Regulatory issues surrounding nanomedicines: setting the scene for the next generation of nanopharmaceuticals

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'Directive 2004/27/EEC on medicinal products of human use addresses directly the need for the study of environmental impact of medicinal products, which we can well predict will be of major importance for a series of new nanomaterials to be used in second-generation nanomedicines.'

More and more nanotechnology incorporates converging sciences through an integrated approach. Basic knowledge from new material synthesis, characterization and manufacturing promotes this integration with a new perspective on materials physics in the context of their technological usefulness.

Among different areas in nanotechnology, support and evidence has been accumulated on the differentiation of nanomedicine as an interdisciplinary area of knowledge at the crossroads of converging sciences [101–104].

Toxicology aspects have been highlighted along the way, with a major focus on the long-term toxicity produced from unwanted exposure (environmental) and purposeful challenge (e.g., the therapeutic use of nanostructured materials) [1].

One of the most important issues currently discussed deals with the question of whether or not the currently required toxicological studies, established in well-regulated areas, such as medicinal products, will be sufficient and adequate. The issue of the adequacy of current tests and models is at the forefront of scientific discussion, highlighting the question with regard to the need for new testing models, both *in vitro* and *in vivo*, at the preclinical stage.

Moreover, a number of environmental problems must be addressed when looking at the issue of medicinal product manufacturing at the nanoscale [105–107]. Most of the systems currently in clinical use deal with colloidal suspensions in which the dispersing liquid phase plays an important role for preventing environmental contamination by nanoparticles. However, the introduction of new generations of nanomaterials in nanomedicine will face challenges from problems already existing in other nanotechnology areas. Questions relating to facilities design and its limitations, as well as the impact of nanomaterials in the environment, are in fact heavily dependent both on reported physical characteristics and available information from the biologic effects of specific nanomaterials.

Critical issues relate closely to the need to limit cross-contamination among different products manufactured in the same facility, with physical properties very different from conventionally manufactured materials that are manufactured in the same facilities. Aspects related to manufacturing environment exposure, contamination of components of machinery used in the manufacturing process and disposal of unused or expired products all pose a number of difficult questions that must be answered before new categories of materials can find a routine.

These environmental aspects correlate well with the new regulatory environment for medicinal products in Europe. In fact, Directive 2004/27/EEC on medicinal products of human use addresses directly the need for the study of the environmental impact of medicinal products, which we can predict will be of major importance for a series of new nanomaterials to be used in second-generation nanomedicines [108].

Current framework & future challenges

Nanomedicines have been on the market for more than 17 years. But, as the first generation of products was able to pass regulatory approval by meeting general standards, this will not always be the case for new products. Even if some can, and in fact a lot of them are meeting the required specifications according to present standards, that will not be the reality for some of the new therapeutic strategies and materials. The fact that they can be more complex in their structure, with major differences in biofate and increased complexity of clinical use, integrating different technology subsets from therapeutics to imaging and integrated noninvasive diagnosis will probably force the creation of a new regulatory environment. The new regulation will have to solve difficult situations, frequently bridging medicine and medical devices regulations.

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Current guidelines for the assessment of biologicals for medical devices are based on the application of voluntary standards, none of which contain standards validated specifically for nanoparticles. The fact that the current methodologies were not developed in order to accommodate existing standards for the testing of new nanoparticles in the frame of drugs and biologics assessment illustrates how fragile the borderline issues between medicinal products and medical devices could be.

Issues relating to the understanding of how the nanoparticles are presented to organs, cells and organelles are of the highest importance when looking at the different mechanisms for intracellular trafficking in order to understand their full therapeutic potential. Those aspects cannot be established without improving appropriate basic knowledge of cell and molecular biology at the intracellular level. However, at the same time, critical physical and chemical properties, including residual solvents, processing variables, impurities and excipients, should all be well known. Again, this points to the need for well-established standard tools to be used in the characterization of nanopharmaceuticals, including availability of validated assays to detect and quantify nanoparticles in tissues, medicinal products and processing equipment.

A set of standards must be established in a harmonized and global regulatory environment. Among the most important quality aspects, there is the need to incorporate novel techniques for the characterization of different materials and technological options, looking at different structures, from colloidal systems to carbon nanotubes. A differential approach should bring into consideration the requirements for different administration routes in an integrated good manufacturing practice (GMP) environment, not forgetting to integrate the most recent advances in pharmaceutical concerns with risk management and quality management systems, bringing together statistical methods and new technological paradigms, such as in Process Analytical Technology (PAT). A subset of standards for the nonactive part of medical devices fosters again the discussion about the thin line dividing pharmaceutical and medical devices regulations.

The critical attributes of nanotechnology products certainly include aspects related to material characteristics, such as particle size and size distribution, surface area, surface chemistry, surface coating, porosity, hydrophilicity and surface charge density. Additionally, some of the classical attributes for pharmaceuticals will also be at the forefront of standardization and manufacturing issues, including purity, sterility, stability (aggregation but also protein adsorption), manufacturing operations and related industrial control standards.

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A full review of production processes and the link to appropriate industrial standards is needed, both for quality normalization and prevention of environmental unintended impact. Environmental, GMP, good automated manufacturing practice (GAMP) and other current industrial requirements should be adapted to a new technological reality.

New methods and standards need to be considered (e.g., particle size and materials characterization) simultaneously with new analytical tools to assess drugs inside nanosystems.

Who will do this? The European Department for the Quality of Medicines should play an important role, bringing together the experience of dealing with quality standards for the pharmaceutical sector in the last decades. However, an increased level of knowledge is also coming from the normalization initiatives within the USA [109]. As a consequence, the use of International Conference on Harmonization (ICH)-type initiatives for building a specific set of regulatory guidelines could be explored but does not exclude the possibility of establishing standards and standardized methods of characterization using a more permanent level of global standardization between the USA and EU focused on nanomaterial characterization, including those useful in medical applications [110,111].

A number of nonclinical issues must be considered when looking at specific questions dealing with nanomedicines. In the case of *in vitro* models, a relation of causality needs to be established in an appropriate manner with the clinical situation, such as assessing target binding or receptor screening. The mechanisms of cellular uptake have to be evaluated and profiled to

determine, not only therapeutic potential, but also the pharmacodynamics of cellular toxicity. Subsequently, studies in *in vivo* models must establish efficacy and proof of concept, using not only appropriate effect quantification and imaging, but also performing specialized toxicology studies that are able to relate functional effects with mechanisms of tissue uptake and tissue clearance (pharmacokinetics [PK] versus pharmacodynamics [PD]).

The toxicology studies have to establish, in an appropriate manner, how reduction in size will impact the activity of specific materials, namely in terms of cell or tissue access and clearance, including residence time in potentially harmful sites. The impact on cellular functions correlated to tissue- or organ-impaired physiological functions within a specific pathology situation will vary according to the nanomaterials used and their physical and chemical characteristics, having a major impact on their biocompatibility, immunotoxicological or inflammatory potential.

When looking at the currently required studies for nonclinical assessment of medicinal products, most of them relate to *in vivo* short-term toxicity in rodent and nonrodent species, absorption, distribution, metabolism and elimination (ADME) pharmacology, safety pharmacology, genotoxicity, developmental toxicity, irritation and sensitization studies, immunotoxicology, carcinogenicity and other such studies. The current system is expected to identify possible problems originated from drug exposure. Additional studies will be a priority for systems, considering materials never used before in clinical applications.

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One of the main concerns is related to the chronic exposure of humans to a wide range of nanomaterials and the potential for inflammatory or proinflammatory consequences that would bring a spectrum of inflammatory or immune disorders, limiting the extensive use of nanopharmaceuticals. This inflammatory and immunologic potential needs to be well investigated according to dose, posology and administration routes in order to establish safe limits before engaging in clinical trials.

Specific aspects related to target disease and target cell populations (essential aspects could be illustrated in cancer) must be addressed at an early stage when studying the development of nanopharmaceuticals. Adequate *in vivo* nonclinical studies should relate closely to disease localization, disease progression and access to target tissues and cells, correlating the appropriate pathophysiology scenario in specific clinical situations (e.g. different phases of cancer progression in ovarian, breast or prostate carcinoma, melanoma or leukemia), identifying the impact of angiogenesis progression and of the immunity status, highlighing the need for adequate biomarkers.

Modeling techniques used to assess PK parameters should take into consideration target tissues and pathophysiology, closely relating PK and PD aspects. A case-by-case approach should be used in most cases but most general aspects should be integrated into guidelines or adequately framed points, alongside integration of experience attained by the European Medicine's Agency (EMEA)'s scientific advice working group (eventually with participation of the US FDA within their joint advice program) and appropriate forum with discussions involving the scientific community.

One of the important issues regarding ADME profiling of nanopharmaceuticals relates to the impact of size and surface characteristics on organ, tissue and cellular localization. Sensitive questions arise, for example, how to identify and prevent a certain level of dermal exposure by cosmetics containing nanoparticles from gaining access to the systemic circulation. Another relevant issue relates to how to establish *in vitro* or *in vivo* screening tests that would be useful to identify potential risks and hazards resulting from the use of nanosized delivery systems administered by different parenteral or nonparenteral administration routes.

The ethical discussion about nanomedicine has taken a further step recently with the welcomed 'opinion 21 document' coming from an European group of experts (The European Group on Ethics in Science and New Technologies to the European Commission) working closely with the European Commission [112].

Meanwhile, a number of more focused ethical issues have to be addressed in the context of the use of nanopharmaceuticals. The need to promote

a research environment appropriate for availability of 'better medicines faster' indicates the urgency of accelerated processes in an appropriately established manner, with full integration of the toxicological implications for specific products. From the final part of the drug development process, issues relating to the need to guarantee access of patients to nanopharmaceuticals are central. This new generation of medicinal products will target unmet medical needs and will be of critical importance in life-threatening situations. These aspects will make even more critical the definition of who will pay and who will be guaranteed access to new medicinal products from nanotechnology.

Meanwhile, first-generation nanopharmaceuticals have gone through the process of evaluation using assessment tools common in pharmacoeconomics in order to establish economic advantage and identify their therapeutic added value with the intent of establishing reimbursement or co-payment decisions (concerning public sector or private insurers systems) [113].

New regulatory actions

Indeed, the current regulatory framework has proved to be sound enough until now. A first generation of nanomedicines (nanopharmaceuticals) got access to the market in a regulated environment, most of them before a real awareness existed about a number of issues related to safety concerns of nanomaterials, and with a demonstrable relative success, in terms of their clinical safety assessment and safe use, namely in the oncology area.

That fact, by itself, showed again how robust, safe and flexible the current regulatory environment is when it relates to innovative products.

But, we should also be cautious, admitting that materials, such as phospholipids or biodegradable/bioerodible polymers, are of a completely different nature from other anticipated materials that will be produced in the near future from the research pipeline. Carbon nanotubes, quantum dots and other nonbiodegradable and potentially harmful materials should be given different and more closer attention, looking at their toxicological potential impact in a number of different applications.

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By the same standards and in the new context, already existing nanopharmaceuticals, when administered for the same or new therapeutic indications making use of different administration routes (e.g., pulmonary), should not be waived of a full assessment of their differential potential toxicology impact, particularly in the proinflammatory area.

The way to move forward is not different from what regulators have done in the past 15–20 years. Building new regulatory guidance with the consultation and participation of research institutes from academia and industry will promote a better regulatory environment in a stepwise transparent manner, as has been the case time and time again in Europe and the USA. This can use a very successful European regulatory model now built into the genetic code of the European and national agencies for medicinal products, incorporating ICH-like approaches, closer and closer (from the scientific advice part) to a permanent global cooperation between the EU and USA, as well as Japan and a number of non-ICH-associated partners. Nanotechnology in biomedicine presents a number of highly complex problems for which the solutions should come from the frontiers of scientific knowledge in a global integrated manner, improving regulation and promoting better access to new technologies.

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