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Review Article

Nanomedicine Clinical Use, Regulatory and Toxicology Issues in Europe

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ABSTRACT

Nano medicine is a revolutionizing field that can benefit both diagnosis and treatment and contribute to a better quality of life. Despite the expected huge benefits, the potential risks on human health are significant as well. This thesis aims to defense a perspective that in case of nascent technologies, where the data are still emerging and scientific uncertainty prevails, risk governance should sustain the process of scientific knowledge by developing guidelines, codes of conduct and public information and provide a minimum level of safety acceptable to protect human health. Although Nano medicine is at an early stage of development some cautious measures should be taken that will provide regulatory mechanisms able to respond to the challenges posed by Nano medicine, establish a minimum level of safety but will also allow the further promotion of scientific knowledge. This multidisciplinary approach can contribute in adopting regulatory choices and tools that will help manage the risks, protect human health and promote scientific knowledge. As the technologies are designed based on a clear understanding of a particular disease, disease specific oriented focus is required for the development of novel pharmaceuticals. In addition, it will be important to establish a case-by-case approach to clinical and regulatory evaluation of each Nano pharmaceutical. High priority should be given to enhancing communication and exchange of information among academia, industry and regulatory agencies encompassing all facets of this multidisciplinary approach.

Keywords: novel pharmaceuticals, Nano pharmaceuticals, toxicological issues, clinical use, Nano medicines

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INTRODUCTION:

As for any other conventional medicine, the entire life cycle of Nano pharmaceuticals includes production, distribution, clinical administration, consumer safety (human body effects and side-effects), and waste disposal. While the clinical applications usually concern only the selected stages of the life cycle, toxicological effects may exist in all the stages. Both clinical applications and toxicology of Nano pharmaceuticals must be studied and examined comprehensively.

When designing a clinical protocol for a Nano pharmaceutical there are new challenges. Clinical trials and epidemiology studies may be significantly different from those for conventional diagnostic and therapeutic agents. Early dialogue and collaboration between scientists, clinicians, toxicologists and regulatory authorities are

increasingly recognized as one of the important issues to ensure rapid clinical uses of safe Nano pharmaceuticals.

Nano scale objects, typically but not exclusively with dimensions smaller than 100 nm, smaller than 200 nm for ultrafiltrable range and smaller than 1000 nm for dendrimers, exhibit fundamentally different physical, chemical and biological properties from those of the corresponding mass materials. These distinctive properties, together with the Nano scale size which is in the same scale of the naturally occurring biomolecules, promise revolutionary potential applications in clinical practice. Nano medicines or Nano pharmaceuticals may therefore be defined as Nano scale material to be used for clinical diagnosis, treatment, and prevention of human disorders. Nano medicine application depends on the structures and mechanisms which are functional only on Nano scale-mediated macro-molecular and supra-molecular assemblies.

In particular, the following areas were considered:

Technology	Application
Nano pharmaceuticals – in current use or entering routine use in the short-term future (within 5 years)	Cancer Antiviral agents Arteriosclerosis Chronic lung diseases Diabetes
Nano pharmaceuticals – with potential clinical applications in the longer term future (10 years)	Gene therapy Tissue engineering Tissue/cell repair
Nano devices	Delivery of diagnostic and therapeutic agents

REGULATIONS & CLINICAL USES:

There are very strict regulations and approval processes for any medicine (via regulatory agencies such as FDA, EMEA etc.) or any material proposed for human use. It must undergo rigorous toxicology studies as part of the regulatory approval process. However, the special properties of Nano-objects that are only exhibited at the Nano scale suggest that Nano pharmaceuticals may also require a new array of toxicological and safety tests. It was agreed that new strategies in toxicology for Nano medicine must go hand-in-hand with the development of Nano pharmaceuticals in order to ensure the safe yet swift introduction of Nano medicines to clinical use.

The toxicology of Nano pharmaceuticals, Nano imaging agents and nanomaterial's used in device manufacture should be considered during their entire life cycle:

- Stages of production/manufacture
- Preclinical and clinical development (or for other uses e.g. veterinary)
- Consumer and staff safety
- Waste management/fate in environment.

Although the Nano pharmaceuticals that have already entered routine clinical use have been rigorously tested with regard to safety, there have been comparatively few toxicological studies published on Nano pharmaceuticals. However, this issue needs to be explored, based on the large literature in the toxicology field describing the effects of nanoparticles, either present in the environment as pollutants or made as a result of the industrial production of non-medical and non-biological materials.

Europe has considerable experience in the clinical development of Nano pharmaceuticals (particularly in cancer). Pre-clinical toxicology to 'good laboratory practice' (GLP) has assessed antibody drug conjugates, polymer-drug conjugates and nanoparticle-based chemotherapy. During the development of novel anticancer treatments there is always a careful evaluation of risk-benefit.

Since Europe has particular strengths in the research areas of toxicology of inhaled ambient or occupational fine and ultrafine particles there is an excellent opportunity to redress the current mismatch between studies on toxicology of nanomaterial's and those involved in research and development of Nano medicine-related technologies.

As there seems to be enormous prospects for the application of nanotechnology in medicine, the European Nano medicine research community should act proactively

to seize the opportunity to clearly define the ground rules for the related toxicological research, and the related clinical and industrial development of these important technologies.

Apart from those Directives and Regulations, there are a variety of Guidelines and Principles, as Directive 2001/20/EC for Good Clinical Practice – Clinical Trials of Medicinal Products, Directive 2003/94/EC for Good Manufacturing Practice for Medicinal Products and Directive 2005/28/EC for Good Clinical Practice-investigational Medicinal Products. In order to complete the regulatory puzzle, attention should be paid to the fact that medicinal products for Advanced Therapy, Pediatric Use and Orphan are subject to different rules. Finally, other provisions are applicable to GMOs, Human Blood and Plasma as well as Human Tissue and Cells. Our analysis will focus on the medicinal products and medical devices regime.

TOXICOLOGY ISSUES:

There is an urgent need to improve the understanding of toxicological implications of Nano medicines in relation to the specific Nano scale properties currently being studied, in particular in relation to their proposed clinical use by susceptible patients. In addition, due consideration should be given to the potential environmental impact and there should be a safety assessment of all manufacturing processes. Risk-benefit assessment is needed in respect of both acute and chronic effects of Nano medicines in potentially pre-disposed patients – especially in relation to target disease. A shift from risk-assessment to proactive risk-management is considered essential at the earliest stage of the discovery, and then the development of new Nano medicines.

REGULATORY GUIDELINES:

As yet there are no regulatory authority guidelines specific to Nano medicine. As the number of Nano pharmaceuticals increases there is a need to review and define appropriate regulatory authority guidelines directed towards each new class of Nano medicine. It would be timely to produce 'Good Clinical Practice' (GCP) guidelines that may be applied to the clinical development of specific families of drug delivery systems or therapeutics. Some examples of well-established categories of pharmaceuticals involving Nano-objects are polymer protein, polymer-drug conjugates and nanoparticle associated chemotherapy. There may be specific clinical endpoints that are unique to these Nano medicines, and there may also be specific issues relating to good manufacturing practice (GMP) compliance.

Second generation Nano pharmaceuticals are already being, or will be, developed based on first generation systems. An integrated strategy will be the key for toxicological evaluation of new nanomaterial's that are emerging. There is a need for preclinical and clinical test standardization and an evaluation of the environmental impact of these systems in the context of academic research and industrial development. On a case by case basis there is a need to define toxicokinetics, toxicogenomics, and toxicoproteomics. This field might be defined as 'Toxiconanomics'. This research effort should be conducted by virtual networks of basic and applied scientists using existing expertise as a starting point. Industrial collaboration should be used to establish standard reference materials.

The current regulatory system within Europe was not designed having Nano medicine in mind. As a consequence, one of the biggest challenges that regulators face nowadays is to adjust Nano medicine to the current regime. The existing legal background is established on European Union

legislation, legislation of other international instruments and national legislation. The general regulation is supported by a series of guidelines for the assessment, approval and control of the medicinal products within European Union.

The regulatory framework in the European Union under which the Nano medicine may fall is complex and multilevel. To be more specific, for Medicinal Products Regulation 726/2004 on Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Directive 2001/83/EC on Medicinal Products for Human Use are applicable. For Medical Devices the normative framework consists of Directive 93/42/EEC concerning Medical Devices, Directive 90/385/EEC for Active Implantable Medical Devices and finally Directive 98/79/EC concerning In Vitro Medical Devices.

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CONCLUSION:

This Forward Look on Nano medicine has defined the remit of this emerging and important field. Nano medicine is clearly multidisciplinary and builds on the existing expertise in a large number of different scientific fields. European strengths have been identified, as have the short- and long-

term opportunities, and priorities for the development of Nano medicine-related technologies have been recognized. When applying nanotechnology to medical uses, it is particularly important to ensure thorough safety evaluation of any new technologies and also to review the likely environmental impact. In each specific case, careful risk-benefit evaluation is required. Most importantly, an open and continuing dialogue is required to ensure all interested parties, including the general public, are well informed as to the ongoing technology developments in the field of Nano medicine. As much has been written in the popular press, quality information is required to assist policy makers and scientists to distinguish “science fact” from “science fiction”.

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