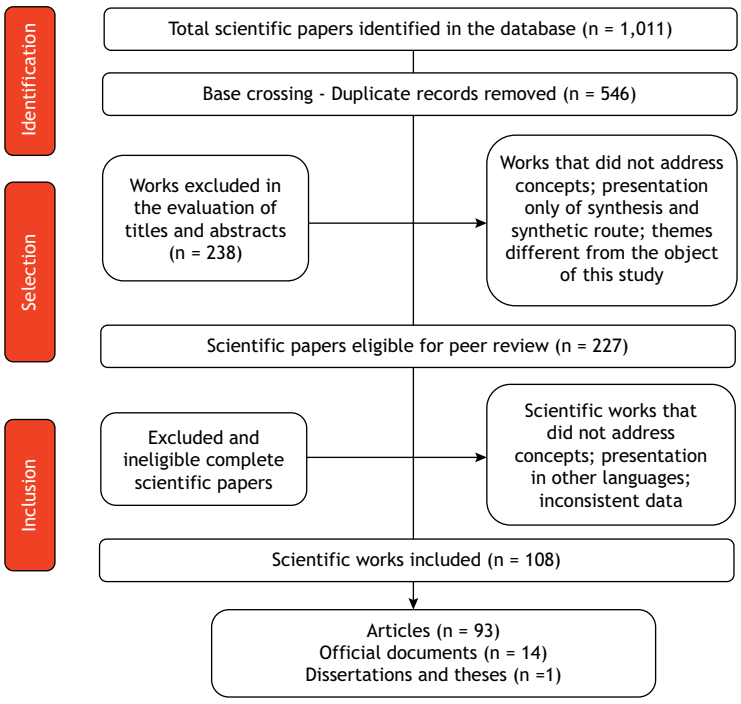
### Nanocarriers and nano drugs

Most nano drugs involve the use of nanocarriers which can be understood as biocompatible and inert nanostructures, associated or enveloped by a pharmacologically active substance (drug), capable of transporting it and directing it to a specific target in the organism, executing its release, usually controlled[12].

Data have shown that several nanoparticles have the qualities required by the industry for a good carrier, that is: increase local and systemic efficacy and tolerance (avoid foreign body reactions), protect healthy cells, reduce toxicity, and produce fewer secondary side effects[16,17,18,19].

Thus, a wide variety of nanocarriers has been used in the development of nano drugs that have been classified into lipid-derived, polymeric, and derived from carbon and inorganic material nanoparticles[20]. The diversity of available nanocarriers, each with characteristic properties, requires that their choice follow some parameters, such as: the type of disease and the target population, the type of drug to be used, the administration route, the biological barriers to be overcome, the target sites, the release kinetics, and the intended dose. The characteristic properties of each type have been the subject of several publications[5,8,9,14,16,21,22,23,24,25,26,27].

However, it is important to consider that the contact of these nanoparticles with the biological environment can result in significant changes in their physicochemical characteristics and, consequently, in their drug and toxicological properties. These modifications are mostly determined by superficial




Source: Elaborated by the authors, 2020.

**Figure 1.** Flowchart of identification, selection and inclusion of the reviewed scientific papers.

processes such as protein adsorption, coagulation etc. Another important factor related to the use of nanocarriers is the knowledge of the incorporated and released fractions of the drug in bioequivalence studies. In fact, traditional pharmacology holds that the free (unbound) drug is the biologically active form, so the simple determination of the total drug concentration can lead to significant errors in the interpretation of transport mechanisms and pharmacokinetic/pharmacodynamic relationships[28,29].

Currently, there are just over 60 nano drugs on the international market, of which 13 use liposomes; 22 polymeric nanomaterials and 27 inorganic nanomaterials. An overview of the current market availability and use of nano drugs in clinical medicine, as well as their diversity, pharmaceutical classification, and the benefits of using the nanometric scale, can be found in some studies[12,16,30,31,32,33,34].

Due to the characteristics that differentiate them from traditional drugs, nano drugs have different toxicities and side effects. It is believed that these differences occur due to nanocarriers, but further studies are needed to confirm this suspicion. Allergies, hypersensitivity, and immunosuppression have been attributed to the use of certain nano drugs[35,36].

Given the potential benefits obtained with the use of nanotechnology, the pharmaceutical industry has been encouraged to use it mainly for the production of nano drugs aimed at the treatment of diseases such as: Alzheimer[37], acquired immunodeficiency syndrome[37,38,39], malaria[40,41], Parkinson[42], tuberculosis[43] and cancers, since their treatments still entail many side effects and the desired efficacy is not always achieved[44,45,46,47,48,49,50,51,52,53,54,55,56,57]. This is because nano drugs have a set of advantageous parameters, such as the lowest recommended dose and highest maximum tolerated dose (MTD) when compared to drugs not nanoformulated. In addition, nano drugs can be more effectively targeted to target tissue through passive targeting mechanisms, via enhanced permeability and retention effect (EPR) and/or active, made through the use of specific ligands capable of increasing the interaction between the nano drug and receptors of target tissue cells, such as receptors of cancer cells[58].

In addition, several studies focus on obtaining greater efficiencies of antibiotics[59,60] and antioxidants[61] in the treatment of leishmaniasis[62], chemical dependency[63], metal poisoning[64], in periodontics[65], in psoriasis[20], and in ulcers[66].

## Regulation of nano drugs

The use of nanotechnology in medicine, as it is a new field of knowledge, still involves several doubts that limit or hinder the regulation of nano drugs. These gaps range from the lack of a single international definition for this type of material to the lack of knowledge about the possibility of impairment of brain functions resulting from the permeation of the blood-brain barrier; the systemic accumulation of nanoparticules in certain organs; of its potential for genotoxicity; the effect of morphology variation on physicochemical properties and their biological interactions and therapeutic efficacy; the difference in *in vitro* and *in vivo* behavior and even between animals and humans; the need to develop new analytical methods to monitor the efficacy and safety of nano drugs; the environmental impacts and the differences between the pharmacokinetic characteristics of nano drugs and those determined by standardized norms for small molecules[67,68].

The difficulty that these gaps have brought to the proposition of regulatory standards and guidelines has allowed the pharmaceutical industry to use the toxicological studies of active pharmaceutical ingredients (API) already registered and traditionally marketed to produce the data required in the registration processes of the nano drugs, disregarding any differences between the *in vivo* and *in vitro behaviors*[58].

For example, pharmacokinetic studies that show that important parameters such as half-life, area under the absorption curve and clearance of nanoformulations differ considerably when compared to traditional formulations. In general, nano drugs remain in the body longer and, consequently, allow the reduction of the number of administered doses, but in cases of intoxication or adverse effects, their elimination from the different biological compartments occurs more slowly, and may even cause death[58].

Other examples involve the difference in the *in vivo* and *in vitro* behaviors of the same drug when produced in nanoscale and in conventional scale, a lack of regulation for the evaluation of some toxic effects caused by nano drugs, such as effects on the immune system; the lack of a consensual standard method to measure the bioequivalence of a new drug compared to the reference drug already on the market, among others. In this regard, while the FDA recommends the use of the classic method for determining pharmacokinetic parameters (area under the curve or maximum plasma concentration), the European agency (EMA) requires much more detailed information from the bioequivalence study. The same scenario spreads and magnifies for drugs considered generic and similar[36,68].

Another important gap is the interaction of these nano drugs with the environment. Among the uncertainties that need to be resolved to allow a more complete environmental risk assessment resulting from the disposal of nano drugs the following can be mentioned: the lack of pharmacokinetic data; exposure and potential environmental hazards; the existence of contradictory experimental data on effects on the environment and organisms; uncertainties about the physical-chemical relationship and toxicity; the lack of ecotoxicological data for many nanomaterials and the uncertainties about how to assess the dose of the nanoproduct. In this regard, the *US National Research Council* created its own system for environmental risk assessment[69,70].

Regarding nanosimilars and nanogenerics, the European Economic Community, for example, recognizes that biological tests

must also be requested in the registration of these formulations, demonstrating the complexity of regulation of such products. Even so, such results cannot always be transferred from one species to another[71,72].

As can be seen, the multiplicity of factors that influence the biological effect of a nano drug makes the regulatory requirements for this class more complex, as changes can be observed even between different batches of the same product. As a large part of these nanoproducts are of controlled release and this property depends on the physicochemical characteristics of the carriers, detailed studies of these characteristics are fundamental requirements for regulatory agencies to be able to carry out their regulatory activities with complete safety. This is still a little-known and open field for further research[73,74].

The FDA, for example, listed the factors it considers important for evaluating a new nano drug. They are: adequate characterization of the nanomaterial structure and its functions; complexity of the nanostructure; knowledge of the mechanisms by which the physicochemical properties of the nanomaterial impact its biological effects (eg effect of particle size on pharmacokinetic parameters); understanding of the *in vivo* release mechanisms based on the physicochemical properties of the nanomaterial; prediction of *in vivo* release based on results obtained *in vitro;* physical and chemical stability; maturity of nanotechnology used in production and control (including analytical methods); potential impact of changes in the production process on the quality of the nano drug; physicochemical status of the nanoproduct after administration; administration route; dissolution, bioavailability, distribution, biodegradation, accumulation, and its prediction based on physicochemical and animal studies[75].

These requirements are varied and still constitute a challenge to be met today, as certain requirements, such as the chemical structure of some drugs, particularly non-biological complex drugs (NBCD), cannot be met. This is because NBCD does not have homomolecular, structures, but rather a complex mixture of similar structures that cannot be isolated, quantified or described through physicochemical analysis. For this reason, their qualities are highly dependent on their production processes[76,77].

In view of this, several institutions have chosen to produce manuals and guides to guide the pharmaceutical industry in the development of nano drugs. In other words, it seeks to standardize production processes. Among them we have the *European Chemical Agency* (ECHA), the Organization for Economic Cooperation and Development (OECD), the *International Conference on Harmonization* (ICH), EMA, *the Scientific Committee on Emerging and Newly Idetified Risks* (SCENIHR) and FDA[22,75,78,79].

Under the seal of the program *Registration, Evaluation, Authorization and Restriction of Chemical Substances* (REACH), established by the European Economic Community in 2006, and in order to address these needs, the European Union sponsored between 2013 and 2017 a pioneering research project called *NANoREG framework for the safety assessment of nanomaterials*, aiming at the development of scientific content to assist regulatory bodies in the implementation of standards and quality control of products that use nanotechnology in their manufacturing process[80,81]. This project consists of a collaborative study of more than 50 institutions from different countries such as: Australia, United States, Japan, Canada, Brazil, China, and South Korea.

In addition to providing policymakers with a set of tools for risk assessment and decision-making instruments, including exposure, monitoring and control for a group of already used nanomaterials, this project proposes the development of tests that analyze the impacts on the environment and human health of the nanomaterials most used by industries[82].

The main objectives of this project originated a compendium of guiding protocols for the regulation of nanomaterials produced by multidisciplinary and multinational groups. These protocols guide how to assess the risks and toxicity of nanoproducts, as well as provide the scientific data obtained so that lawmakers and inspection bodies can develop procedures to monitor and control the quality of this new class of products. The material produced can be accessed through the project website[83].

The NaNOREG project was later continued with the approval of H2020 (*Ensuring the safe and sustainable develpment and application of nanotechnologies*), *ProSafe initiative* (www.h2020-prosafe.eu) and the NanoReg2 projects, NanoRoadMap and GoNanoBioMat that propose to promote multidisciplinary studies in order to better understand the impacts of this technology on human health and the environment, the complexity of these formulations and propose a methodology for regulation, evaluation of quality and similarity[81,84].

Other groups, such as the regulatory agencies of the United States, Japan and even the European Economic Community, joined together to create common guiding documents for the entire pharmaceutical community[73]. However, the biggest challenge is still the establishment of sufficiently sensitive and specific assays to detect low concentrations of nanoparticles and to differentiate the free forms from the aggregated ones, as well as the metabolized and non-metabolized forms[85,86].

In fact, until now, regulatory agencies have worked differently, each in its own way. An interesting example of these differences is described by Rocco et al.[77], who compared the procedures adopted by the FDA and the EMA in registering products containing glatiramer acetate, a non-biological complex drug (NBDC) consisting of a heterogeneous mixture of synthetic polypeptides[77]. This substance was initially registered under the name Copaxone and later under other names (Glatopa, Copemyl, and others). In the United States, Copaxone was identified as the original product and the others as generics and, as such, pharmaceutical equivalence and bioequivalence tests

were required for registration. However, the demonstration of pharmaceutical equivalence is applied when the products contain the same active substance, which is not possible to demonstrate through physicochemical or biological tests for glatiramer. In Europe, EMA adopted a hybrid procedure, initially registering as generic, but requesting a series of additional comparative studies. In addition, it left to the discretion of the national regulatory authorities the possibility of substitution between these products[77].

In Brazil, the Brazilian National Health Surveillance Agency (Anvisa) has not yet elaborated specific regulations, it only established the Internal Nanotechnology Committee (CIN) in 2013 and, in 2014, it published a document entitled: Institutional Diagnosis of Nanotechnology of the Brazilian National Health Surveillance Agency, which highlights some issues subject to regulatory action by the agency. The proposal also defends the elaboration of an inventory of nanoproducts existing in the consumer market in Brazil, with about 637 products registered with Anvisa using nanotechnologies[87].

However, the current regulation of nano drugs is still not adequate and requires continuous improvement, especially in the environmental area[68,88]. However, some products have already been developed and are being widely marketed. Therefore, the *International Standard Organization* (ISO) recently published ISO/TR 22019:2019, entitled: *Nanotechnologies- Considerations for performing toxicokinetic studies with nanomaterials*. This document outlines the basic principles for relevant studies in nanomaterials toxicokinetics[89].

## Quality of nano drugs

Until the advent of nanoproducts, the quality of a drug was determined through some physicochemical, chemical, and/or biological tests. However, with the influence of other purely physical or physicochemical factors on the pharmacokinetic/dynamic behavior, there was a need to introduce new laboratory tests, which were not common in a pharmaceutical laboratory, which required the consequent training of the personnel involved The importance of these factors is so striking that it is currently known that understanding the relationships between the physicochemical properties, performance and safety of a nano drug are the first steps in product quality control[78,79].

It is observed that even small changes in the physicochemical properties or morphology of nanoparticles can have significant effects on the therapeutic efficacy and biological safety of the nanoproduct. The variability of these factors has an impact on the production of nano drugs and may cause differences in biological behavior between batches of the same product and their bioequivalence, particularly important aspects for nanosimilares products and nanogenerics[73]. As a consequence, it is believed that, due to this complexity of intervening factors in the pharmacological action of a nano drug, the replacement of a nanoproduct by its similar is difficult, if not impossible[71]. For these reasons, theoretically similar and/or biosimilar products produced using different types of nanocarriers or forms of nanoencapsulation that do not have pharmaceutical equivalence and bioequivalence studies have been registered as new products[31,90,91].

An interesting discussion on pharmaceutical equivalence and bioequivalence, which involves biosimilarity and generics, for complex drugs obtained by nanotechnology and by biotechnology and how regulatory agencies have conducted some registrations can be found in Hussaarts et al.[92].

The influence of multiple factors on drug effects brings with it the difficulty of predicting the interactions between nano drugs and biological systems and makes it difficult to develop norms, standards, and tools to assess risks[93].

The impact of these properties on pharmacological behavior meant that the use of national pharmacopoeias, as a code and quality regulator, failed to meet the peculiarities of these nanoproducts[31,73]. In many cases, even today nano drugs are being produced and marketed using the same standards of good manufacturing practices applicable to medicines formulated on a traditional scale[31].

As a consequence of these limitations, new, more sophisticated and robust methods must be developed and applied both in the control of raw materials and in the finished product[31]. Thus, the important factors in this context that must be considered in the control of the manufacturing process, quality, and similarity of nano drugs are shown in Figure 2.

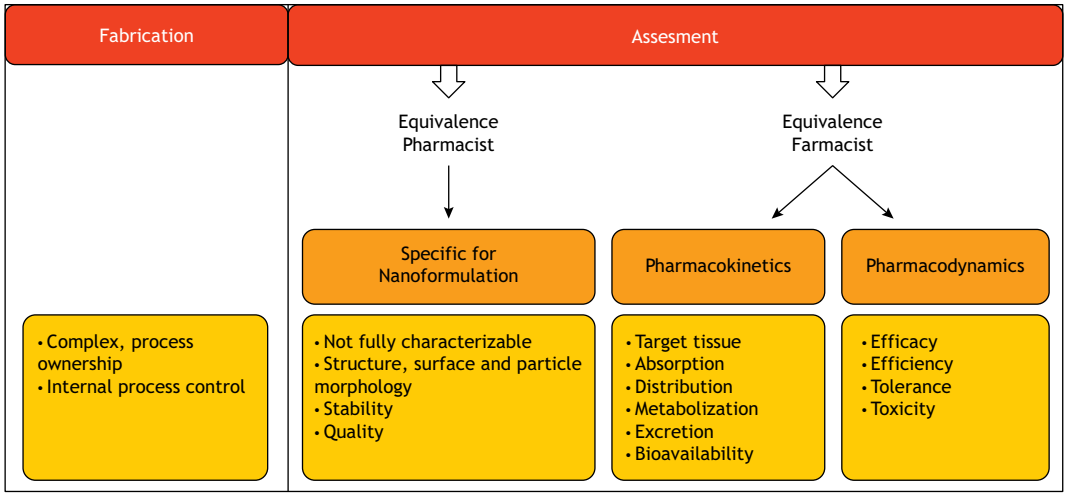
## New approaches

The current stages of planning for the production of nano drugs or nanocarriers[2] occur as follows: production of nano drug <-> physicochemical characterization <-> biocompatibility and nanotoxicology <-> pharmacokinetics and pharmacodynamics <-> process and production control[2].

However, the complexity of interactions between nanomaterials and organisms results in only a partial understanding of the risks associated with their uses and has created new challenges to control its potential adverse effects on man and the environment. Furthermore, since the introduction of nano drugs on the market, the costs of development, production, quality, and safety have been worrying factors and often determining the success or not of an undertaking. Due to this, in contrast to the traditional approach to quality, some new integrative approaches have been directed to the production process in order to guarantee quality, reduce its costs, and reduce the risks associated with the use of these products[94].

As early as 2000, the FDA proposed an initiative called Quality by Design (QbD) to be used in the production of drugs and especially of nano drugs. In 2009, the International Conference on Harmonizatin of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Q8) recommended the adoption of this approach by the pharmaceutical industry.

The main steps of this process are shown in Figure 3. Although this concept is not new, this approach, in contrast to the usual




Source: Adapted[31].

**Figure 2.** Factors needed to control the manufacturing process, quality, and similarity of nano drugs.

model until then, proposes the construction of quality throughout the production process[78,95,96].

This tool can be understood as a systematic approach applied during the design and production of a drug in order to consistently ensure the pre-defined quality at the end of the process based on current scientific knowledge and occupational risk management[97].

This involves defining the product's intended quality profile, designing the product and production processes, identifying critical quality attributes, process parameters and sources of variability, and controlling the production process so that you get products with consistent quality[97].

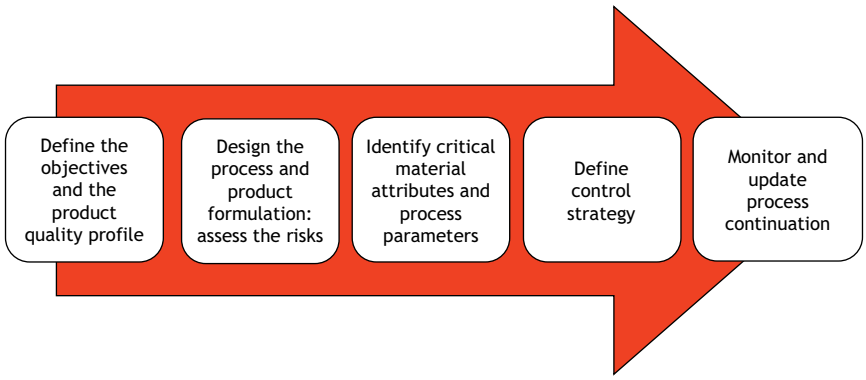
This methodology requires the establishment of a series of critical attributes for quality, for the process, and for production. Among the 20 critical attributes adopted for the quality of nano drugs, the following stand out: the size of the nanoparticles, size heterogeneity (polydispersity index), efficiency in encapsulation, the zeta potential, and the amount of drug released[78].

A detailed example of the application of the QbD methodology in the production of a nano drug can be found in Raina et al.[98].

In Brazil, Anvisa, through Collegiate Board Resolution (RDC) No. 301, of August 21, 2019, incorporated this concept in its text on Good Manufacturing Practices for Drugs[99].

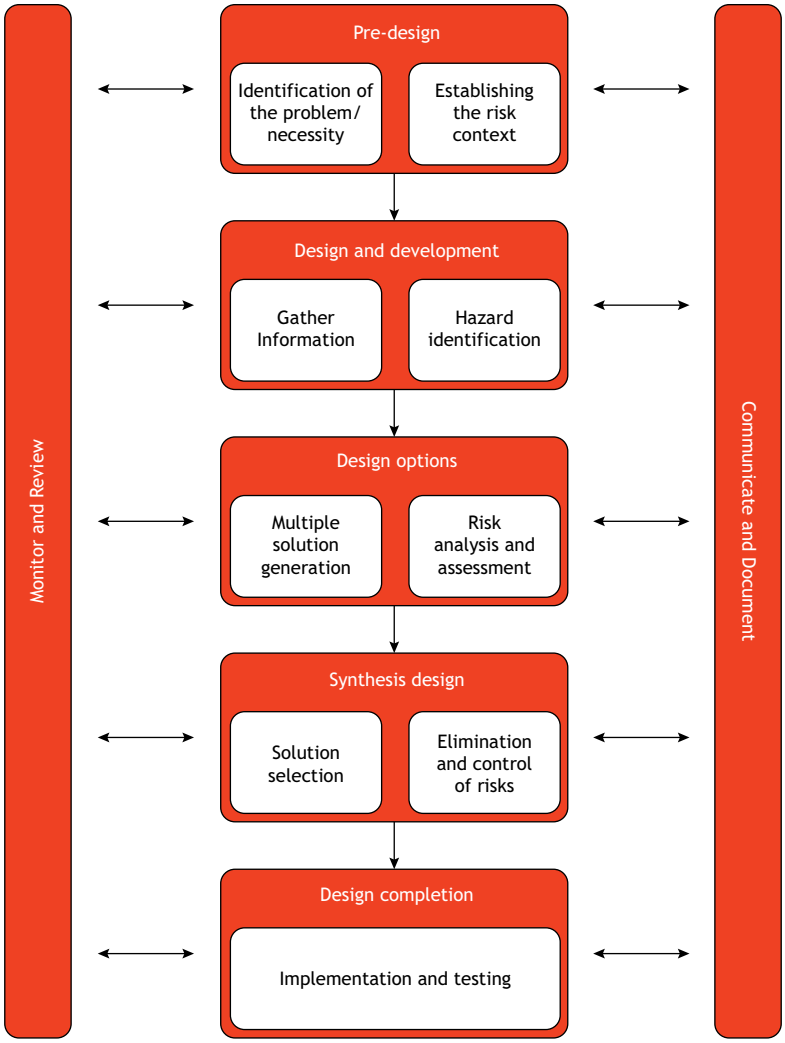
More recently, another proposal has gained a lot of attention especially in Europe: the Safe-by-Design (SbD) (Figure 4)[27,100]. This process-based safety concept applied to nano drugs, seeks to eliminate or reduce and control health hazards from potential risks identified in light of current knowledge and minimize them from the early stages of the product design process. This approach is used in the GoNanoBioMat project, funded by the European Economic Community, but has not yet been included in the standards produced by the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH), EMA or FDA.

This concept seeks to anticipate and reduce the risks and uncertainties related to the safety of human health and the




Source: Modified[97].

**Figure 3.** Main steps of a Quality by Design process.




Source: Adapted[104].

**Figure 4.** Constituent steps of the Safe by Design process.

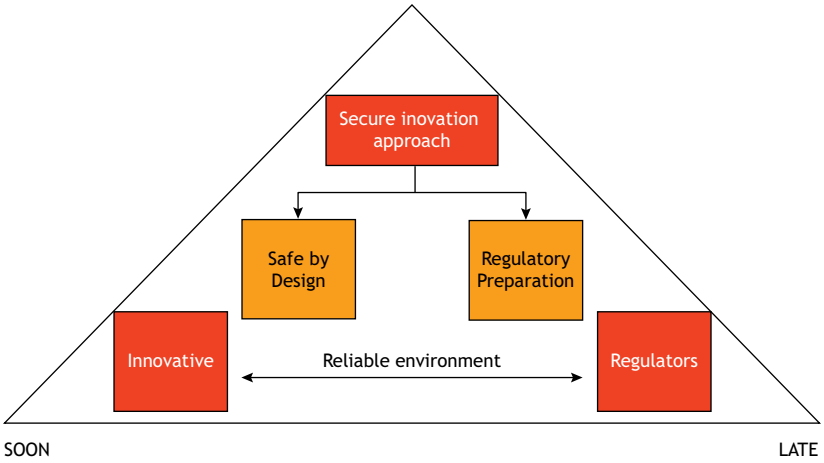
environment, based on safety and efficiency requirements. It considers safety as a fundamental property, as well as those of a physical or chemical nature, arising from the biological and environmental characteristics and effects of the nanomaterial. In other words, it involves the integration of the stages of hazard identification and risk management to the initial stages of the design and production process of nano drugs and is based on three pillars: 1 – nanobiomaterials safe for human health and the environment; 2 - safe and controlled production to ensure safety and quality, eliminating occupational hazards and the production of waste and 3 - safe use and life cycle (safe transport and storage to ensure the safety and quality of nanobiomaterials) defining recycling and final disposal routes[27,101,102].

This approach has been used in the NaNOReg, NaNOReg 2, GoNanoBioMat, and CALIBRATE projects, all funded by the European Economic Community[102,106].

More recently, the concept of the *Safe Innovation Approach* (SIA), which adds to the SbD the concept of regulatory preparation, that is, in addition to using all the criteria of the SbD, methodology, it adds a proactive attitude towards regulatory bodies, facilitating the development of regulatory standards and the final approval of products, as shown in Figure 5[105].

These procedures are still in the exploratory phase and, being a relatively new area, they need further studies[27]. These approaches require the production of nanomaterials that are safer in terms of risks and uncertainties related to human health and environmental safety. Even so, some uncertainties arising from changes in the physicochemical properties of nanoparticles in contact with biological material (adsorption, aggregation, corona effect, etc.) still persist and are capable of affecting their toxicities and functions [27,100,104].

In 2016, the FDA published an industry guide called Safety consideration for product design to minimize medication error, with recommendations applicable to drugs and biological products[107].




Source: Adapted[106].

**Figure 5.** Conceptual representation of the Safe Innovation Approach (SIA).

## CONCLUSIONS

With industrial development, the technologies used for the production of drugs underwent changes in an attempt to increase efficiency, reduce costs and doses administered to patients, as well as the adverse effects associated with some active pharmaceutical ingredients. Thus, nano drugs were designed to directly reach the specific site of the pathology with the lowest recommended dose and the highest maximum tolerated dose, with fewer adverse effects for the individual.

However, this technology brought with it a series of factors that greatly increased the complexity of interactions between nano drugs with living organisms, requiring an adjustment of regulatory standards for production processes, quality control, testing and for registration, constituting a major global concern and a priority for health authorities.

Thus, groups of regulators from different countries are establishing partnerships and projects to discuss and expose the knowledge to be able to establish standards for production, evaluation of effectiveness, control of the production process, and quality of nano drugs, as well as the protection of the professional involved in the manufacture and the final consumer, and also the environment. However, there are several points that still require further development, such as the issue of bioequivalence and pharmaceutical equivalence for the nano drugs produced. This collective construction directly impacts the regulatory frameworks for the registration, efficacy and safety of these products, but it still fails to fully address the gaps in knowledge as presented in this paper.

Thus, despite nanotechnology associated with drugs being at the center of global research, there are still many doubts to be resolved. The current trend is to regulate production processes in order to increase their safety, guarantee reproducibility, quality, efficiency, and reduce the possible risks of their products. However, this still requires mastering a series of variables and filling in several gaps, being an open field for research.

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## Acknowledgment

This work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel, Brazil (CAPES) - Financing Code No. 001, of the INOVA Program/Fiocruz - Knowledge Generation Notice 2019, of the FAPERJ Notice No. 02/2019 project - Nanotechnology Research Networks Program in the State of Rio de Janeiro.

## Author's Contributions

Barata-Silva C, Moreira JC – Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. dos Santos LMG, Vicentini Neto SA, Magalhães CD, Jacob SC – Conception, planning (study design), and writing of the work. All authors approved the final version of the work.

## Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.