NanoDialogue
of the German Government

Stakeholder Dialogue Nanomedicine

Report on Nanomedicine by the German Ministry of the Environment, Nature Protection and Nuclear Safety, including the discussion results of the Stakeholder Dialogue on Nanomedicine

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1 Introduction

In the context of a dialogue workshop in the frame of the German NanoDialogue which took place in Berlin on November 13/14 2013, the topic “nanomedicine” was discussed among representatives from different stakeholder groups and institutions. This report provides an overview of how nanomaterials are used in medical applications and how medicinal products and medicinal devices are regulated. Additionally, the core results of the dialogue workshop on nanomedicine are presented.

Medical applications of nanotechnologies raise many expectations and hopes. The combination of an increased understanding of diseases at the molecular level with innovative technologies, in particular nanotechnological processes and materials, enables the development of new approaches for diagnosis, therapy and monitoring of diseases.

In medical applications of nanotechnologies, the evaluation of risks and opportunities of the new technological path takes place in a specific context. These applications may pose particular risks, because by definition medicinal products and medical devices are introduced into the human body or are used in direct contact with it. This is balanced by particular health benefits normally present when using nanotechnologies in medical applications, which should by far exceed the risks. Environmental risks also need to be taken into account. A direct emission to the environment frequently occurs from the use of medicinal products used in animals, whereas the releases from human medicinal products normally occur via sewage treatment plants.

2 Nanomedicinal Application Areas

The term “nanomedicine” is generally understood as addressing the use of nanotechnologies for the manufacture and use of drugs, diagnostics and medical devices[1]. This definition includes well established methods and medicinal products.

Nanotechnologies may play a role in a large number of physical, chemical, biological and medical processes. In the following, the main fields of application are briefly described.

[1] The working group ‘nanomedicine’ of the German Federal Institute for Drugs and Medical Devices (BfArM) developed the following definition: Nanomedicine is the application of synthetically manufactured substances and structures, which, due to their size (< 100 nm), have new specific properties and which are intended for medical purposes, such as diagnosis and therapy of disease in the sense of the Law on Medicinal Products and the Law on Medical Devices, respectively.

2.1 Drug delivery and drug targeting

The aim of the use of nanotechnologies in drug delivery and targeting is to achieve a more efficient dosage of active substances.

The targeted accumulation of active substances in body tissues may be achieved passively via the size of carrier molecules or actively, via specific functionalization. In the latter case, molecules are used which specifically bind to the target tissue and to either the active substances or the carrier molecule. Respective technologies may either optimise the dosage of active substances or may make it possible to reach specific body regions (penetration of biological barriers).

Other methods aim to protect active substances from degradation or coagulation in the body in order to maintain an effective dose in the body for a longer time. This may be achieved by the encapsulation of active substances in liposomes or micels or by coupling them to other stabilising molecules, such as polymers or inorganic nanoparticles.

The enlargement of a pharmaceutically active ingredient's surface area by decreasing the particle size with an additional stabilisation is another technology which achieves an increased bioavailability of the active substance and thereby improves its dosability.

2.2 Diagnostics

The use of nanotechnologies in diagnostics aims to detect diseases earlier and more precisely. Nanotechnologies can either increase the sensitivity of existing detection methods or enable the use of new/different disease indicators for diagnosis, which would not be accessible by other means. Diagnostics are divided into in-vivo and in-vitro methods.

The most important application area of nanotechnologies in in-vivo diagnostics are the imaging techniques: Molecules are introduced into the body which emit signals indicating the existence and/or the extent of disease to a measurement device. Nanomaterials are used, among others, as carriers with similar function as described for drug delivery and drug targeting (c.f. Chapter 2.1). They may promote the transport and the accumulation of signal molecules in specific (ill) tissues and/or enable the penetration of biological barriers. Nanomaterials can also be directly used as signal molecules, if they have the respective optical properties.

In the field of in-vitro methods (test systems) nanotechnologies enable increased efficiency and use of new types of sensors. Efficiency gains are obtained, for example by miniaturization and automation of test systems (lab-on-a-chip, self-diagnostics etc.). For example new sensors may be based on the detection of (new)

disease indicating molecules (makers in nanoform) or the use of nanotechnology-based measuring technologies, such as cantilevers, which react to very small physical changes.

Improved contrasting agents and miniaturized or automatized test systems have already been in use for a long period of time. According to a recent study[2] the majority of nanomedicinal products on the market or in late phases of clinical testing belong to the application area of diagnostics.

2.3 Advanced therapies

The use of nanotechnologies in the field of advanced therapies combines molecular medicines with the possibilities of placing nanomaterials in specific body regions and use their specific properties for new forms of therapy.

How these therapies work depends on the type of disease and the therapeutic approach. On the one hand, therapeutic properties of nanoparticles such as of dendrimers and fullerens are used, and on the other hand nanoparticles which are introduced into the body in a targeted way are 'activated' via ultrasound, heat, magnetic fields etc. in order to achieve a therapeutic effect. The use of biological materials and molecules in the field of regenerative medicines may also be attributed to this field of application.

There are only a few medicinal products for advanced therapies on the market, the majority of which are applied in cancer treatment.

2.4 Improved materials and prostheses

Nanotechnologies are applied in the design of improved materials and prostheses, among others, to improve the incorporation into the body at a higher degree of compatibility, a higher durability and an overall better performance. This is mainly achieved through the selection of specific materials and / or surface coatings.

Examples of nanotechnologically enhanced products can be found in the area of joint prostheses and implants but also concern dialysis membranes, which decrease the risk of infections through an improved filtration capacity.

Antimicrobial coatings and biocompatible implants manufactured with the use of nanotechnologies are already on the market.

[2] Etheridge et al.: "The big picture on nanomedicine: the state of investigational and approved nanomedicine products" in: Nanomedicine: Nanotechnology, Biology, and Medicine, 9 (2013) 1–14. www.http://download.journals.elsevierhealth.com/pdfs/journals/1549-9634/PIIS1549963412002882.pdf

3 Regulation of Nanomedicine

The processes and requirements for medicinal products and medical devices in the different regulations, directives and laws on the production, marketing and use of products for medical application do not differentiate between products with and products without nanomaterials. In the following, the core aspects of regulation are provided.

3.1 Medicinal Products

According to Article 1(2) of the European Directive on Medicinal Products for Human Use[3] medicinal products are defined as follows:

> *„Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product."*

The marketing of medicinal products is regulated by the above mentioned directive, which is complemented by the EU-Directive on Clinical Testing[4] and the EU-Regulation[5] on the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use.[6]

The European requirements are integrated into the German Law on Medicinal Products. Therefore, the provisions for the national authorisation of medicinal products are identical to the European ones.

Medicinal products must be assessed either by a national authority or the European authority (European Medicines Agency – EMA). In the German national system medicinal products for human use are either authorised by the Federal Institute for Drugs and Medical Devices or by the Paul-Ehrlich-Institute. In the centralised process, the authorisation is granted by the European Commission.

[3] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

[4] DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

[5] REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

[6] The authorization of medicinal products for veterinary use is regulated by DIRECTIVE 2001/82/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to veterinary medicinal products

The authorisation decision is based on the authorisation application. The application must contain a demonstration of the quality, efficiency and safety of medicinal products by means of laboratory tests on animals as well as by clinical trials on humans. Minimum standards for the toxicological and clinical studies are defined in legislation. These should be adapted depending on the type of medicinal product, the medical indication and the pharmaceutical form. The assessing authorities may request additional studies and information from the applicants during the authorisation process, if necessary.

In addition to the above, the producers of medicinal products are required to assess and document potential environmental risks from the use of the product in the authorisation application. This only includes a standard assessment of releases from the intended use of medicinal products (human excretion after taking in medicines). Depending on the identified potential exposure level, information on the environmental fate and the environmental toxicity are to be provided and evaluated. The environmental assessment should be conducted according to the assessment of environmental risks from the release of genetically modified organisms. The manufacturers of medicinal products should, based on the assessment result, make proposals for communicating disposal information for the product in the package insert. In Germany, the assessment of environmental information in the authorisation application is performed by the Federal Environment Agency and is finally evaluated by the above mentioned authorising authorities.

The methods for the environmental assessment are not fully appropriate for the evaluation of nanomaterials because of their particularities in size and surface activity. The existing methods should be partly adapted and respective research and development is needed, particularly regarding the environmental fate. In addition, only some of the existing measurement methods for the identification of exposure levels in different environmental are appropriate for nanomaterials.

The authorisation decision for medicinal products is based on the evaluation of benefits and risks (adverse effects). This evaluation is not methodologically standardised and the national or European assessment bodies consider the current scientific knowledge and various factors in their decision making.

Authorisations may be refused if the benefit-risk-ratio is disadvantageous, if the product efficiency is not sufficiently demonstrated or if there are differences between the actual and the stated composition. Potential environmental risks from medicinal products cannot be a reason for authorisation to be denied. They may, however trigger the requirement to communicate disposal recommendations.

The authorisation decisions are documented and published by the assessing authority (EMA or national authority) in form of European Public Assessment Reports (EPAR)[7].

After the authorisation, the authorisation holders, normally the manufacturers of the medicinal products, are required to collect, assess and report further information on adverse effects of the medicinal products regarding the pharmacovigilance and implement measures, if necessary. Through the system of pharmacovigilance it is possible to detect rare adverse effects and/or combination effects with other medicinal products. There are different ways information is collected (e.g. spontaneous reports or controlled studies).

3.2 Medical Devices

Article 1(2) of the European Directive concerning Medical Devices[8] defines medical devices as follows:

> *"medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:*
>
> - *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
> - *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
> - *investigation, replacement or modification of the anatomy or of a physiological process, control of conception,*
>
> *and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;"*

Medical devices are regulated by the above mentioned directive and its daughter directives[9]. The European Directives are transposed into the German Law on Medical Devices and are implemented, respectively.

[7] The „European Public Assessment Reports" by EMA are available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&startLetter=A&keyword=Enter+k.
The reports by the German authorities can be found at:
http://www.pharmnet-bund.de/dynamic/de/am-info-system/index.html

[8] COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

Medical devices may only be placed on the EU market if they carry a CE-marking, which means that the legal requirements for the product are complied with. To obtain a CE-marking, the manufacturers of medical devices must provide a declaration of conformity. This declaration must document that the basic requirements on the performance, the design, the manufacturing practice and the safety of the product have been fulfilled. The demonstration of conformity may include the conduction of clinical tests. It is not necessary to generate data on potential environmental risks for the declaration of conformity of medical devices.

The nature of the requirements a medical device is to fulfil depends on its product classification. Four classes differing in the potential risk of products are defined[10].

The manufacturers submit the declaration of conformity to a notified body for the respective product group. The notified body evaluates the appropriateness and correctness of the manufacturer's declaration and certifies conformity, if this is achieved. In Germany the notified bodies are appointed and regularly controlled by a central organisation, the "Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten".

After the CE-Marking is assigned to a medical product, it can be placed on the market in the entire European Economic Area.

After the conformity is confirmed, safety and potential adverse effects of medical devices are to be monitored and reported by the manufacturers in the frame of the medical devices vigilance system.

The EU-legislation on medical devices is currently under revision. Whether or not additional classification criteria should be established regarding the content and intended use of nanomaterials in medical devices is being deliberated. In the context of the revision, the environmental impacts of medical devices should also be considered, especially if nanomaterials are used.

3.3 Medicinal Products for Advanced Therapies

Advanced (innovative) therapies frequently involve the application of living materials. An example of an advanced therapy is the incorporation of human materials (cells, tissues) into a patient's body following manipulation of the material in the laboratory. These therapies are highly personalised, if the original human material is taken from the same patient who receives the material.

[9] Among others: COUNCIL DIRECTIVE of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices and DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices

[10] Class I: low risk; Class IIa: medium risk; class IIb: high risk and class III: very high risk

Medicinal products for advanced therapies are regulated by the legislation on medicinal products (not medical devices) and are covered by the EU-regulation on medicinal products for advanced therapies[11]. The obligatory central authorization procedure includes very strict provisions regarding the risk management and the traceability of the used materials.

Under defined conditions advanced therapy medicinal products may be used prior to their authorization (exemption for hospitals). This exemption was introduced to universities to perform the experimental therapy development until maturity and a regular authorisation, among others.

4 Research

Research and development in the field of nanomedicine cover all application areas described in Chapter 2. EU and German research programs in most cases do not differentiate between products with and products without nanomaterials anymore. Instead the intended therapeutic indication constitutes the research objectives rather than the technologies used.

The German Ministry of Education and Research (BMBF) funds research activities on nanotechnologies in the programme area of “material sciences” and products for nanomedicine are also attributed to the programme area “health”.

At EU-level, research on nanomedicine is structured according to different research areas[12] in the 7th research framework programme. Also here, respective measures are covered by the topics “health” and “nano-science, nanotechnology, material science and production processes”. German research institutions receive funding as participating and leading partners in various projects. EU research funding will be continued in the future programme “Horizon 2020”, however with a different structure.

There are several funding activities at EU-level and in Germany which aim at linking research projects and promoting transnational cooperation. Small and medium sized enterprises (SME) are considered important, because they play a central role in the development of medicinal products and medical devices: SMEs frequently develop the medicinal products and medical devices based on basic science results. For testing and authorisation of these products larger enterprises take over as they have more capacities to bear the testing and authorisation costs. Therefore, some

[11] REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

[12] Topics of the last calls were: „Ethical, regulatory, social and economic aspects of nanomedicine”; “In-vivo diagnosis and therapy”, “Diagnosis and therapy of diabetes, inflammations and musculo-sceletal disorders”, „Molecular diagnosis and imaging“, “Diagnosis and therapy of cancer“, “Transport of macro molecules through biological barriers”, “Diagnosis and therapy of arteriosclerosis”, “Bacterial infections”

research funding is directed particularly to support small and medium sized enterprises. The „European Technology Platform on Nanomedicine“ (ETPN) for example requests the establishment of a laboratory for the standardised characterisation of nanoparticles, similar to the „nano characterisation lab“ located in the U.S.

In contrast to the EU research programs, the German BMBF funding targets early product and technology development phases. The primary objective is to support the development of technological possibilities and to make them available for different application areas. Therefore, respective research funding concerns the development phase before testing and frequently does not have a specific therapeutic indication.

5 Ethical and Socio-Economic Aspects of Nanomedicine

The application of new medical methods raises several basic ethical questions. These are not specific for nanomedicine. Therefore, the respective discourse should be integrated into the general medicine-ethical debate on new medicinal methods. Central aspects discussed in relation to new medicinal methods and products are:

- Health, safety and the environment
  Do the benefits of new (nano-)medicinal methods outweigh the risks?
- Data protection
  How can data generated via the new methods, such as for diagnosis and monitoring be appropriately protected?
- Right to know / right not to know
  How can the patients’ rights to know / not to know be protected and implemented as to the increasing possibilities of diagnosis (and potentially missing therapies)?
- Consequences of individualised medicine
  Which consequences will the individualised medicine have on society as a whole, the development of costs in the health sector and the therapy methods for all patients?
- Distributive justice
  (How) Can it be ensured that the advantages of the new (nano-) medicinal treatments are justly distributed and that also patients in lesser developed countries benefit from medical progress?
- Change of the human self-concept and the understanding of disease and health
  (How) Will the borders between “ill” and “healthy” change and what

consequences a changed understanding may have on the individual life plans and on society?

In particular the “combination” of different technologies, such as information and communication technologies, nanotechnologies and biotechnologies may enhance the following trends in medicine already present:

- The individualisation of diagnosis and therapy on the one hand enables the use of preventive measures already before symptoms of disease occur. On the other hand, patients may have to deal with diagnoses of diseases, for which no treatment exists. Furthermore, the pressure to carry out early diagnoses will increase.
- The new possibilities for self-diagnosis and self-therapy grants more autonomy to patients. This is also connected to an increase in responsibility, which may cause considerable overburdens, especially if respective offers for advice are missing.
- The current developments may lead to further changes in the organisation of medical competences.

It is unclear and not assessed in detail if and to which extend these trends in medicine will lead to improved life quality and/or cost savings in the health system. If the possibilities of nanomedicine are to be optimally used, it would be necessary to implement changes in the health, social and economic systems, such as to adapt cost models, further develop criteria for the assessment of medicinal products and medical devices, establish new supply chains in industry and new communication between all actors about (the ethical implications of) a “new medicine”.

6 Discussion of Nanomedicine by the Stakeholders

The following sections introduce some of the main discussion point of the Stakeholder Dialogue on Nanomedicine.

6.1 Nano-specifity in Medicine

According to the participants of the Stakeholder Dialogue on Nanomedicine the assessment of “nanomedicine as such” is not possible. It is regarded as inevitable that a differentiated view on at least the following aspects is taken:

- the product type,
- the presentation form and application form,
- the respective medical indication,

- the type of particle or materials and
- the question whether or not the nanomaterials are (intended to be) released (in the body).

The necessity for a differentiated evaluation was also identified in earlier Stakeholder Dialogues on nanotechnologies concerning other application fields[13].

The stakeholders stated that the properties of nanomaterials enabling the improvement of existing or the development of new therapies, diagnosis methods and monitoring approaches constitute the specific chances and opportunities of nanomedicine.

Specific challenges are posed by the characterisation of the used particles and the assessment of their toxicity and their environmental impacts, respectively.

6.2 Risk Assessment of the Use of Nanomaterials in Medical applications

Similar to other fields of application, the standardized characterization of the used materials is a challenge in the development and testing of nanomaterials, also in the area of medicine. Similar to other applications, the scientific actors stated a lack of standardized methods and respective shortcomings in the scientific literature. These shortcomings are particularly relevant, as the physical properties of the particles (e.g. their solubility and surface charge) as well as potentially existing coatings and changes of the properties and coatings (aggregation, formation of a corona), need to be considered in any testing. These effects, among others, were analysed in the project NanoMed[14].

Standard toxicity tests for chemicals are generally applicable to nanomaterials but may have to be adapted. This is not specific to the use of nanomaterials in medicine but to any nanomaterial application. The OECD Working Party on Manufactured Nanomaterials (WPMN) is currently developing respective solutions.

In contrast to other regulatory areas, in the field of medicine the stakeholders do not see a direct necessity to include nano-specific provisions regarding human health risks into legislation or to differentiate research activities, respectively. This is due to the fact that the existing procedures are already very detailed, include control and supervision by state authorities and that it is generally understood that the legal requirements have to be adapted according to the recent state of scientific knowledge and the specific product and its properties.

[13] http://www.bmu.de/themen/gesundheit-chemikalien/nanotechnologie/nanodialog/

[14] http://www.nanomed.uni-jena.de/

Regarding the assessment of environmental risks, the stakeholders at the Stakeholder Dialogue on Nanomedicine acknowledged that appropriate methods to model fate and distribution of nanomaterials in the environment are missing. While the benefit-risk evaluation is the determining factor for the authorization of medicinal products for human use, the environmental assessment does not have any practical or procedural impacts, apart from the potential need to communicate disposal recommendations. The lack of an environmental risk assessment for medical devices was recognized at the Stakeholder Dialogue on Nanomedicine but could not be discussed in-depth.

6.3 Information and Risk Communication on Nanomedicine

The participants at the Stakeholder Dialogue on Nanomedicine commonly opined that the human health risks of nanomedicine can generally be considered as "controlled". Therefore, it would be necessary to openly and clearly communicate risks and benefits of medicinal products and medical devices containing nanomaterials to consumers and patients and to disclose what information is available and what is missing.

According to the stakeholder's opinions it should be avoided that patients perceive nanomaterials as such as a risk. The content of nanomaterials in medicinal products and medical devices is not generally seen as a problem and potential risks should be carefully communicated, as is being done for any other active substance. Consequently, some of the stakeholders at the NanoDialogue had reservations towards a nano-labelling of medicinal products and medical devices.

The information situation for experts was stated to be characterised by a high amount of data on well-assessed particles, which is difficult to evaluate (missing particle characterisation, use of non-standardised test etc.) and the lack of sufficient information on "seldom used materials".

In principle, multipliers such as physicians and consumer organisations have access to information, e.g. via expert information, the public assessment reports by the authorities and/or package inserts. However, some stakeholders at the NanoDialogue remarked that it should be checked if and to what extent the content of nanomaterials in the products is specified therein and if the information is sufficiently understandable for the target group. The relevance of the information on the content of nanomaterials in medicinal products and medical devices regarding the benefit-risk decision related to the use of a product was not conclusively discussed.

Patients mainly receive information from the package insert and from physicians and pharmacists. However, the package inserts do not contain information on nanomaterials.

7 Conclusions from the Stakeholder Dialogue

The discussions at the Stakeholder Dialogue on Nanomedicine showed, similar to earlier events on other application areas in the context of the German NanoDialogue that a well-founded discussion on the potential benefits and risks (adverse effects) requires a concretisation of the object of assessment. In this context it should be clarified if and to what extent the differentiation of medical devices and medicinal products reflects the potential risks of these products concerning the contained nanomaterials.

There were no specific aspects identified which would currently require a further differentiation of the regulatory requirements or would call for an additional, targeted funding of research in the field of nanomaterials in medicine. An exemption is the assessment of environmental risks, which requires further research and development of methods, in particular regarding the exposure assessment. This is not a specific problem of nanomedicine.

Transparency, communication and information provision appropriate for the respective target groups on the use of nanotechnologies was identified as central challenge and task of all actors. Only this could prevent a stigmatisation of the technology and create (further) acceptance for innovations.