vfa. Die forschenden Pharma-Unternehmen

vfa / vfa bio-Position Paper
"Nanobiotechnology / Nanomedicine"

EXECUTIVE SUMMARY

Nanotechnology is characterized by the fact that it uses materials ranging between 1 and 100 nanometers. A nanometer is the millionth part of a millimeter.

By international comparison, Germany holds a strong position in the field of nanotechnology, a cross-sectional technology, implemented in many different fields. Nanobiotechnology, or the application in areas of medicine, pharmacy and life sciences to be precise, has the potential of opening up new or improved/earlier diagnostic or therapeutic opportunities for diseases that were previously insufficiently curable or completely incurable.

Special risks or issues with regard to ethical, legal or social concerns are not perceived in the medical/pharmaceutical sector. Scientists have long been working with small particles in this field and testing and warranty of patient safety are clearly regulated and established via the rules in the Pharmaceutical Act (Arzneimittelgesetz, AMG) and within the scope of the regulatory approval process.

Nanobiotechnological methods are already being used in the medical and pharmaceutical field today. This includes high-throughput screening to search for new target structures and substances. Furthermore, there are already nanoparticles in place which release drug substances at a local level (e.g. a nanoparticle based paclitaxel containing product to treat cancer) as well as nanostructured surfaces to manufacture bioactive prostheses. In addition, several nano-cancer therapies have been approved since 2010 as medical device to treat brain and liver tumors. Many other nanobiotechnology-based projects in life sciences are currently undergoing various stages of development.

The vfa advocates expanding the technological leadership in the field of nanobiotechnology systematically, exploring the potential of nanomedicine for the benefit of patients and forcefully advancing the developments in this area in the interest of patients while considering all safety and efficacy criteria.

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Inhalt

A) The basics

In what areas is Nanobiotechnology present?

Both biotechnology and nanotechnology are among the key technologies of the 21st century, since both are typical cross-sectional technologies that fundamentally change a variety of technological areas and therefore offer enormous potential for innovation and growth.

Nanotechnology

It is the characteristic feature of nanotechnology that it operates with materials that are in the range of approximately only 1 and 100 nanometers. One nanometer is one millionth of a millimeter. In comparison: The diameter of a human hair amounts to 50,000 nanometers, 100 nanometers correspond to the diameter of influenza viruses or – illustrated even differently – one meter compared to one nanometer equals the proportion of the diameter of the earth compared to that of a cent coin. These particles have completely different mechanical, chemical, optical, electrical, magnetic and other properties than conventional materials.

Nanobiotechnology is located at the interface between nanotechnology and biotechnology. Bridging animate and inanimate nature, it attempts to understand biological functional units at a fundamental level. Furthermore, nanobiotechnology seeks to generate functional components at nanoscale while incorporating technical materials and interfaces in a controlled manner.

What is the aim of nanobiotechnology? What are possible fields of application?

In life sciences, nanobiotechnology is currently primarily directed at using the nanoscaled range for the miniaturization and support or control of biotechnological and biological processes. The goal is the development of nanoscaled biomolecular components and analytical instruments for the investigation of cell biology on cellular and molecular levels. For example, scientists are developing techniques for handling smallest sample volumes or even for examining individual molecules. This allows further miniaturization of chip-based testing techniques to facilitate quick and targeted investigation of even the smallest sample quantities. Based on these possibilities, experts hope to gain completely new insight into cell biology functions. On the other hand, the development of new biocompatible and biodegradable materials will also be advanced.

Other research programs aim at developing new therapeutic options involving the use of nanobiotechnological methods. Scientists

are predominantly working on systems that transport genes or pharmaceutical substances to their target in a goal-oriented manner (drug delivery systems). Nanoparticles as carriers for active ingredients are supposed to guide conventional and modern substances such as peptides, proteins and nucleic acid derivatives and release them at the desired pharmaceutical target. The goal is to increase therapeutic effectiveness and improve substance tolerability.

What risks may be associated with nanobiotechnology?

With nanobiotechnology there are no special risks in the area of medicine/pharmacology. This is also confirmed in the European Medicines Agency's (EMA) "Reflection Paper on Nanotechnology-based products for human use" (EMEA/CHMP/79769/2006) dated June 2006 which is still relevant today. Nanobiotechnological methods are already being used in the medical and pharmaceutical field today. This includes high-throughput screening, which uses nanoscale biosensors to search for new target structures and substances. This method established its role in the development of pharmaceuticals.

B) Current situation

Approval of nanobiotechnological medicines

By now, some drugs have already been approved in Europe based on the positive evaluation by the European Medicines Agency EMA. In these drugs, the drug substance itself is either present in nanoscale or is embedded in liposomes (microscopic fatty structures containing the active substance). The oncology products containing doxorubicin and mifamurtide belong to the lipsome-based drugs. Drugs with the drug substances paclitaxel against cancer, aprepitant against nausea of cancer patients due to chemotherapy and sirolimus to prevent rejection after organ transplantation belong to the first group.

In addition, the Federal Institute for Drugs and Medical Devices (BfArM) has established a nanomedicine working group that deals on an interdisciplinary basis with issues of clinical testing, approval and risk assessment of nanobiotechnological pharmaceuticals, among other things (https://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/Zulassungsverfahren/ZentralisiertesVerfahren/nano.html).

EMA's position concerning nanobiotechnology

The EMA has included the topic nanomedicine in the agenda of the "EMA Innovation Task Force" (https://www.ema.europa.eu/human-regulatory/research-development/innovation-medicines). Additionally, the EMA published different guidelines and other documents concerning the handling of nanotechnology in the area of human medicine and the development of pharmaceuticals in the area of nanomedicine, respectively (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-nanomedicines):

- Joint Japanese Ministry of Health, Labour and Welfare (MWLW) / European Medicines Agency reflection paper on the development of block-copolymer-micelle medicinal products (EMA/CHMP/13099/2013) (in force since 10th of January 2014);
- Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA/CHMP/806058/2009/Rev. 02), adopted in February 2013;
- Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (EMA/325027/2013), adopted in June 2013;
- Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (EMA/CHMP/SWP/620008/2012), adopted in March 2015.

The last document on this list contains requirements for the development of iron-based nanosimilars. Nanosimilars are pharmaceuticals based on nanobiotechnology which are similar to a reference pharmaceutical after patent expiry.

Nanobiotechnological based therapies that are already in use

There are already nanoparticles in place which release drug substances at a local level (e.g. a nanoparticle based paclitaxel containing product to treat cancer) as well as nanostructured surfaces to manufacture bioactive prostheses. Several nano-cancer therapies have been approved since 2010 as medical device for the treatment of brain and liver tumours, with the following principle: Iron nanoparticles are being injected into the tumour tissue. Subsequently, these particles are being stimulated by an alternating magnetic field so that heat is generated which kills the tumour cells. Thereby, the selective absorption of magnetic nanoparticles by tumour cells allows targeted local heating without significant

negative impact on healthy tissue. Additional tumour indications are currently being clinically tested.

Many other nanobiotechnology-based projects in life sciences are currently undergoing various stages of development (see Appendix I)

Nanobiotechnology – the international perspective

The 'International Organization for Standardization' (ISO) has launched a dedicated technical committee for nanotechnologies (TC 229) with three working groups (terminology and nomenclature; measurement and characterization; health, safety, and environment) which elaborated uniform standards for nanotechnology. The 'European Action Plan' has been established for Europe outlining the attitude of the European Commission regarding societal and ethical aspects of nanotechnology as well as underlining the support for innovation and research and development – including appropriate risk research – in the field of nanotechnology. The European Parliament has described nanomedicine in September 2006 as a promising and interdisciplinary field with the potential of breakthroughs regarding early diagnosis and cost efficient therapy for a number of diseases. Within the scope of the EU framework programme "Horizon 2020" 70 billion Euros are budgeted for research and innovation from 2014 to 2020, in addition to private investments. Thereof, 13.5 billion Euros are planned for the area called "Leadership in enabling and industrial technologies" which also contains the field of nanotechnology.

Nanobiotechnology in Germany

For Germany, the federal government has developed a "National Action Plan Nanotechnology 2020" (https://www.werkstofftechnologien.de/fileadmin/media/publikationen/Aktionsplan_Nanotechnologie_2020.pdf) under the leadership of the Federal Research Ministry within the high-tech strategy, which was announced in 2016. It shows that nanotechnology has great potential in the field of diagnostics and innovative therapy methods. In Germany, some 1,100 companies are involved in various stages of the value chain with the development, production and marketing of nanotechnological products and methods. Three-quarters of those are small and medium-sized companies. In order to establish Germany as the leading location for research, development and production of nanotechnology-based products, the action plan proposes a number of measures, including strengthening the German nanotechnology professional scene, targeted support of innovations in the various nanotechnology areas, especially at small and medium-sized companies, and promoting the competition for specialized staff.

A comprehensive discussion of the opportunities and risks of nanomedicine took place in 2013 as part of a specialist event – the federal government's NanoDialog (https://www.bmu.de/fileadmin/Daten_BMU/Download_PDF/Nanotechnologie/nanodialog_4_fd1_zusammenfassung_bf.pdf).

End of 2007, a study of the Federal Institute for Risk Assessment (BfR) has shown that with regard to nanotechnology two-thirds of the interviewed Germans overall expect more benefits than risks and support further developments in this field. In 2013 the BfR published the final report of a follow-up-study executed in 2012, called "Nanoview". According to this study, the major part of the population mainly considers nanotechnology positively. Thus, the public dialogue should keep underscoring the great opportunities of nanobiotechnology as well as of those applications of nanobiotechnology from which patients can already benefit today. The overall goal should be to create an understanding of this new technology on a broad societal basis and to prevent reservations concerning its use. In doing so, a clear dissociation from any potential or speculative risks of nanotechnology in general should be made. Within the scope of the "Nanoview"-study, the BfR included a communication strategy based on study results to satisfy the informational needs in the population.

Because pharmaceuticals in Europe are subject to an extensive examination of their efficacy, safety and technical quality during the approval process and beyond, no need for changes in regulations is seen in the specific field of nanobiotechnology. In addition, both the European regulatory authority EMA and the German BfArM have already set up the appropriate committees of experts to take into account the specific needs around the use of nanobiotechnology in medicine.

C) vfa/vfa bio's position

By international comparison, Germany holds a strong position in the field of nanotechnology, including nanobiotechnology. The still quite young field of research holds the potential to further improve diagnostic and therapeutic opportunities for diseases that were previously either incurable or insufficiently treatable.

The vfa advocates exploiting this potential for the benefit of patients and for the systematic increase of the existing technological leadership. Special risks or issues with regard to ethical, legal or social concerns are not perceived in the medical/pharmaceutical sector, especially in view of the fact that scientists have long been working with small particles in this field and that testing and warranty of patient safety are clearly regulated and established via the

rules in the AMG and within the scope of the regulatory approval process.

Some stakeholders have addressed the need for a “Nano” product registry and for a special “Nano” labelling. These measures are not considered necessary for pharmaceutical products because of possibly resulting double registrations and overlaps with already existing information and labelling responsibilities.

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Appendix I – Nanobiotechnologies in development

- "Biochips" to be used in tests for quick and early detection of diseases such as Alzheimer's disease, cancer, multiple sclerosis or rheumatoid arthritis;
- Nanoparticle-based contrast agents that are designed to specifically bind ill cells to allow improved and significantly faster diagnostics;
- Nanoscaled polymer capsules through which chemotherapy drugs will be transported directly to a tumor and released with a laser pulse; this approach will allow the protection of surrounding healthy body tissue;
- Nanoparticles that are capable of overcoming the blood-brain-barrier, thereby contributing to e.g. the targeted treatment of brain tumors;
- Nanoparticles that can easily penetrate the cell membranes due to their small size, thereby facilitating controlled and targeted transport of pharmaceutical substances;
- Coatings (e.g. for pacemakers, neuronal implants or vascular prosthetic devices) that withstand mechanical strain, are biocompatible and are equipped with a highly specific surface; these coatings are meant to improve the coupling properties;
- Coating of e.g. insulin-producing islet cells or liver cells; this could reduce or even avoid rejection reactions during transplantation;
- Packaging of insulin with nanotechnology to allow oral application
- Pharmaceutical products to treat Alzheimer's disease: nanotechnology to allow passage through blood-brain-barrier
- Nano-gel for the regeneration of cartilage mass
- Nanoparticles with antigens for vaccines without syringes
- Nanoparticles with antigens that aid in better diagnosing an infection via rapid detection of antibodies in sera
- "Gene taxis" as basis for efficient and safe somatic gene therapy. One of the major challenges of gene therapy is the controlled and targeted delivery of genes which are - compared to conventional drug substances – gigantic molecules. Gene therapy is designed to treat diseases by introducing certain DNA

sequences into the organism. These DNA sequences are supposed to replace defective (altered or missing) genes to cure hereditary diseases or to facilitate the production of additional substances within the cell. For example, the latter principle can be used to stimulate immune defenses. In the past, gene therapy employed carrier viruses for this purpose. The problem with this procedure is that the insertion of the DNA sequences may proceed in an uncontrolled manner and that vital gene functions may be negatively impacted in the process. Gene taxis are based on nanoparticles which bind DNA sequences on their surfaces. The nanoparticles themselves are being excreted without change whereas the DNA remains in the nuclei.

- In this context, nano magnetic medicine (magnetic drug therapy) is worth mentioning: DNA sequences are bound to magnetic nanoparticles which are specifically directed to their target cells via a magnetic field.

- Current research is aimed at using iron nanoparticles, which can specifically block the extensions of certain cancer cells (integrins), to prevent tumors from metastasizing. The integrin bound nanoparticles can also be irradiated using a low-energy infrared laser, which would lead to the heating up and thereby destruction of the tumor cells.