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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON NANOTECHNOLOGY-BASED MEDICINAL PRODUCTS FOR HUMAN USE

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Reflection paper on nanotechnology-based medicinal products for Human Use

Executive Summary

The scope of this document is to reflect the current thinking and the initiatives taken by the EMEA in view of recent developments in relation to nanotechnology-based medicinal products.

Nanotechnology is an emerging scientific research field with a wide applicability and in the context of medical science it is expected that it will contribute in developing a more proactive paradigm for the diagnosis and therapy of diseases.

Medicinal products containing nanoparticles have already been authorised both in EU and the US under the existing regulatory frameworks.

Although nanosizing does not necessarily imply novelty, it is expected that nanotechnology will yield innovative products. Such products could span the regulatory boundaries between medicinal products and medical devices, challenging current criteria for classification and evaluation. Appropriate expertise will need to be mobilised for the evaluation of the quality, safety, efficacy and risk-management of nanomedicinal products and the need for new or updated guidelines will be reviewed in the light of accumulated experience.

Applicants developing nanomedicinal products are encouraged to interact with the EMEA from the early stages of development through the EMEA Innovation Task Force [http://www.emea.eu.int/htms/human/itf/itfintro.htm] and / or the Scientific Advice procedure [http://www.emea.eu.int/pdfs/human/sciadvice/426001en.pdf].

Introduction

Nanotechnology is an area that has seen a surge in research activity over recent years. It is considered to be one of the emerging fields in science with great potential in a wide range of applications including drug delivery, diagnostics and theranostics and regenerative medicine. The development of tools like the scanning tunnelling microscope and the atomic force microscope has enabled researchers to observe structures on the nanoscale, where materials may exhibit different properties, because of their size.

The development of these tools and of new materials like carbon nanotubes[1] and buckyballs[2], combined with the improved understanding of the molecular processes linked to diseases has potential to provide novel approaches in improving current therapeutic and diagnostic tools and eventually addressing a range of unmet medical needs.

The majority of current commercial applications of nanotechnology to medicine is geared towards drug delivery to enable new modes of action, as well as better targeting and bioavailability of existing medicinal substances. Novel applications of nanotechnology include nanostructure scaffolds for tissue replacement, nanostructures that allow transport across biological barriers, remote control of nanoprobes, integrated implantable sensory nanoelectronic systems and multifunctional chemical structures for drug delivery and targeting of disease.

[1] Carbon nanotube: A fullerene having a cylindrical or toroidal configuration (fullerenes: various cagelike, hollow molecules composed of hexagonal and pentagonal groups of atoms.)

[2] Carbon buckyballs: These were some of the first synthetic nanostructures and are spheroidal fullerenes. The one consisting of 60 carbon atoms is most stable and symmetrical and resembles a soccer ball. The term derives from the name of the American architect Buckminster-Fuller, famous for his spheroidal polyhedral structures.

Definitions

Nanotechnology is a broad term, which covers a wide range of methods, tools and possible applications. There are a variety of definitions reported in literature each generated for different purposes. For the purpose of this document, the definitions are based on those provided in the UK Royal Society and Royal Academy of Engineering report[3], the European Science Foundation foresight study on nanotechnology[4] and the Vision paper and Basis for a strategic research agenda for Nanomedicine by the European Technology Platform on Nanomedicine[5]:
Nanotechnology is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around 0.2 nm (2 Å) up to around 100 nm.[6]

Nanomedicine is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale.

Recent European Commission's initiatives

The nanotechnology arena in general is subject to much current discussion with an emphasis on safety and ethical considerations. In view of the growing interest in this field, the European Commission has developed a number of initiatives in order to stimulate research and facilitate commercialisation of the new technologies (more information can be found in the Nanotechnology Homepage of the European Commission, http://cordis.europa.eu/nanotechnology. Among these initiatives is a recent consultation on nanotoxicology and nanoecotoxicology, and a round table promoted by the European Group of Ethics in Science and New Technologies.

In parallel, the European Commission has requested the independent experts of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to evaluate "the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies". The conclusions of their Opinion[7] can be summarised as follows:

- There is insufficient knowledge and data concerning nanoparticles characterisation, their detection and measurement, the fate (and especially the persistence) of nanoparticles in humans and in the environment, and all aspects of toxicology and environmental toxicology related to nanoparticles, to allow for satisfactory risk assessments for humans and ecosystems to be performed.

- Although the existing toxicological and ecotoxicological methods are appropriate to assess many of the hazards associated with the products and processes involving nanoparticles, they may not be sufficient to address all the hazards. Existing methodologies will need to be adapted and new methods will need to be devised.

EMEA experience and perspective

Medicinal products containing nanoparticles in the form of liposomes (i.e. Caelyx, Myocet), polymer protein conjugates (i.e. PegIntron, Somavert), polymeric substances (i.e. Copaxone) or suspensions (i.e. Rapamune, Emend) have already been granted Marketing Authorisations within the Community under the existing regulatory framework. For their manufacture standard processes have often been employed, which are well-described and understood, such as the formation of mixed micelles (Liposomal Doxorubicin) or colloidal dispersions (Sonovue), the manufacture of large peptides by

[3] UK Royal Society and Royal Academy of Engineering, (**2004**). Nanoscience and nanotechnologies: opportunities and uncertainties.
[4] European Science Foundation, (**2005**). Nanomedicine – An ESF –European Medical research Councils (EMRC) Forward Look report.
[5] European Technology Platform on Nanomedicine, (**2005**). Vision paper and Basis for a strategic research agenda for Nanomedicine.
[6] 1nm = 10^{-9}m ; 1Ångström (Å) = 10^{-1} nm
[7] http://europa.eu.int/comm/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003.pdf

standard synthetic techniques or the manufacture of large molecules by standard polymerisation methods. In addition the development of large soluble molecules of nanometre size, like recombinant peptides or oligonucleotides, which have been manufactured using well-established techniques, should not be considered necessarily as arising from innovative nanotechnology methods.

It is important to point out that in the European Union the evaluation and prevention of potential hazards related to the use of any given nanomedicinal' product is already foreseen under the existing pharmaceutical legislation. As for any medicinal product, the EU competent authorities will evaluate any application to place a nanomedicinal product on the market, utilising established principles of benefit/risk analysis, rather than solely on the basis of the technology *per se*.

- As for any medicinal product, nanomedicinal products will have to be characterised, their fate and toxicology will have to be established and the appropriateness of test methods will have to be demonstrated. Before marketing, toxicology and ecotoxicology for a specific nanomedicinal product, as well as the methodologies used for the evaluation of toxicity, would be assessed in the context of the evaluation of the Marketing Authorisation Application, which foresees evaluation of benefits and risks to patients as well as an environmental risk assessment. A description of the pharmacovigilance system will be submitted and, where appropriate, a EU risk management plan will be required.
- Once a specific product is allowed on the market, based on a positive benefit/risk balance, the supervision and Pharmacovigilance will continue in accordance with the Pharmaceutical legislation.

Although the development of medicines at nanoscale size does not necessarily imply novelty, it is however expected that research in nanotechnology will result in innovative therapeutic or technological approaches.

It is likely that many novel applications of nanotechnology will span the regulatory boundaries between medicinal products and medical devices. Under the current legislation, the mechanism of action is key to decide whether a product should be regulated as a medicinal product or a medical device (*(Directive 2001/83/EC, as amended, Article 1., 2.(b))*. Nanomedicinal products, however, may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological and immunological properties and combining diagnostic and therapeutic functions. Furthermore, additional specialised expertise may be required for the evaluation of the quality, safety, efficacy and risk management of such nanomedicinal products.

It is likely that the evaluation of products of such novel technology will require special consideration. The accumulation of experience, in particular from informal discussion in Briefing meetings, Scientific Advice or Marketing Authorisation applications evaluation procedures, will allow, on an ongoing basis, to assess the need for the development of guidance specific to nanomedicinal products or for the update of existing ones to accommodate for the specific aspects of these products.

Conclusions

In order to deal with the above issues, the EMEA has created the Innovation Task Force (ITF) http://www.emea.eu.int/htms/human/itf/itfintro.htm to ensure EMEA-wide coordination of scientific and regulatory competence in the field of emerging therapies and technologies, including nanotechnologies, and to provide a forum for early dialogue with applicants on regulatory, scientific or other issues that may arise from the development.

In the absence of specific guidance, applicants are encouraged to contact the EMEA from the early stages of the development of their products (http://www.emea.eu.int/pdfs/human/itf/ITF%20Briefing%20meeting%20request%20form.doc) and to seek both Regulatory (http://www.emea.eu.int/pdfs/human/itf/Regulatory%20Classification%20Request%20Form%AFEMEA-6276-04-Final.doc) and Scientific Advice http://www.emea.eu.int/htms/human/sciadvice/Scientific.htm