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Nanomedicine: Drivers for development and possible impacts

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Preface

The Institute for Prospective Technological Studies (IPTS) was requested by DG Enterprise in November 2004 to provide information on academic nanomedicine research and commercial activities in Europe, to identify drivers and challenges for commercialisation as well as possible socio-economic impacts. This report is the outcome of this project, carried out in collaboration with the European Science and Technology Observatory (ESTO) network, in particular the VDI Technologiezentrum GmbH, Germany, and the Fraunhofer Institute for Systems and Innovation Research, Germany, between February 2005 and March 2006.

The IPTS and the ESTO team would like to thank Dr. Rickerby from the JRC Institute for Health and Consumer Protection (IHCP), who contributed a thesis paper about "Societal and policy aspects of the introduction in Healthcare" and Dr. Vanececk from Technology Centre AS, Czech Republic, who analysed nanomedicine activities in the Czech Republic. Furthermore, the team would like to thank the experts who took the time to participate in interviews.

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Executive Summary

Over the past 5 years nanomedicine has taken the shape of an emerging new field of nanotechnology applications, encompassing applications of nanotechnology to health. By exploiting the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale, it aims to provide targeted, site-specific therapeutics with reduced adverse effects, novel imaging methods for the early diagnosis of diseases, and novel implant materials that support tissue regeneration processes. A comprehensive picture of the state-of-the-art of nanomedicine research and commercial activities in Europe is currently missing. Against this background a study was carried out to provide information on academic nanomedicine research and commercial activities in Europe, to identify drivers and challenges for commercialisation as well as possible socio-economic impacts. This document summarises the results of this study[1].

Research and Development

Nanomedicine includes several distinct application areas: Drug delivery, drugs and therapies, in vivo imaging, in vitro diagnostics, biomaterials, and active implants. In these fields, nanomedicine has seen a surge in research activity over the past decade with publication numbers rising from some ten per year in the late 1980s to more than 1200 in 2004. Currently, nanomedicine accounts for about 5% of nanotechnology publications worldwide. The dominant research field in nanomedicine is drug delivery contributing 76% of the scientific publications followed by in vitro diagnostics with a contribution of 11%. EU25 countries account for 36% of all nanomedicine publications worldwide, compared to the USA with a contribution of 32% and Asia with 18%. The intense research efforts in nanomedicine are driven by significant governmental nanotechnology funding programmes worth an estimated EUR 3 billion in 2004. Three countries, the USA, Germany and Japan, have recently given clear commitments to nanomedicine by establishing focussed nanomedicine research programmes.

Commercialisation

Commercialisation efforts in nanomedicine have now started around the world. Of the 200 companies identified being active in nanomedicine worldwide, 159 are start-ups and SMEs that focus on the development of nanotechnology-enhanced pharmaceuticals and medical devices. Further, 41 major pharmaceutical and medical device corporations have nanomedicine products on the market or run development projects in which nanotechnology plays a role. Over the past decade 38 nanotechnology-enhanced medical products were placed on the market with estimated total sales of EUR 5.4 billion in 2004. Based on a pipeline of about 157 products that are in an advanced development stage, the market of nanomedicine products is estimated to increase to about EUR 15 billion in 2012. Currently, similar to research activities, nanomedicine products are dominated by drug delivery systems accounting for about 80% of the market. Nanotechnology-based therapies, in vitro diagnostics and imaging agents are still in an early development state but it is expected that their importance will significantly increase in the future. Although the EU is leading with regards to scientific publications it shows less competitiveness when it comes to commercialisation: US companies are involved in 46% of the marketed nanomedicine products while EU25

[1] See also Wagner V. et al (2006) "The emerging nanotechnology landscape". Nature Biotechnology Vol. 24, No. 10, p. 1211 - 1217

companies have only a share of 37%. Looking at the product pipeline this gap seems to widen. This reflects mainly the weak position of EU25-based nanomedicine companies in the drug delivery sector, where they represent only 23% of the companies compared to 60% for US companies. The share of European companies in the drug delivery sector, which is the nanomedicine sector with currently the highest market potential, is about a factor of two lower than in the other nanomedicine application areas.

There are various drivers for nanomedicine product development. On the one hand, increased knowledge of molecular processes linked to diseases and advances in nanotechnology allowing to manufacture and manipulate materials on the nanoscale create a certain scientific-technological push. On the other hand, hitherto unmet medical needs, such as the direct targeting of diseased tissue, the early diagnosis of cancer, the transport of drugs across the blood-brain barrier and the development of implant materials with longer lifespans, create a strong demand for innvovative solutions. Nanomedicine sets out to contribute to overcoming these problems in concert with other medical technologies such as biopharmaceutical drugs, cell therapy or gene therapy. Though likely to be of great importance for medical progress nanotechnology is only one of several drivers for innovation in medicine.

There are a variety of challenges for the development of nanomedicine and a particularly important one is the still very moderate interest of the pharmaceutical and medical device industry in this emerging technology. Start-ups currently pursue a plethora of ideas how to improve disease treatment and diagnosis based on nanotechnology, but it is difficult for them to find major pharmaceutical or medical devices companies that licence their technology or partner with them to bring their novel nanomedicine approaches through the regulatory approval process. This situation is not entirely new to the medical sector and reminds of the development of biotechnology drugs over the last two decades. Apart from a lack of interest by big pharma, experts caution that there is also a structural reason for the slow pace of nanotechnology take up in the medical sector, particularly in Europe: The markets of major EU25 countries are cost-regulated and experts see this as an important limiting factor for the development of innovative high value drugs, including nanomedicine. Additionally, much of the improvement for therapy and diagnosis by nanotechnology-based drugs and contrast agents will be related to their ability to target diseases more patient specific and to deliver more specific diagnostic information. This implies smaller patient populations and thus smaller markets for nanomedicine products, which makes it more difficult to recover development and regulatory approval costs, and which may make a development economically unattractive.

Cost-effectiveness

In the past, health innovations were mainly assessed with respect to efficacy and improved quality of life of patients. Nowadays, health innovations will increasingly be assessed also with respect to the costs at which the improvements come. Nanomedicine products will have to show cost-effectiveness in comparison to conventional alternatives, as health care systems increasingly face cost pressure. Nanomedicine innovations are likely to reduce future health care costs if they

- aim at major cost-causing diseases, such as cardiovascular diseases, diseases of the nervous system, musculosceletal diseases, and neoplasms,

- reduce personnel costs, e.g. by reducing the required days of inpatient care, for a given disease,
- contribute to "healthy ageing", i.e. in raising the health status of the population.

On the contrary, nanomedicine innovations are likely to increase future health care costs if they come as add-on technology, which offers a measurable, but only small health effect at significant costs, so that the cost-benefit-ratio is unfavourable.

Currently, cost-effectiveness studies for nanomedicine products are scarce. A broader set of health economic data was only available for two drugs with nanotechnology-based drug delivery systems: liposomal amphotericin B and pegylated liposomal doxorubicin hydrochloride. Liposomal amphotericin B is an example for a conventional drug whose profile of side effects (nephrotoxicity) can be positively changed due to liposomal drug delivery. However, the additional positive health effect of reduced nephrotoxicity comes at comparatively high costs, which has up to now restricted the use of liposomal amphotericin B to exceptional cases. By contrast, pegylated liposomal doxorubicin hydrochloride shows a similar or even better effectiveness than the current gold standard topotecan for cancer treatment, but shows a different pattern of adverse effects. Although there is a high probability that treatment with pegylated doxorubicin is cheaper than conventional treatments due to lower treatment costs for adverse effects, more studies are required to establish its overall cost-effectiveness. Based on these two first generation nanomedicine products, an estimation of (future) cost efficiency of nanomedicine as a whole is not possible. Among the 38 products on the market and more than 150 in the pipeline are developments that bear the potential to significantly reduce costs of medical procedures. For a well-founded assessment of the overall cost-effectiveness of nanomedicine many more nanomedicine products need to reach the market and need to be analysed.

Social and ethical issues

The systematic exploration of social and ethical issues of nanotechnology has begun only a few years ago. It is hoped that a better understanding of the interaction and mutual interdependence of science, technology and society could lead to better informed decisions about how to shape the development of nanotechnology, and that mistakes that have been made with other technologies, such as biotechnology and genetic engineering, might be avoided by dealing proactively with the social and ethical embedding of nanotechnology. Until recently, the majority of these analyses related to nanotechnologies in their entirety, and were not yet differentiated to specific application areas such as nanomedicine. It is striking that in cases nanomedicine applications were covered, the discussion of social and ethical issues often dealt with the potentially disruptive character of nanotechnologies and futuristic visions, but rarely covered the stepwise and incremental innovations which are currently pursued by public and private research institutions and companies. In general, there are no completely new social and ethical issues arising from nanomedicine applications, but nanomedicine might add new dimensions, e.g. molecular diagnostics and monitoring will increase the amount of available data and thus raise the issue of data privacy more urgently. Equal access of patients to appropriate diagnostic and therapeutic procedures needs to be ensured and a “nano-divide” should be avoided. The just and transparent allocation of scarce health care resources might require the integration of health technology assessments and cost-effectiveness studies in the development of nanomedicine.

Public debate

Also research into the public's attitudes towards nanotechnology has, so far, only addressed nanotechnology in its entirety and not looked at subfields, such as nanomedicine. The limited social science research done until now indicates that attitudes to nanotechnologies are generally positive, and major benefits are anticipated, especially from health and environmental applications. However, focus groups and citizens' juries also reveal many aspects which are of concern for the layman, e.g. how to deal with the inherent uncertainty, and the low trust in governmental bodies as well as industry to take decisions for the benefit of the general population. Against this background, there is a high demand for effective regulation and control. In addition, governance issues are stressed and transparency of and public involvement in technology decision-making are called for.

At the present stage of discussion, only few non-governmental organisations (NGOs) have developed a position towards nanotechnology applications and taken a visible role in the debate, especially Greenpeace and the ETC group. Whereas the ETC group has called for a moratorium of nanotechnology products, Greenpeace stresses the importance to clarify on the toxicological potential of nanoparticles but at the same time recognes the importance of nanotechnology to overcome current global environmental and energy problems. The majority of potentially affected non-governmental organisations in the field of biomedical applications of nanotechnologies such as consumer organisations or industry unions, are still in an earlier stage of engagement and the prevailing activity is the monitoring of developments of nanotechnology.

Regulatory issues

Nanoparticles and their potential health and environmental risks are currently the focus of discussions at European and international level. At present, no specific regulations exist in Europe which refer specifically to the production and use of nanoparticles either for workers', consumers' or patients' safety or for environmental protection, so that current regulations and operational practices are applied. The need for novel regulations for nanotechnology products that takes into account the environmental impact and the toxic potential of nanoparticles is currently discussed in governmental committees of some of the EU Member States and the European Commission. Prerequisite for such a regulation would be more research that clarifies the toxicity of nanoparticles, their fate and persistence in the environment and an assessment of the exposure.

With regard to clinical applications nanomedicine products are currently regulated within the conventional regulatory framework of medicinal products and medical devices. To obtain market approval, these regulations require a risk assessment and management. However, the required knowledge about the behaviour and biological effects of nanoparticles is presently patchy and assessment schemes are not specifically tailored to assess nanoparticle-specific questions, so that further development and amendment might be required. Whether novel regulation is needed to account for borderline cases such as implants with drug delivery function or to account for special interactions between nanoparticles and biological matter is controversly debated among scientists.

Whereas the regulatory requirements must be sufficiently rigid to ensure safety and quality of the medicinal products and medical devices, the possibly negative impacts of overly extensive requirements on the introduction of innovative products into the

market must also be considered. Against this background, it is being discussed in the nanomedicine community whether regulation should be adapted to take into account the trend to a more personalised medicine which may imply smaller markets, or whether the novel combination of already approved drugs and drug delivery systems should have to pass a less restrictive regulatory regime than the newly introduced individual components.

Nanomedicine is an emerging field that is now gaining wider attention owing to first products on the market and a variety of studies conducted over the past couple of years. Nanomedicine has widely been associated with revolutionary new applications. However, as this report shows, nanomedicine as currently pursued by the scientific community uses nanotechnology as an enabling technology playing an important part in the medical innovation process, but there are currently only few examples for innovations with breakthrough potential.

1 Introduction

Nanotechnology is emerging as one of the key technologies of the 21st century and is expected to enable developments across a wide range of sectors that can benefit citizens and improve industrial competitiveness. There is as yet no common definition of nanotechnology. In their recent report the UK Royal Society and the Royal Academy of Engineering define nanotechnology as " the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale" [The Royal Society & the Royal Academy of Engineering, 2004]. The nanometre scale is usually set at 1 to 100 nm and nanotechnology makes use of the new properties of materials at this scale that differ from those at a larger scale. Recent advances in the capabilities to manipulate atoms and molecules have pushed the development of nanotechnology.

Nanotechnology is a generic term used for a broad range of different activities and applications ranging from energy production and storage, manufacturing, information technologies to medicine. For that reason often the plural form " nanotechnologies" is used. Nanotechnology is rapidly expanding with about EUR 3 billion public R&D funding in 2004 worldwide [European Commission, 2005].

Against this background the European Commission in May 2004 adopted the Communication Towards a European Strategy for Nanotechnology, and a related action plan for nanosciences and nanotechnologies 2005-2009 in June 2005 [European Commission 2004, 2005]. These initiatives aim at a co-ordinated R&D approach to nanotechnology to enable reaping the benefits of this new technology and its applications. Apart from boosting research funding, technology transfer, and the creation of favourable conditions for EU industry to commercialise useful products and services, it is stressed that any potential public health, safety and environmental risks need to be addressed upfront. This also includes a reassessment of existing EU legislation. Furthermore, ethical principles and societal considerations should be integrated in the R&D process at an early stage, dialogues with the public are considered essential.

Nanobiotechnology, the convergence of nanotechnology and biotechnology[2], and in particular its applications in the medical sector are considered as one of the most promising and most advanced areas of nanotechnology. Applications include e.g. nanoparticles for molecular diagnosis, imaging and therapy as well as complex nanostructured surfaces to control tissue repair on a cellular level. It is expected that nanobiotechnology applications in medicine will bring significant advances in the diagnosis and treatment of disease. This has lead to a steadily increasing research activity in this area over the past decade. However, a comprehensive picture of the state-of-the-art of research and commercial activities in Europe was missing. Furthermore, to enable the exploitation of nanobiotechnology and a proactive approach to increase European competitiveness, information was needed on future directions of

[2] Nanobiotechnology is defined as a field that applies the nanoscale principles and techniques to understand and transform living or non-living biosystems and which uses biological principles and materials to create new devices and systems integrated from the nanoscale [Roco, 2003].

nanobiotechnology applications and on possible drivers and barriers for its development.

The present document, based on a study carried out between February 2005 and March 2006, aims to contribute to fill this information gap. It focuses on nanobiotechnology applications in medicine, which in the last two years are referred to as "nanomedicine", a term that will also be used in this document. There are many ways of defining nanomedicine, in this report we follow the definition used by the European Technology Platform on nanomedicine: *Nanomedicine is the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale* [ETP, 2005]. In contrast to the often used limitation to size dimensions of 1-100 nm, in nanomedicine size dimensions of 1-1000 nm are included. This is due to the fact that in medicine nanotechnology aims to improve and optimize material properties for their interaction with cells and tissue, to allow e.g. passive tumour targeting, crossing of the blood-brain barrier, or to improve the bioavailability. This approach makes use of nanoscale materials larger than 100 nm. Polymer therapeutics are situated at the borderline between nanotechnology and macro-molecular chemistry, they are, however, often classified as nanomedicine. On the other hand biochips are often considered per se as nanotechnology, regardless if they include nanoscale components. In this document biochips are only included if they contain nanoscale components. The above given definition of nanomedicine, is therefore amended by the following statements:

1) Nanoparticles for medical applications are defined, as common in pharmaceutical sciences, as particles with a size between 1 and 1000 nm.

2) Biochips are only classified as nanotechnology, if they include nanoscale components.

3) Polymer therapeutics are classified as nanomedicine.

The study covers several nanomedicine application areas: drug delivery, drugs and therapies, in vivo imaging, in vitro diagnostics, biomaterials, and active implants. Tissue engineering and regenerative medicine are included as far as biomaterials are concerned. Further information on tissue-engineered products is available in two recent reports from JRC/IPTS[3]. Cosmetics are included because the cosmetics sector seems to be an early user of new technologies. For example liposomes, which meanwhile are also used for drug delivery purposes, have been first used in cosmetic products.

The study was carried out in collaboration with the European Science and Technology Observatory (ESTO) network. The VDI Technologiezentrum GmbH, Germany, provided the market analysis, literature and patent search and the analysis of the nanomedicine industry[4]. The Fraunhofer Institute for Systems and Innovation Research (ISI), Germany, analysed the impact of nanomedicine products on health care costs and

[3] Bock et al (2003) Human tissue-engineered products – Today's markets and future prospects. Synthesis report. EUR 21000 EN; Bock et al (2005) Human tissue-enginered products: Potential socio-economic impacts of a new Euroepan regulatory framework for authorisation, supervision and vigilance. Synthesis report. EUR 21838 EN

[4] See also Wagner V. et al (2006) "The emerging nanotechnology landscape". Nature Biotechnology Vol. 24, No. 10, p. 1211 - 1217

the environmental, social and ethical issues of nanomedicine applications. This document is based on the results of this work.

Dr. Rickerby from the JRC Institute for Health and Consumer Protection (IHCP) contributed a thesis paper about “Societal and policy aspects of the introduction in Healthcare” and Dr. Vanececk from Technology Centre AS, Prague analysed nanomedicine activities in the Czech Republic.

2 Nanomedicine Applications[5]

2.1 Advanced Drug Delivery Systems

Advanced drug delivery systems aim to improve bioavailability and pharmacokinetics[6] of pharmaceuticals and to replace invasive by non-invasive routes of administration. Examples for advanced drug delivery systems are controlled release formulations or pulmonary dosage forms of proteins, such as insulin. Nano drug delivery systems (NDDS) are a sub-class of advanced drug delivery systems that consists of drug carriers with a size of less than one micrometer and mostly less than 200 nm. Examples for NDDS are liposomes, nanosuspensions, polymeric nanoparticles, dendrimers, fullerenes, carbon nanotubes, and inorganic nanoparticles. Furthermore, so-called "polymer therapeutics" such as polymer-protein conjugates, polymer-drug conjugates, polymeric micelles and polymeric drugs are frequently classified as NDDS. Research and development on some of these systems, e.g. liposomes, has started as early as the 1960s. Dendrimers, fullerenes or carbon nanotubes have entered the drug delivery arena more recently [Allen et al., 2004; Duncan, 2004; Wagner and Wechsler, 2004]. The systems with currently the highest pharmaceutical and commercial potential are described in the following:

Liposomes: Liposome drug delivery systems are nanoscale spheres composed of a lipid layer surrounding the drug. First liposomal formulations of the anti-cancer drug doxorubicin were launched beginning of the 1990s, such as Doxil®/Caelyx® or Myocet®. By using a liposomal formulation the cardiac safety of the drug doxorubicin could be improved (see also Chapter 5). There are currently 11 liposome-enhanced drugs on the market and about 30 in clinical trials.

Nanosuspensions: Nanosuspensions are dispersions of pure nanosized drug particles, which are stabilized by surfactants. By reducing the size of drug particles to about 10 to 100 nm (nanonisation) the solubility of the drug can be significantly increased. This technology is of interest for about 40% of drugs in the development pipeline which are poorly water soluble and therefore cannot be administered. There are five drugs on the market and more than ten drugs in clinical trials that are formulated with nanosuspension technology [Bushrab, 2003, VDI, 2004; Rabinow, 2004].

Polymeric Nanoparticles: Polymeric nanoparticles are either nanosized solid particles or capsules which consist of natural or synthetic polymers and to which the drug is attached. They are investigated as drug delivery systems for site-specific targeting of tumours and for the transport of drugs across biological barriers, particularly the blood-brain barrier. At present the number of companies that work on polymeric nanoparticle drug delivery systems is quite small; only six companies were identified in this study. The anticancer drug Abraxane™, the substance paclitaxel stabilised by albumine is the only drug on the market that uses a (bio)polymeric nanoparticle drug delivery system. One additional product was identified being currently in clinical trials.

[5] This chapter is based on the report of Work Package 1 - Current status of medicinal nanobiotechnology in Europe, V. Wagner, VDI Technologiezentrum GmbH, 2005.

[6] Pharmacokinetics refer to the processes of absorption, distribution, metabolism, and excretion of a drug or vaccine in a living organism.

Polymer Therapeutics: The term "polymer therapeutics" describes a family of compounds and drug delivery technologies that uses water-soluble polymers as a common core component. The term includes polymeric drugs, polymer-drug conjugates, polymer-protein conjugates, polymeric micelles, polymeric non-viral vectors (see below) and dendrimers. Polymer-protein conjugates using polyethylene glycol (PEG) as polymer component are currently the most advanced class of polymer therapeutics (six products on the market). They are developed to overcome some of the limitations of peptide-, protein- and antibody-based drugs such as a short plasma half-life, poor stability and immunogenicity. Examples for commercially successful PEGylated protein conjugates are the two PEG-interferon-α conjugates Pegasys® and PEG-Intron® with sales of EUR 0.8 billion and EUR 0.4 billion, respectively. About 15 polymer-protein conjugates are currently in clinical trials.

Nanoparticles for Gene Delivery: Viruses are particularly efficient gene vectors and are used in more than 70% of gene therapy clinical trials. However, there are several concerns regarding the use of viruses, such as their toxicity and their potential for generating a strong immune response. Non-viral delivery systems can circumvent some of these problems and are emerging as favourable alternatives to viral vectors. Polymeric delivery systems (DNA-polymer complexes) and liposomal delivery systems are used as nanotechnology-based non-viral gene vectors [Mastrobattista et al. 2006].

According to experts the benefit of NDDS for the patient will be less side-effects and improved efficacy of drugs, and the possibility to treat diseases and disease stages that currently cannot be treated with conventional drugs. Although drugs which come with an additional function of a drug delivery system will be more expensive than the drug alone, the expected benefits are hoped to result in an overall reduction of the costs of disease treatment.

Apart from the pharmacological potential, NDDS are also of interest for the pharmaceutical industry with regards to the life cycle management of drugs: To defend drugs that come off patent against generic products, pharmaceutical companies try to develop and patent new galenic formulations[7] and thus extend the life cycle of the drug. With about 70 products coming off patent per year, few products in the pipelines and increasing generic competition, the life cycle management is expected to become an important driver for the development of NDDS [VDI, 2004].

In the 1970s and 1980s major scientific hurdles were overcome such as the rapid clearance of nanoparticles from the blood and the synthesis of suitable biocompatible polymers. This paved the way for the first NDDS-enhanced products that were launched in the early 1990s. Since then research and patent activities have strongly increased: At present the total number of publications is about 800 per year up from 200 in the mid 1990s and patent filings have increased seven-fold since the mid 1990s to about 1400 in 2003. This indicates that the interest of the industry in NDDS is picking up worldwide.

113 companies were identified that work in the field of NDDS, 52% of them are based in the USA and 23% in EU25 countries. Currently there are about 23 NDDS enhanced

[7] Galenic formulation is named after a 3rd Century AD Greek physician, Claudius Galen, and describes the principles of preparing and compounding medicines.

drugs on the market, with total sales of estimated EUR 4.2 billion in 2004. This is only a tiny share of the worldwide pharmaceutical market that generates sales of about EUR 390 billion per year. However the high research activity and the fact that about 98 NDDS-enhanced drugs are currently in clinical trials indicate that nanoscale drug delivery systems will gain more and more importance in the pharmaceutical sector.

With regards to commercialisation US companies show worldwide the strongest interest in NDDS. US companies have developed or co-developed 61 of 98 NDDS-enhanced drugs in clinical trials compared to 28 developed or co-developed by EU25 companies. Very similar proportions exist for the 23 identified NDDS-enhanced drugs that are on the market. US companies are involved in the development and marketing of 17 of those drugs compared to 5 drugs that have been developed or co-developed by EU25 companies.

Products currently on the market are first generation products. They use early development stage NDDS in which nanotechnology is used to increase the solubility or to concentrate drugs in the diseased tissue by physical effects. Next generation products will try to tailor pharmacokinetic properties of drugs and therewith also their efficacy. Further, the whole research field of NDDS is still in its infancy compared to small molecule drugs or even biologics[8]: Scientists are just beginning to understand the interaction of NDDS with the immune system, cells, and organs. An improved understanding of these interactions over the next years will allow to gradually employ the full potential of NDDS to increase the efficacy of drugs.

2.2 Drugs and Therapies

In addition to drug delivery systems, there are also applications in which nanoparticles and nanoscale molecular structures act as pharmaceutically active compounds. Molecular nanoscale entities that are used for developing drugs are dendrimers and fullerenes. Additionally, nanoparticles are used in novel magnetic or photodynamic hyperthermia treatments of cancer and for cell sorting procedures as used in cell therapy.

Dendrimers: Dendrimers are tree-like branched polymeric molecules that can act as drugs if they also incorporate certain chemical functionalities. The dendrimer drug in the most advanced development status is Vivagel™, a vaginal microbiocide to prevent HIV/AIDS infections. Dendrimers are seen as highly promising nanoscale molecules for pharmaceutical applications because size and surface functionality can be tuned with precision. Thus dendrimers can potentially be tailored for optimum activity, mode of action, pharmacokinetics, biocompatibility, and stability [BCC, 2004; Starpharma, 2005].

Fullerenes: Fullerenes are hollow spherical molecules composed exclusively of carbon atoms. Fullerenes can very efficiently bind and inactivate radicals that play a crucial role in the development of diseases of the central nervous system (e.g. Parkinson, Alzheimer) and cardiovascular diseases. Because fullerenes scavenge

[8] Biologics are biological and biotechnological medicinal products, including a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

radicals more efficiently than any other medical antioxidant, there are hopes that they could be used as active core structures of a new class of extremely efficient drugs to treat radical related diseases. C Sixty, USA, is currently the only start-up that works on fullerene-based therapeutics. However, no product is as yet on the market or in clinical trials.

Magnetic Nanoparticles for cell therapy: In cell therapy magnetic nanoparticles coupled to antibodies are added to a blood or bone marrow sample that contains the target adult stem cells. The magnetic particles bind the target cells, which then can be recovered using a magnet. This technique is used in cell therapies to isolate adult stem cells that are then retransplanted in the patient e.g. to treat blood disorders or cardiac diseases. These cell therapies are applied worldwide at hospitals and university clinics on a case by case basis, and reimbursed by insurances for selected diseases, such as leukeamia or heart diseases.

Magnetic Fluid Hyperthermia: In Magnetic Fluid Hyperthermia superparamagnetic iron-oxide nanoparticles are used for hyperthermic treatment of tumours. The procedure involves the selective concentration of magnetic nanoparticles in tumour cells making use of their unique metabolism. Based on the aminosilane coating, iron-oxide nanoparticles are incorporated by the tumour cells much faster than by healthy cells and the iron nanoparticels become concentrated in the tumour cells. By applying a magnetic field the particles are caused to heat above 41°C and thus to destroy the tumour cells. The development of nanoparticle-based hyperthermic methods is spearheaded by the start-up company Magforce, Germany. Magforce expects regulatory approval for its tumour therapy as a medical device in 2007.

Phototherapy: Gold nanoshells absorb infrared light at wavelengths for which human tissue is transparent. For cancer treatment the nanoshells are conjugated to antibodies or other proteins as targeting mechanism to deliver the particles to specific cells or tissues. By irradiating the tissue with an external infrared laser the shells are heated and the temperature in the tissue raises to about 55°C so that the tumor cells are destroyed. Nanospectra Bioscience, USA, is currently the leading company, developing this technology for the treatment of lung cancer [BCC, 2004; Nanospectra Bioscience, 2005].

About 150 publications have been published in the field of nanotechnology-based drugs and therapies over the past ten years (1994-2004). This comparatively small number of publications is indicative for the still very explorative character of this research field that currently is only pursued by a small research community. However, the number of publications has been increasing steadily from about ten in the mid 1990s to about 50 in the year 2004. Patenting activity is increasing, too, with about 60 patent filings in 2003. These developments indicate that this technology field is slowly gaining momentum.

At present only Vivagel™, a dendrimer-based gel to prevent HIV/AIDS infections (Starpharma, Australia), nanoparticle-based Magnetic Fluid Hyperthermia to treat brain cancers (Magforce, Germany) and the use of magnetic nanoparticles for stem cell therapy for cardiac diseases have proceeded to clinical trials. All other drugs and medical therapies that were identified in this study are still in a preclinical development

stage. The described novel nanotherapeutic methods are all developed either by small technology firms or by start-ups.

Owing to the early development stage of nanotechnology-based drugs and therapies any prediction of the market volume is very speculative. However, many of the companies pioneering nanotherapeutic methods see their target market in the range of several hundred million euro for the first generation of their products. These numbers add up to about one billion euro for dendrimer and magnetic nanoparticle applications. The market introduction of fullerene-based therapies is still a long way off, though owing to their unrivalled properties they are believed to have blockbuster potential.

Nanotechnology-based therapeutic approaches have in common that they try to treat diseases with radically new drug or treatment concepts. According to experts interviewed for this study, nanotechnology-based drugs and therapies have a great chance to deliver significant improvements to the patient as these novel approaches bear the potential for real progress in certain areas of medical treatment such as cancer, infectious and neurological diseases.

Nanotechnology-based drugs and therapies have also the potential to reduce the cost of disease treatment. For example, the treatment costs of nanoparticle-based hyperthermia is expected to be just a fraction of the cost of traditional chemotherapeutic treatment of solid tumours. Furthermore, this method might overcome the problems of severe side effects of chemotherapy.

2.3 In Vivo Imaging

Progress in genomics and proteomics has led to a much increased knowledge of molecular processes linked to diseases that can now be used to develop diagnostic procedures to image pathogenic processes on a molecular level. This new diagnostic regimen is called molecular diagnostics and it aims to diagnose diseases on a molecular level before the development of symptoms [Schaeffter, 2005]. It might be the basis for a paradigm shift in healthcare from the treatment of symptoms to the prevention of the outbreak of diseases [Li et al., 2004; Wickline and Lanza, 2003]. In vivo imaging aimed at molecular diagnostics uses conventional imaging technologies such as ultrasound, magnetic resonance imaging, nuclear and optical imaging. To be able to operate these techniques on a molecular level (molecular imaging), however, special contrast agents are needed and the instrumentation including the software for data analysis needs to be adapted accordingly. In the field of in vivo diagnostics nanotechnology is likely to have its greatest impact on molecular imaging, as contrast agents need to be designed and optimised on the nanoscale level to be able to efficiently target molecular markers for diseases.

Magnetic Resonance Imaging (MRI): As the molecular constituents of pathological processes are too small to be imaged directly by MRI, they have to be visualised using sensitive, site-targeted contrast agents that accumulate at a pathological site. Nanoparticulate systems have emerged as the most successful molecular MRI contrast agents to date [Lanza et al., 2004]. For example, iron oxide nanoparticles are used as contrast agents, e.g. in the product Resovist®, since 2001 on the market, that accumulate passively in liver, spleen or lymph nodes depending on their size. Furthermore, nanoparticles with an extremely high payload of gadolinium ions have been developed to create paramagnetic contrast agents,

targeted at specific tissues via antibody ligands. The start-up Kereos, USA, pursues this technology with the goal to image tumours as small as 1 mm and unstable plaque (deposits in arteries that cause heart diseases). The product is expected to enter clinical trials in 2006.

Nuclear Imaging: In nuclear imaging a radionuclide contrast agents is introduced into the body of the patient. The uptake of the radionuclide contrast agents by organs depends on their metabolism, thus the contrast agents allow the imaging of physiological processes. None of the 12 currently approved nuclear imaging agents is based on nanotechnology. However, there are nanoparticle-based contrast agents in development. One example is a tumour specific contrast agent developed by the start-up company Kereos, USA, that consists of perfluorocarbon nanoparticles carrying Technetium-99 [Rollo, 2003].

Ultrasound Imaging: Ultrasound has an important role in delivering morphological information about tissues and organs. Commercial ultrasound contrast agents consist of gas-filled microbubbles which typically have a size of 1-2 µm. At present only a small number of publications describes work on nanosized ultrasound contrast agents and none of the described systems seems to have reached clinical trials yet.

Optical Imaging: The most prolific nanotechnology-based optical contrast agents are quantum dots (QDs)[9]. First in vivo studies with QDs in cell lineage-tracing experiments with frog embryos were reported in 2002 by Dubertret et al. [2002]. Since then QDs have been used to image cell signal transduction [Lidke, 2004], cancer markers [Wu, 2003], and tumors in living animals [Gao, 2004]. Researchers consider these experiments as an indication for a realistic chance that QD technology can be further developed for medical in vivo imaging. However, the main roadblock to reaching this goal is the high toxicity of the semiconductor materials used for manufacturing QDs.

MRI and ultrasound methods are likely to profit most from nanotechnology. With regards to MRI, nanotechnology is of importance for several reasons: 1) nanoscale iron oxide particles are superparamagnetic and give a particularly strong contrast, 2) by tuning the size and surface properties of particles loaded with contrast agents, plasma half-lifes can be controlled and passive targeting of organs is possible and 3) for imaging of molecular targets with gadolinium contrast agents, gadolinium needs to be concentrated at the target structure to enhance the contrast and this can only be achieved by nanosized particles or molecular structures that contain up to tens of thousands of gadolinium atoms. For ultrasound contrast agents nanotechnology is an important tool to control and modify the surface parameters of the gasbubbles that eventually will allow their application as molecular contrast agents.

The development of nanotechnology-based imaging agents started about a decade ago. Research activity in this field is still relatively low but has significantly increased over the past years. From 1980 to 2004 about 350 papers were published and in the period 1993-2003 about 1250 patents were filed. The only nanotechnology-based contrast agents that are at present on the market are nanoparticulate iron contrast agents for MRI

[9] Quantum dots are fluorescent semiconductor nanocrystals coated with inorganic materials. The emitted wavelengths can be tuned over a wide range by varying the size and composition of quantum dots.

(3 products). The leading contrast agent in this class is Resovist®, developed by Schering, Germany. Total sales of iron oxide nanoparticle contrast agents were an estimated EUR 15 million in 2004. Nanoparticle-based contrast agents currently target only a small niche of the imaging market which is valued at about EUR 15 billion. Five products were identified being in clinical trials.

The imaging equipment manufacturers, such as Philips, Siemens and General Electric generally show high interest in the field of molecular imaging as documented in scientific publications and white papers [Hämisch, 2003]. Their interest is also indicated by co-operations with academic institutes and start-ups such as Kereos, USA, or Ferropharm, Germany. In the USA molecular imaging receives much governmental support with seven molecular imaging centers established since 1999 funded by the National Cancer Institute [NCI 1998].

According to experts interviewed, there are currently no general technological hurdles that are likely to block the market entrance of nanotechnology-based contrast agents, though the technology is seen as very challenging as the chemistry and physics of nanoscale molecules and particles are still very new and need to be better understood. It is expected that the first targeted nanoparticulate MRI contrast agents will be available for clinical use by the end of the decade. For the other imaging modalities market entrance is likely to be later.

2.4 In Vitro Diagnostics

In the context of in vitro diagnostics nanotechnology is used for the development of novel sensors and in vitro tests for many different reasons: To improve and make existing tests more sensitive, to allow for point-of-care applications or to develop completely new diagnostic test platforms. Nanotechnology applications can be broadly divided into two main approaches: 1) the use of nanoparticles as markers for biomolecules and 2) novel sensor platforms that use nanomaterials, such as carbon nanotubes, lateral nanostructures or nanothin surface layers.

Nanoparticles: Fluorescent dyes serve as an indispensable tool for detecting pathogens, diagnosing cancer or carrying out genetic tests. The currently used organic dyes, e.g. in medical laboratory tests, in polymerase chain reaction assays and in biochips, are not photostable or suitable for multiplexing. Scientists have been investigating for the last ten years inorganic fluorescent nanoparticles as an alternative, such as semiconductor nanoparticles (quantum dots), resonance light scattering gold labels or nanoparticles doped with rare earth metals (nanophosphors) with the aim to :

- Increase the sensitivity
- Enable the analysis of multiple analytes
- Develop cheaper measurement concepts
- Facilitate mass production

The most prevalent medical use of nanoparticles are rapid tests such as pregnancy testing kits in which gold nanoparticles are used as a colour marker since the 1980s. Another important type of nanoparticles are semiconductor nanocrystals coated with inorganic materials, so called quantum dots (QDs). As QDs have been

successfully used in cell biology research, companies consider now their application in clinical diagnostic tests. Regarding research applications, nanoparticle tagging systems and respective biochip reader platforms are already on the market by Invitrogen (USA), Quantum Dot Corp. (USA), and Evident Technologies (USA). A further example for the application of nanoparticles in medical analysis are superparamagnetic iron oxide nanoparticles that have become the backbone for magnetic separation in several health-care and bioprocessing applications, such as cell sorting, nucleic acid extraction/purification and bacterial detection. Examples for products are CliniMacs from Miltenyi Biotec, Germany, and Dynabeads from Dynal/Invitrogen, Norway/USA.

Nanotechnology-Based Biosensors: At present, from a commercial point of view, biochips with a nanotechnology-enabled electrical detection system are the most interesting development in this field. Electrical detection systems allow to detect a binding process directly via an electrode, avoiding the need for a complicated optical instrumentation. Electrical detection systems in general are expected to be superior compared to optical systems with regards to robustness and production costs. Companies that work on such approaches are Siemens Medical Solutions, Germany, CombiMatrix, USA, and Genefluidics, USA. Market introduction of the first systems is expected within the next two years.

Nanoarrays, nanowire sensors, surface plasmon resonance sensors and cantilever sensors are all nanotechnology-based sensor principles that are still in a fairly early development status and that currently find applications only in biomedical research. However, there are a variety of companies that further develop these systems for clinical applications such as Bioforce, USA, Protiveris, USA, or Concentris, Switzerland.

First publications in the field of nanotechnology-based in vitro diagnostics appeared only in the late 1980s, although lateral flow tests using gold nanoparticles are on the market since the 1980s. Since then about 900 publications have been published and the number of publications per year has increased to more than 200 in 2004. Patent filings show a similar development: They have increased from about ten in the early 1990s to nearly 200 patents in the year 2003. Although the number of publications and patents is steadily increasing, the total numbers are still comparatively small and indicate that the field is still in an early development state.

The only nanotechnology-based in vitro diagnostics products that have already reached the market are lateral flow tests, containing conjugated gold nanoparticles, and magnetic nanoparticles for clinical immunodiagnostics. The market of these nanotechnology-enabled products is estimated to be EUR 600 million in 2004. All other identified biosensors (about 30) are still in development with the first systems likely to enter the market in 2006/2007. Estimates for sales for first generation products that are released by start-up companies range from about ten to several hundred million euro per year. Experts expect that these new diagnostic systems have a good chance to conquer significant segments of the evolving multibillion point-of-care diagnostic market.

Most of the interviewed experts consider nanotechnology as an important part of the development of in vitro diagnostic tests with breakthrough potential: Nanotechnology allows to develop completely new in vitro diagnostic test designs for mass markets and

it also enables the development of novel sensors for cheaper clinical diagnostic tests. However there are also many sensor concepts for molecular diagnostics and point-of-care applications, that come without the use of nanotechnology. Therefore nanotechnology is considered as a very important but only one out of several building blocks for innovation in the field of in vitro diagnostics.

2.5 Biomaterials

Over the past decades life expectancy has increased and degenerative diseases affecting organs and joints have become a critical issue. Nanotechnology is seen by experts as one approach to improve the biocompatibility and lifetimes of implant materials. As diverse as implant technology itself are the ways to use nanotechnology to improve their performance. Major application fields of nanotechnology are hard tissue implants, bone substitute materials, dental restoratives, soft tissue implants, and antibiotic materials:

Hard Tissue Implants: Crucial for the integration of an implant in the surrounding tissue is the cellular recognition of implant surfaces. Since bone is composed of constituent nanostructures, it is believed that nanophase materials, with constituent features of less than 100 nm, will facilitate the precise control of cell interactions with the implant. Scientists and companies currently work on special coatings and nanophase bulk materials for implants that improve cell adhesion to the implants. Nanocrystalline surfaces are also developed to avoid the generation of wear debris in articulating components that decrease the life time of implants by contributing to bone cell death [Sato and Webster, 2004].

Bone Substitute Materials: Current bone substitute materials show good biocompatibility, but their degradation is very slow. Since the late 1990s a number of research projects have investigated nanocrystalline bone cements with the objective to develop more bone-like cements with improved mechanic properties and a higher biofunctionality [Tadic et al., 2004]. Vitoss® and Ostim are two examples for currently available nanocrystalline bone substitutes based on nanohydroxyapatite, that improve bone regeneration.

Dental Restoratives: Nanoparticles are added to dental restorative materials to diminish their polymerisation shrinkage and improve their wear resistance and biocompatibility. Furthermore, the so-called nanofillers can contribute to increase the modulus of elasticity or to improve the optical properties of the dental composites [Moszner and Klapdohr, 2004]. Filtek™ Supreme was the first nanocomposite restorative in the market, launched 2002, and is now one of the leading products in its segment.

Soft Tissue Implants: The application of nanotechnology in the field of soft tissue implants is still in an embryonic state and has not yet been established as a coherent research field. Nanotechnology is used for developing:

1) Coatings or structuring surfaces to increase the biocompatibility of stents or catheters. Further, coatings with drug delivery function are developed to reduce the restenosis rate of stents.

2) Nano-featured scaffolds for tissue engineering to mimic the natural environment of cells. This entails approaches such as scaffolds with nanotopographical surface patterns and nanofiber schaffolds. The interconnective pores of the nanofibre

matrices and appropriate mechanical properties make them ideal candidates for developing scaffolds that can be customised for specific tissue growth [Norman and Desai, 2006].

3) Nanotechnology engineered membranes for cell therapy, to protect transplanted foreign cells from te host immune system. Such membranes with nanopores exclude passing of large molecules such as antibodies, but allow the passing of small molecules such as nutrients or hormones (e.g. insulin).

Antibiotic Materials: The antiseptic properties of silver have been known and used since a long time. By producing nanoscale silver particles the antibiotic effect of silver can be increased and the same antibiotic effect can be achieved with less material. Silver nanoparticles can be used for antibacterial coatings of implants, catheters, wound dressings and medical instruments. The nano-silver based wound dressing Acticoat® is on the market since 1998 [Wagener, 2001].

Nanotechnology research related to medical implants is documented in about 500 publications (1980-2004), the first appearing in the early 1990s. There is a strong increase in the publication activity since the year 2000, with publication numbers doubling every 18 months. In 2004, the number of publications in this field reached 140, reflecting a growing number of scientists that now work on nanotechnology-based implant materials. The patenting activity is increasing too, with first patents appearing in the mid 1990s. In 2003, about 180 patents were filed that describe nanotechnology applications for medical implant devices.

Nanotechnology-enabled implant materials as identified in this study had a market of about EUR 50 million in 2004. Most of the sales are generated with dental materials (5 products) and silver nanoparticles-based wound dressing (1 product) with minor contributions by bone substitute materials (3 products). To our knowledge there are currently no nanotechnology-enabled implants on the market and only four products were identified being developed. Thus it is unlikely that nanotechnology-based products will have a significant impact on the EUR 8 billion orthopaedic implant market within the next 5 years .

The interest of the industry in nanotechnology-enabled implant materials varies for the different application fields. The dental industry shows high interest in this material class, as development hurdles are manageable and first products have proven superior material properties. Generally, bone cements and orthopaedic implants are mature markets with products that meet very high standards, leaving little room for breakthroughs. Additionally, according to expert opinion, the generally conservative attitude of clinicians and the medical implant industry as a whole results in a comparatively slow uptake of new technologies.

According to experts, nanotechnology-enabled products are not necessarily more expensive or at least they do not lead to a significant increase in medical treatment costs. Products such as nanotechnology-enabled dental restoratives, wound dressings and bone substitute materials that are already on the market show that reimbursement by health insurances is not an issue. In case novel orthopaedic implant materials are able to significantly increase the lifespan of implants and therewith to reduce revision rates, this could lead to reductions of the total costs of disease treatment.

All of the interviewed experts see nanotechnology as an important driver for innovation in the medical implant industry. However, compared to drug delivery much of the development work seems to be in an earlier phase. Research on the impact of nanostructured surfaces on the adhesion, proliferation and gene expression of cells has just begun and it is likely that this field will gain considerable momentum in the future. This will be in particular important for the realisation of regenerative medicine, aiming at in situ regeneration of pathological tissue, for which biomaterials will play a crucial role [ETP Nanomedicine, 2005].

2.6 Active Implants

Active implants are defined as implants with an active electronic function such as neural prostheses and implantable electronic drug delivery devices. Examples for neural prostheses include retinal and cochlear implants, pacemakers, bladder stimulators and brain implants to help patients with Parkinson disease. The development of active drug delivery implants is still in its infancy and strongly driven by American research teams. At present, nanotechnology certainly does not play a key role in the development of active implants, but there are already some examples for the application of nanostructured materials for specific components of active implants:

Retina Implant: The most common degenerative diseases of the retina are macular degeneration and retinitis pigmentosa. Both eye diseases cause destruction of the rods and cones located in the retina rendering the retina insensitive to light. Since the late 1980s several research projects have been initiated to develop retina implants. The key element of a retina implant is a chip that substitutes the function of the rods and cones and electrically stimulates the ganglion cells. The chip either transforms incoming light into electrical pulses or it receives the signal from a miniature digital camera located on the patient's glasses. Nanotechnology is used for the production of the electrodes and for the development of biocompatible housings for the implant. The first pilot studies with a retina implant were conducted by the Retina Implant AG, Germany, in 2005.

Cochlear Implants: Profound deafness is caused by loss of the sensory hair cells in the fluid-filled, snail-shaped inner ear, or cochlea, that transduces sound waves into electrical impulses, which are then transmitted to the brain. Profoundly deaf individuals who still have an intact auditory nerve have profited from the advances made over the past 30 years in the field of cochlear implants. These implants consist of a microelectrode array implanted in the cochlea that directly stimulates the auditory nerve [Rauschecker, 2002]. According to experts, nanotechnology might be used in the future to improve the biocompatibility of cochlear implant housings or to add a drug delivery function to the implant that supports the healing process of the tissue or that prevents infections after implant surgery.

Cardiac Implants: A permanent pacemaker sends electrical signals to start or regulate heartbeats. These devices are implanted in case the heart's natural pacemaker has a dysfunction and the signals it sends out become erratic. The only example of a nanotechnology-enabled component of a pacemaker are electrodes with a nanostructured coating (developed by Biotronik, Germany) that improves the electrode-tissue interface and thus the electrical sensing and pacing properties.

According to experts, there is little additional potential for nanotechnology to improve current pacemaker or defibrillator technology.

Drug Delivery Chips: Drug delivery microchips are developed with the objective to precisely control the release rate of drugs for several months or even years. Traditionally, drugs are delivered to the human body mainly via oral and intravenous means. These delivery routes have several disadvantages: 1) High initial concentrations of the drug that are often higher than the therapeutic range and cause side effects, 2) the requirement of multiple injections, because only a very small percentage of the injected drug reaches the affected area and 3) pulse-like delivery as required for certain drugs, such as insulin, is not possible. Currently, drug delivery microchips are classified as microsystem technology with regards to fabrication methods and to their functional parts. However, they might also make use of nanotechnology for the design of certain components of the implant, such as nanopore membranes or biocompatible implant coatings. According to experts, there are currently no drug delivery microchips on the market or in clinical trials.

Coatings Making Implants Save for MRI: MRI cannot be applied to millions of patients with certain implants, such as pacemakers or brain electrodes, because the scanners can dangerously heat the implant's metal parts. Biophan, USA, develops nanomagnetic particle coatings that are supposed to render biomedical devices safe for MRI application and to reduce the interference these devices cause to the quality of MR images. The technology is still in a preclinical phase [Biophan, 2005].

40 publications (1980 - 2004) and 75 patents (1993 – 2003) were identified covering nanotechnology research and applications related to active implants. This shows that nanotechnology is not yet a research area of great importance for the development of active implants.

The number of companies considering nanotechnology as an enabling technology that might be used to improve the biocompatibility and technical performance of their active implants is, however, increasing. There is no information available if this interest has already gone beyond the status of pure technology screening. The interest in nanotechnology is certainly high if it comes to approach specific technical problems such as to enhance the charge transfer at the electrode/tissue interface or to improve the biocompatibility of implant materials. In this study five start-ups were identified that visibly pursue activities in this field. But only in the case of Biophan's coating, that makes active implants MRI compatible, nanotechnology is the key component and as such this technology deserves to be classified as nanotechnology. In all other cases nanotechnology has only an enabling function. Electrodes with nanostructured coating are the only nanotechnology-enabled active implants that have reached the market.

Apart from nanotechnology-based coatings nanotechnology is not perceived as to deliver major contributions to overcome the problems that are still in the focus of the medical device industry, such as cable interfaces or issues concerning the mechanic or electronic stability of active implants. Furthermore, there are currently no visible R&D activities to use nanotechnology to address single cells at a submicron level and according to experts, this will not be an issue for the foreseeable future.

2.7 Cosmetics

Cosmetics have been included in this study because the cosmetic industry sometimes appears as an early user of new technology, and innovative products are first introduced in the cosmetic market before they enter clinical use. An example for such an development was the market introduction of liposome-based anti-aging lotions before the first liposomal drugs reached the market. One important trend in the formulation of cosmetics is the use of sensitive ingredients such as vitamins or various plant-based active substances. These ingredients often need to be delivered to deeper layers of the skin to be most effective. Therefore delivery systems that protect and transport these active ingredients to the target skin layer increasingly gain importance. Further, particles can be used to prevent the penetration of active ingredients into the skin or to protect the skin against sensitising organic substances of the cosmetic formulation. There are a variety of microsized and nanosized delivery systems available for use in cosmetics, such as liposomes, solid lipid nanoparticles, nanospheres and inorganic nanoparticles.

Liposomes: The most common nanoscale carrier system in cosmetics is liposomes, which were introduced with the anti-aging lotion Capture by Dior in 1986. Most of the commercially available liposomes for cosmetic formulations are produced from lecithin, a mixture of phospholipids and triglycerides as extracted from soy beans. Small flexible liposomes are used to transport substances in deeper skin layers and rigid liposomes function as depots for substances in upper skin layers as they do not penetrate the skin. Further, liposome formulations help to protect instable chemicals or to reduce skin irritating effects of chemicals [Lasic, 1995]. Experts estimate that several hundred cosmetic products containing liposomes are on the market. Most of the products are anti-ageing skin creams, such as Capture (Dior), Dermo Expertise (L'Oréal) or Liftosome (Guinot).

Lipid Nanoparticles: Lipid nanoparticles with a typical size of 50 to 1000 nm have a similar structure to nanoemulsions. The difference is that the lipid core is solid and not liquid. Lipid nanoparticles appear interesting for the formulation of cosmetics for three reasons: 1) They improve the stability of chemically unstable active ingredients, 2) they allow the controlled release of active ingredients, and 3) they improve skin hydration and protection through film formation on the skin. Lipid nanoparticles are protected worldwide as Lipopearls® (Lipo Technologies, USA) and Nanopearls® (Pharmasol, Germany) [Müller et al., 2004].

Nanocapsules: Nanocapsules have a core-envelope structure and range between 130 and 600 nm in size. The liquid core comprises the active component and is encapsulated with a polymer membrane. This encapsulation technology stabilises sensitive ingredients better than existing emulsion or liposomal technology. The nanocapsules are small enough to penetrate through the first layers of the skin. In deeper layers the skin's enzymes dissolve the outer polymer membrane of the nanocapsules and the active ingredient is released. This delivery principle is of particular value for ingredients such as vitamin A, retinol and beta-carotene that must be delivered to the deeper layers of the skin to be most effective. L'Oreal's nanocapsules have been on the market since 1995. They were first used in higher end brands such as Lancôme and have since been added to less expensive product lines such as Future E and Plénitude [L'Oreal, 2003].

Titanium Dioxide and Zinc Oxide Nanoparticles: UV radiation from the sun consists of sunburn-causing UV-B (290-320 nm) and longer-wavelength UV-A (320-400 nm) radiation. UV-A radiation penetrates deeper into the skin, causing skin wrinkling, and promotes premature ageing. UV-A and UV-B radiation is believed to act synergistically in causing skin cancer. In Europe 26 organic sunscreens are approved. Many of those are basic UV-B filters and often cause allergic reactions in sensitive individuals or produce stains on clothing. Titanium dioxide (TiO_2) and zinc oxide (ZnO) are the most common ingredients of inorganic or physical sunscreens. They act as physical blocks to both long- and short-wavelength UV radiation, but they have the aesthetic shortcoming to appear as a white layer on the skin. By using nanosized particles this disadvantage could be overcome as light by these particles is no longer scattered. Advantages of these sunscreens compared to the organic-based products are the broad-spectrum UV-A protection and their good compatibility even with sensitive skin. Therefore TiO_2 and ZnO are used in products for babies and small children. Though TiO_2 and ZnO nanoparticles in sunscreens are considered save by regulatory bodies there is an ongoing scientific debate whether these nanoparticles can penetrate into deeper skin layers and cause harm to skin cells [Luther, 2004]. At present organic sunscreens account for about 80% of the market, while specialised sunscreens containing TiO_2 and ZnO nanoparticles represent 20% of the market. The share of sunscreens containing TiO_2 and ZnO is increasing mostly in speciality sunscreen brands, but application is also increasing in sensitive skin and baby products and in daily wear skin lotions that provide UV protection. Some brands that contain TiO_2 and ZnO as sun blockers are Suncare SPF 30 (Cellex-C, Canada), Eucerin Ultraschutz (Beiersdorf, Germany) and Nivea Sun Age Defence (Beiersdorf, Germany).

As cosmetics is not a major academic research field it is understandable that only a total number of 230 publications that cover nanomaterials for cosmetics has been published since the early 1990s. However, over the past decade the number of publications per year has increased slowly from less than five to about 30 publications in 2004. The cosmetic industry has started to patent formulations containing nanomaterials in the 1970s. Since then the number of patents has increased to about 280 in 2003. The total number of filed patents that include nanotechnology aspects is 2800.

Experts estimate that about 10% of the EUR 9 billion skin care market are products that contain liposomes and that about 20% of all sunscreens contain titanium dioxide and zinc oxide nanoparticles. A company that shows strong interest in nanoscale materials is L'Oreal that claims that in recent years about 10% of its filed patents are related to nanomaterials. Interestingly, cosmetic companies seem to be leaders with regards to the commercialisation of nanomaterials as in certain product classes, such as anti-aging cremes or sun blockers, nanotechnology-based formulations have already gained two digits market shares. One reason for the widespread use of nanomaterials is certainly the topical application of cosmetics which raises less issues compared to the uptake and metabolism or implantation of nanomaterials in drugs or medical devices.

Based on the accessible information and the development of nanotechnology applications in medicine, the cosmetic sector seems not have a pronounced early user role anymore. The following chapters will concentrate on nanomedicine applications.

3 The Nanomedicine Sector[10]

3.1 Nanomedicine Companies

Commercialisation efforts in nanomedicine are picking up worldwide. In this study 200 companies with nanomedicine activities were identified. These businesses include 92 start-ups[11] (44%), 67 SMEs[12] (32%) and 41 large pharmaceutical or medical device companies (21%). A detailed data analysis revealed that the relative proportion of corporations, SMEs and start-ups are the same for the USA and the EU25. The 159 start-ups and SMEs focus either completely (71 companies) or at least to a great part (87 companies) on nanomedicine. The 41 large pharmaceutical or medical device companies run only individual nanomedicine projects or have individual nanotechnology-based products on the market, i.e. nanotechnology currently contributes only little to the companys' business activities. Importantly, many of the large companies do not release information on their research programmes or products in development stages. Those, that openly communicate their activities are likely to be just the tip of the iceberg and it is assumed, based on expert interviews, that the majority of the major pharmaceutical and medical device corporations pursue R&D projects in which nanotechnology plays a role. Nanotechnology has clearly started to infiltrate R&D activities in the medical sector on a broad level.

Most of the companies involved in nanomedicine (56%) develop nano drug delivery systems (NDDS) (Fig. 3.1). This is in line with the high proportion of the nanomedicine publications in this field (76%) and the share of NDDS of the total nanomedicine market of about 80%. 16% of the companies develop nanotechnology-enabled in vitro diagnostics and 15% nanotechnology-enabled medical biomaterials for implants.

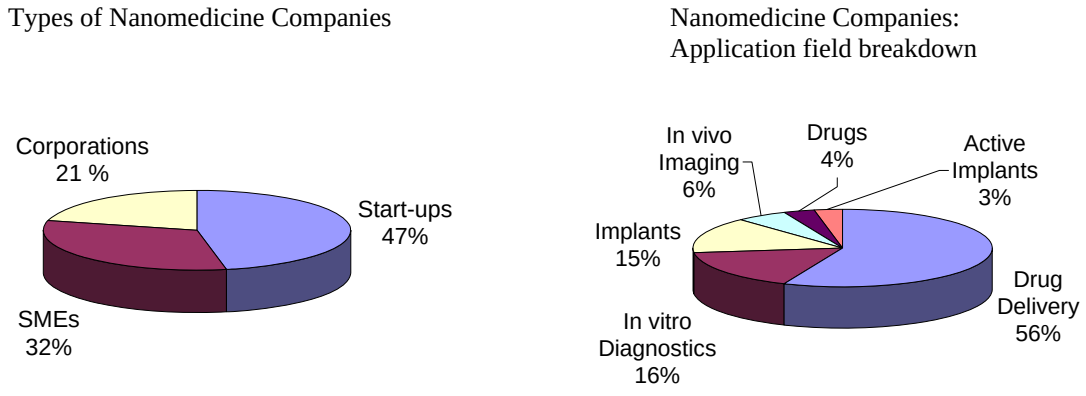

Figure 3.1 Nanomedicine Sector: Types of companies and application field breakdown
Source: VDI Technologiezentrum GmbH

[10] Information in this chapter is based on Work package 2 - Challenges and drivers for medicinal nanobiotechnoloy and its impact on the medical sector, V. Wagner, VDI Technologiezentrum GmbH, 2005.
[11] A start-up company is defined as a new business venture in its early stage of development, generally younger than 5 years
[12] A SME is defined as a company with less than 500 employees.

Currently only few companies focus on nanotechnology applications in the field of in vivo imaging (6%), drugs and therapies (4%) or active implants (3%).

Within the EU25, Germany, UK, and France are leading with regards to commercialisation efforts. In Germany 39 companies are visibly involved in nanomedicine R&D projects, in UK 15 companies and in France 10 companies (Fig. 3.2). In all other countries less than 5 companies could be identified, independent from country size. In Ireland, one comparatively active company was identified, developing NDDS.

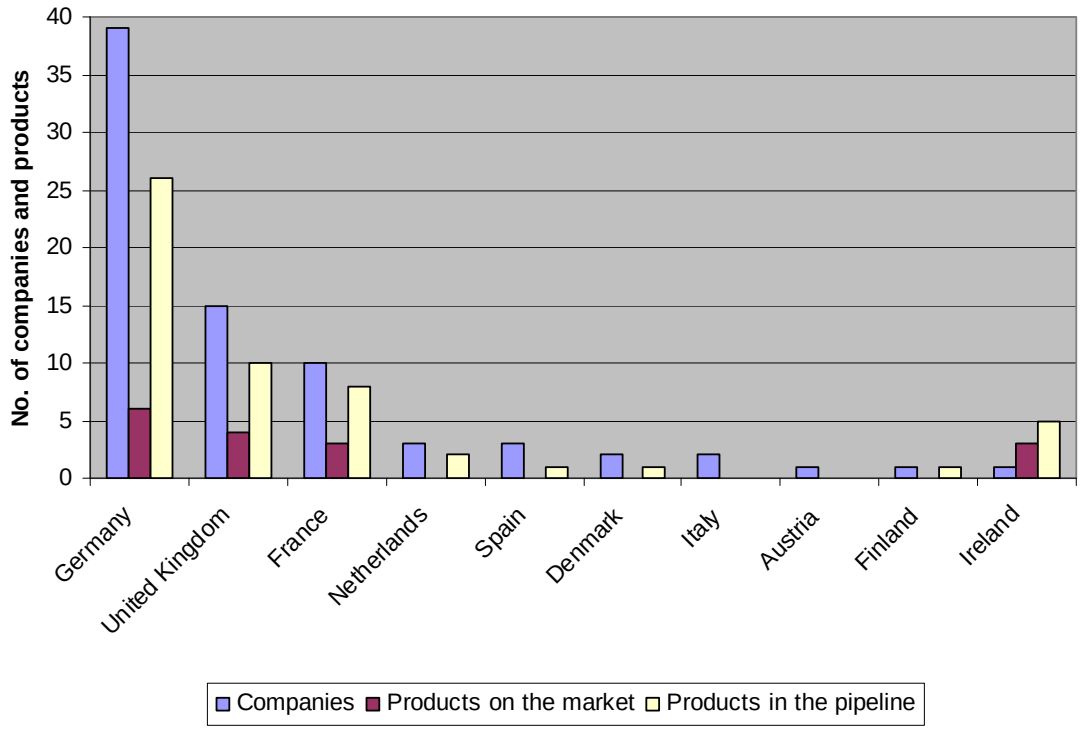

Figure 3.2 Nanomedicine commercialisation efforts in EU25 countries in 2004: Companies with nanomedicine activities, nanomedicine products on the market and in the pipeline
Source: VDI Technologiezentrum GmbH

A breakdown of EU25 nanomedicine companies with regards to medical application fields (Table 3.1) shows that in drug delivery with worlwide the highest research and commercialistion activities, the share of EU25 companies is 23%, whereas in all other fields the share is significantly higher with 40% to 50%. This coincides with the share of EU25 products in the pipeline which is also below average with 27%. This indicates a relative weakness of the commercialisation efforts in the EU25 in the nanomedicine sector with the highest near-term market potential.

Table 3.1 Companies, products and product pipeline in nanomedicine: Breakdown by medical application sectors
* If a product is developed by an EU25 company in cooperation with a company based in a non-EU25 country, this product is counted for each of the two countries). Further information on products is given in the appendix.

	Companies world-wide	Share of EU25 Companies	Products world-wide	Share* of EU25 Products	Products in Pipeline world-wide	Share of EU25 Products in Pipeline
Drug Delivery	113	23 %	23	29 %	98	27 %
Drugs & Therapies	7	43 %	0	NA	7	29 %
In vivo Imaging	11	40 %	3	33 %	8	38 %
In vitro Diagnostics	33	49 %	2	50 %	30	47 %
Biomaterials	30	47 %	9	55 %	9	55 %
Active Implants	6	50 %	1	100 %	5	20 %
Sum	200	35 %	38	37 %	157	34 %

Source: VDI Technologiezentrum GmbH

Compared to the USA the commercialisation efforts in EU25 countries are generally less advanced: 46% of all nanomedicine products are developed or co-developed by US companies compared to 37% pursued by EU25 companies (Fig. 3.3). The gap seems to further widen if we look at products that are currently under development: US companies are involved in 54% of nanomedicine products that are worldwide in the pipeline compared to 34% for EU25 companies.

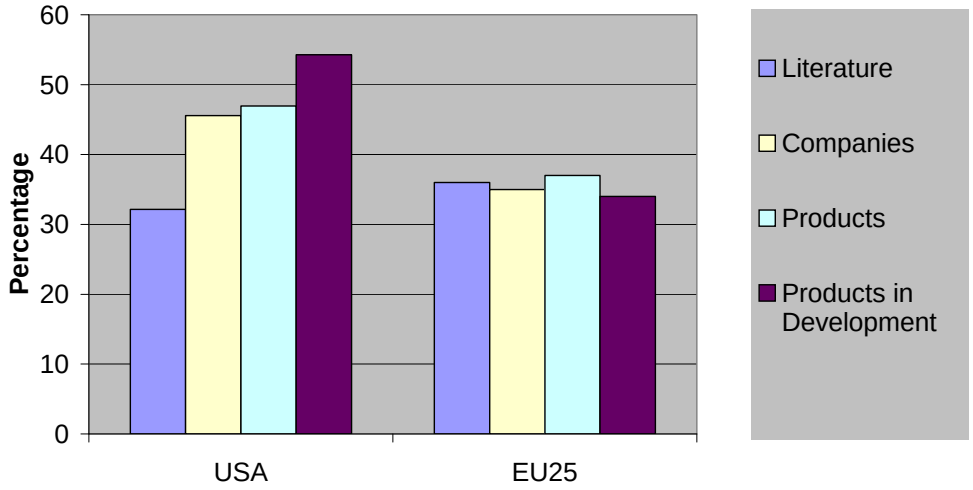

Figure 3.3 Comparison USA and EU25 with regards to nanomedicine research and commercialisation efforts
If a product is developed by companies based in two different countries, this product development is counted for each of the two countries. Source: VDI Technologiezentrum GmbH

In their final report the ESF Forward Look initiative (see Chapter 4.2) comes to the same conclusion and states that the timely exploitation of newly emerging medical nanotechnologies is an area of general weakness within the European Union [ESF, 2005].

3.2 Business Models and Structure of the Industry

The innovation process in nanomedicine is clearly driven by start-ups and SMEs whereas in big corporations nanotechnology enabled products are still of comparatively little importance. There are three business models apparent for nanomedicine start-ups and SMEs:

1) The development of nanotechnology-enhanced pharmaceuticals or medical devices: Start-ups and SMEs with this business model aim to develop a proprietary product pipeline and try to bring to market novel or conventional drugs delivered with a NDDS or to develop e.g. a novel nanotechnology-based diagnostic platform. Examples for companies with this business model are Inex, USA; Starpharma, Australia; Idea, Germany; Kereos; USA, or Ambri, Australia. After proof of concept has been shown these companies try to partner with pharmaceutical or medical device corporations that take the products through the clinical trials and that provide the crucial distribution networks. The majority of start-ups and SMEs, independent from the medical application field, work with this business model.

2) The development of a nanotechnology platform that can be used to add value to second-party products: Such a business model seems to be particularly attractive for drug delivery companies. These companies focus on a particular drug delivery technology that is licensed out to pharmaceutical companies or the drug delivery system is customised and applied to a certain drug in commission of a pharmaceutical company. Pharmasol, Germany and Eiffel Technologies, Australia, both drug delivery companies, pursue such a business model.

3) The development and manufacturing of high-value materials for the medical device and pharmaceutical industry: Some start-ups and SMEs only provide nanomaterials for the production of nanotechnology-enhanced drugs or medical devices. Examples for this business model are Bio-Gate, Germany, producing silver nanoparticles for medical devices, British Biocell, UK, producing gold nanoparticles for lateral flow tests or Raymor Industries, USA, manufacturing nanosized titanium powders for implants.

Few of the major pharmaceutical and medical device companies have shown strong commitments to nanotechnology. They prefer to invest in novel technologies once proof of concept has been shown; for drugs this typically means after a drug candidate has successfully passed pre-clinical trials or phase I clinical trials. The risk of development is therefore assumed by start-up companies and SMEs. According to experts this approach is not specific for nanomedicine, but can also be observed in the field of biopharmaceuticals: The pharmaceutical corporations became interested in protein drugs, after their pharmaceutical potential was proven. As smaller companies and start-ups rely on partnering with big pharma that provide the funding for the clinical trials, there are no signs that the structure of the pharmaceutical sector will change

significantly by the advent of novel nanotechnology-based drug delivery technologies. A further indication that there will be no big changes is the incremental added medical value by nanotechnology and the small market volumes of NDDS-enhanced products.

Novel nanotechnology-based therapies are more likely to introduce change than NDDS, at least in certain market segments. There are several approaches for nanoparticle-based hyperthermia treatments for cancer. These treatments are, according to experts, expected to be significantly cheaper than the currently used chemotherapy. Furthermore, they are regulated as medical devices and not as drugs, which implies notably lower development costs, manageable by SMEs. These types of novel non-drug therapies of cancer might have some impact on the cancer therapy market.

In the long term, however, also NDDS might impact the structure of the market to some degree: Many of the innovative drug delivery systems focus on diseases that occur in comparatively small patient groups such as brain or liver cancer, implying smaller markets. Experts see here a chance for medium-sized companies, since traditionally, big pharma has not shown much interest in niche markets over the past decade. However, if a new market segment can be established focusing on a more individualised medicine developed and marketed by medium-sized pharma companies remains to be seen. The key issue is wether the markets for such drugs are big enough to economically justify the high development costs caused by the clinical approval procedure. The orphan drug regulations targeted at drugs for rare diseases, in place in the EU and the USA, which guarantee market exclusivity for a period of 10 years, might help to bring NDDS-enhanced drugs to the market.

3.3 Market

Inherent to nanotechnology is its enabling function that is used to add new functionality to products making them more competitive. As it is hardly possible to measure the added value of nanotechnology to a product, it has become common praxis in nanotechnology business studies to take the total sales of nanotechnology-enhanced products as a measure for the economic importance of nanotechnology in an industrial sector. Following this procedure, we estimate the total sales of the 38 identified nanomedicine products on the market in 2004 generated sales of estimated EUR 5.4 billion (Table 3.2 and 3.3).

Drug delivery systems present currently the largest market, accounting for about 80% of the sales. Significant sales of several hundred million euro are also generated with lateral flow tests based on gold nanoparticles and pacemakers using fractal electrodes. Interestingly, none of these two product groups is widely perceived as nanotechnology because both have been in use long before it nanotechnology emerged as a buzz-word and because nanotechnology accounts only for a tiny fraction of the added value. However, at least in the case of lateral flow tests gold nanoparticles are of significant functional importance, the reason why it was classified as a nanotechnology-enabled product. In the field of in vivo imaging, nanoscale imaging agents with estimated sales of about EUR 15 million in 2004 represent only about 1% of the market. Also in the sector of medical implants and devices nanotechnology-enhanced products are still of low economic importance with a market of estimated EUR 50 million in 2004. There are currently no approved nanotechnology-based drugs or therapies on the market.

Table 3.2 Nanomedicine market 2004
Estimates for sales of nanotechnology-enhanced products and product groups in medical market segments are based on market analysis in this study.

	Market, Billion €	Market Environment, Billion €	
Drug Delivery	4.2	390	Drugs
Drugs and Therapies	0		
In vivo Imaging	0.015	15	In vivo diagnostics incl. equipment
In vitro Diagnostics	0.6	22	In vitro diagnostics
Biomaterials	0.05	8	Medical implants and devices
Active Implants	0.5	6	Active Implants (Pacemakers and Cochlear Implants)
Sum	5.4	441	

Source: VDI Technologiezentrum GmbH

A market report by NanoMarkets, LC, estimates the sales of NDDS to EUR 3.7 billion in 2012 [NanoMarkets, 2005]. Based on the assumption that on average 30% of the value of a drug is added by a NDDS, it is estimated that NDDS-enhanced drugs with a value of about EUR 12.4 billion will be on the market by 2012. Considering also other nanomedicine products, and based on the information retrieved in this study, it is estimated that in 2012 the total market of nanotechnology-enabled medical products is about EUR 15 billion. It is also assumed, based on the product pipelines of the different application fields, that the relative importance of in vitro diagnostics and in vivo imaging is likely to increase. However, these estimates assume a similar regulatory and reimbursement framework as currently being in place in the future.

Table 3.3 Examples for commercially available nanomedicine products
In case a large number of different products is available that contain a specific nanotechnology component only the product class is listed, e.g. lateral flow tests or magnetic nanoparticles for cell separation. Listed are those products with highest sales for each medical application field. All of the listed products are available in at least one EU25 country.

Pharmaceutical Product / Medical Device	Nanotechnology Component	Indication	Company
Drug Delivery			
Ambisome®	Liposome	Fungal Infections	Gilead (USA), Fujisawa (Japan)
Doxil/Caelyx	Liposome	Cancer	ALZA (USA), Schering Plough (USA)
Visudyne®	Liposome	Eye disease	QLT (Canada), Novartis (Switzerland)
Rapamune	Nanosuspension	Immunosuppresant	Elan (Ireland)/Wyeth (USA)

Pharmaceutical Product / Medical Device	Nanotechnology Component	Indication	Company
Neulasta	Polymer Protein Conjugate	Febrile neutropenia	Amgen (USA)
Pegasys®	Polymer Protein Conjugate	Hepatitis C	Hoffmann-La Roche (Switzerland), Nektar (USA)
PEG-Intron	Polymer Protein Conjugate	Hepatitis C	Enzon (USA), Schering-Plough (USA)
Copaxone	Polymeric Drug	Multiple sclerosis	TEVA Pharmaceuticals (Israel)
Renagel	Polymeric Drug	Kidney failure	Genzyme (USA)
In vivo imaging			
Feridex®/Endorem®	Iron Nanoparticles	Liver tumours	Advanced Magnetics (USA), Guerbet (France)
Gastromark/Lumirem	Iron Nanoparticles	Imaging of abdominal structures	Advanced Magnetics (USA), Guerbet (France)
Resovist®	Iron Nanoparticles	Liver tumours	Schering (Germany)
In vitro diagnostics			
Lateral Flow Tests	Colloidal gold	Pregnancy	British Biocell (UK), Amersham (UK), Nymox (USA)
Clinical Cell Separation	Magnetic Nanoparticles	Immunodiagnostics	Dynal/Invitrogen (Norway), Miltenyi Biotec (Germany), Immunicon (USA)
Biomaterials			
Acticoat	Silver Nanoparticles	Antimicrobial wound care	Nycryst (USA)
Ceram X™ duo, EvoCeram®, Filtek™ Supreme, Tetric	Nanoparticles	Dental Repair	Dentspley (UK), 3M Espe (Germany), Ivoclar Vivadent (Liechtenstein)
Ostim®, Perossal®; Vitoss®,	Nano-hydroxyapatite	Bone Defects	Osartis (Germany), Orthovita (USA), Coripharm (Germany)
Active Implants			
Pacemaker	Electrodes with nanostructured coating	Heart failure	Biotronik (Germany)

3.4 Drivers for Development

Nanomedicine is partly technology push and partly demand pull driven. The progress in genomics and proteomics has led to a much improved knowledge of molecular processes linked to diseases and this has led to a redefinition of many diseases. Crucial for the diagnosis and treatment of diseases are proteins and DNA, both nanoscale biomolecules. Over the past two decades scientists have learned to design, manufacture and manipulate nanoscale materials. At the point where nanomaterials meet with a molecular understanding of cell function and disease development, nanomedicine emerges. Using nanomaterials allows to target cancerous tissue, to transport drugs and

imaging agents into cells or to stimulate cell responses supporting the healing process. For these applications nanomaterials are unique as their scale corresponds to the scale of biomolecules and it is intuitively understandable that nanomaterials could potentially be of great value for medical applications [Ferrari, 2005].

Additionally, there are still important medical needs that need to be met to improve the efficacy of disease treatment: Many drugs show adverse side effects, many diseases cannot be diagnosed early enough for an effective treatment, biological barriers such as the blood-brain barrier cannot be overcome by many drugs, and there is need for more biofunctional materials to increase the lifespan of implants.

Commercialisation of products starts at the cross over of medical needs with novel nanomaterials serving these needs. Some examples for drivers for nanomedicines are given below:

- Drug Delivery: Many anticancer drugs have adverse side effects that can have severe consequences, in particular for risk patients. Drug delivery systems are being developed that concentrate the drug in cancerous tissue and significantly reduce the collateral damage caused by the drug. Another driver for new drug delivery approaches is the low solubility of many, very effective drug candidates which prevents their formulation as drugs. The pharmaceutical industry works on nanotechnology approaches (nanosuspensions) that make these drugs available for the treatment of patients. A commercial driver for NDDS is the extension of the life cycle of a drug that goes off patent by reformulating the drug using NDDS.
- The development of novel nanotechnology-based drugs and therapies is driven by the need to develop therapies that have less side effects and that are more cost-effective than traditional therapies, in particular for cancer.
- An important driver for the development of nanotechnology-based contrast agents is the realisation of molecular diagnostics, i.e. the diagnosis of diseases on a molecular level. This approach potentially allows earlier diagnosis and monitoring of the effects of drugs on an unprecedented short timescale. The vision of molecular diagnostics is a major paradigm change from the treatment of symptoms to the prevention of the outbreak of diseases. For certain imaging modalities nanotechnology will be crucial to realise this vision because nanoscale carriers are needed to transport the contrast agents to the site of disease.
- Molecular diagnostics and point-of-care diagnostics are the two most important drivers for the development of nanotechnology-based in vitro sensors. Nanotechnology contributes to the development of novel sensor systems that are highly sensitive, allowing for ultimate miniaturisation. This could make tests available for point-of-care diagnostics in doctor’s offices or even at home, which currently can only be run by laboratories. Also the pharmacogenetic approach to therapy, i.e. a more patient-specific treatment considering the genetic make-up of the patient, will make use of nanotechnology. Some methods under development use nanotechnology to enable the necessary sensitivity and specificity. However, often there are also suitable microscale methods available so that nanotechnology is not a unique enabler for molecular diagnostics.

- In the field of medical implants the demand pull seems to be not as strong as in drug delivery and diagnostics because important types of implants, such as hard tissue implants, are in a technologically fairly mature status. Drivers for nanotechnology applications are the need for implants with longer lifetimes and biodegradable implants that allow the full restoration of tissue. To meet theses challenges researchers develop nanostructured, more biocompatible materials.

3.5 Challenges for Commercialisation

According to experts, there are no general scientific hurdles that block nanomedicine products from market entry because many of the technologies pursued are now in a fairly mature state, having a development history of more than a decade. However, whether a technology is suitable for commercialisation and has chances to survive in a competitive market environment must be analysed on a case by case basis. Yet, there also seems to be a variety of stumbling blocks for commercialisation that arise from external factors, such as availability of capital, technology transfer management by universities, the intellectual property landscape, and regulatory issues that are detailed below (regulatory issues are discussed in Chapter 8).

Venture Capital

European start-up managers interviewed were of the opinion that there is considerably less venture capital (VC) funding available in Europe compared to the USA. In the USA about 52% of the nanotechnology VC has gone to nanobiotechnology start-ups[13] [Paull et al, 2003]. The high investment into nanobiotechnology start-ups shows that investors see nanobiotechnology as a sector with great business potential, promising high returns on investments. Within nanobiotechnology the prime interest of the investors was drug discovery accounting for 54% of the investments followed by diagnostics (37%), drug delivery (5%) and biopharmaceuticals (4%). The worldwide VC investment in nanotechnology was EUR 386 million in 2005, that is about 2% of the total globally invested VC money [Lux, 2006]. The still abundantly available capital and the more advanced entrepreneurial culture in the USA are certainly two important reasons that commercialisation efforts are further advanced in the USA compared to the EU25. According to European experts, the more restricted private funding situation in Europe is slowing commercialisation efforts in the field of nanomedicine in Europe.

Training and Education for Scientist and Entrepreneurs

Nanomedicine is a research field in which material science is of great importance and many of the ideas for novel nanomedicine applications come from material scientists. However, many of these scientists are not familiar with the biological and pharmaceutical world and hence there is a tendency to underestimate 1) the complex interaction of cells and tissues with synthetic materials and 2) the difficulties of gaining

[13] Nanobiotechnology is defined "as any application of nanotechnology in biological research, drug discovery and drug delivery devices, diagnostic tools, therapeutics or novel biomaterials" [Paull et al, 2003]. Thus the term includes more applications than the term nanomedicine but has a strong medical focus.

regulatory approval for novel drugs and medical devices. This can lead to a situation that scientists put much effort in the early development of materials that generally are considered as too risky to invest in by major pharmaceutical companies because these materials e.g. have no clinical history. Moreover, according to experts, European start-ups have management teams that are generally less market experienced than management teams of US start-ups. This often leads to an underestimation of difficulties to enter the market with new nanotechnology-based products. To improve commercialisation efforts at universities in the EU three measures are considered useful:

- Universities should offer business courses that provide scientists with the essential know-how to run a start-up company,
- Senior management personnel should be involved in the management teams or the advisory panels of start-ups at an earlier stage than it is currently the case,
- Establishment of more, and more professionally managed technology transfer centers at universities.

Uptake by Pharmaceutical and Medical Device Industry

Crucial for the commercialisation of nanomedicine products, particularly for nanotechnology-based drugs but to a lesser extent also for medical devices, is the investment of major pharmaceutical and medical device corporations. Only these companies have the means to finance clinical trials for novel drugs and diagnostic devices and they are also needed for providing the distribution networks. As there is a strong start-up scene in the USA and Europe sparking novel nanomedicine technologies the limiting factor for commercialisation is currently seen by experts in the very cautious investment by the big players. Scientists claim that their technologies are ripe for commercialisation whereas representatives from pharmaceutical corporations caution that many of the novel technologies are not yet in a stage that justifies major investment. Thus the situation is similar to the initially very slow uptake of recombinant biotechnology by the pharmaceutical industry. According to experts pharmaceutical corporations will wait with significant investments in nanomedicine until a nanotechnology-enabled blockbuster has shown the potential of this technology.

Intellectual Property Landscape

Patents are crucial for nanomedicine start-ups to protect their technology but also to attract investors. Patent experts anticipate that intellectual property **(**IP) protection will have a great impact on the success of companies in commercialising their technologies. The IP landscape for nanomaterials is seen as complex and fragmented as these materials are of multidisciplinary nature, situated at the borderline between physics, chemistry and biology, which makes categorisation particularly difficult. Nanomaterials, such as quantum dots, dendrimers or carbon nanotubes, can potentially be used for a broad range of medical applications just by modifying the core nanoscale component. Hence these nanomaterials can be seen as platforms allowing the development of different drugs or diagnostics based on just one core building block. There is a risk that patents on the core nanomaterial could be broad enough to prevent development of any possible medical application by competitors. Examples for

companies that have very strong patent portfolios and broad claims are Starpharma, Australia, for pharmaceutical applications of dendrimers, Quantum Dot (now Invitrogen), USA, for biological imaging applications of quantum dots and C Sixty, USA, for fullerenes as building blocks of novel drugs. Whether the claims are broad enough to prevent competitors from investing in these materials and using them for medical applications remains to be seen. However, experts see the risk that companies might be able to stop competitors from entering the market of certain nanoenabled drugs or diagnostics in a similar way as Affymetrix was able to prevent companies from manufacturing high density DNA chips. Generally, experts agree that it is of paramount importance for companies to check the IP landscape before starting activities in the field of nanomedicine.

4 Nanomedicine – Research and Development[14]

4.1 Publications and Patents

Nanomedicine is an emerging, very dynamically growing technology field with its beginnings more than twenty years ago. The number of nanomedicine publications surged from about ten per year in the late 1980s to more than 1200 in 2004 (Fig. 4.1). The rise in patent filings since the year 2000 is even more pronounced with a total of nearly 2000 patents filed in 2003. Drug delivery is the technology sector that dominates nanomedicine, contributing 76% of the publications and 59% of the patents. The second largest field is in vitro diagnostics accounting for 11% of the publications and for 14% of the patent filings (Table 4.1).

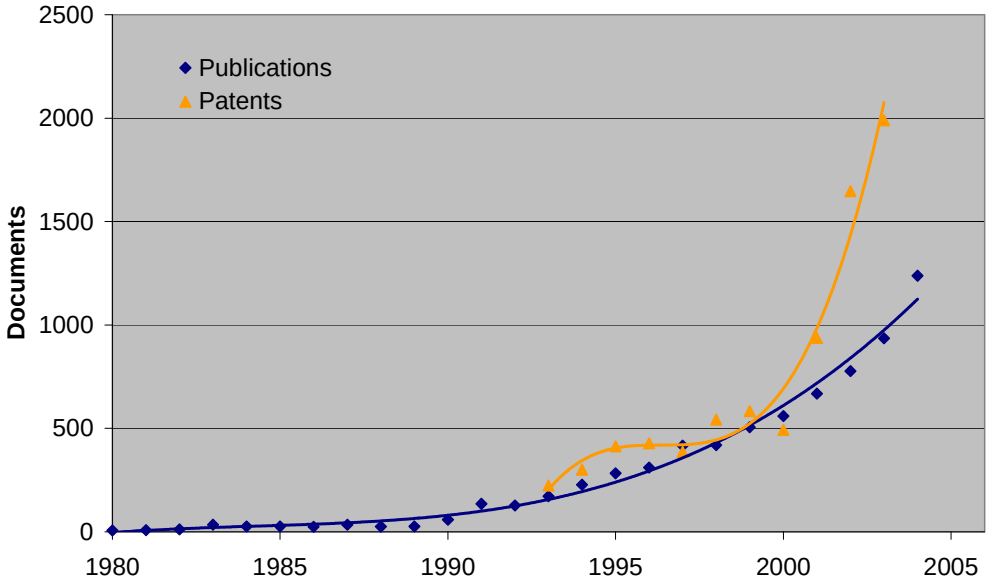

Figure 4.1 Nanomedicine publications and patents worldwide
Publication and patent searches only include technologies covered in this report and was conducted using specific keywords that allow for a clear classification of the document content as nanomedicine or nanomedicine-related (see Appendix). Source: EPO, VDI Technologiezentrum GmbH

Clustering the publications according to the three geographical areas USA, EU25 and Asia (Japan, China, South Korea, Taiwan, Singapore and India) reveals that the EU25 is leading with 36% of the worldwide publications, followed by the USA with 32% and Asia with 18% (Fig. 4.2). With regards to the different application fields of nanomedicine the share of EU25 publications varies between 37% for drug delivery and, at the lower end, 27% for active implants (Tab. 4.1). The USA is leading with regards to patent applications with a share of 53%, followed by the EU25 with 25% and Asia with 12%. There is a consistent trend for all nanomedicine application fields that the contribution of the EU25 to the worldwide patent activity is significantly lower than the publication share.

[14] Information in this chapter is based on Work package 1 - Current status of medicinal nanobiotechnology in Europe, V. Wagner, VDI Technologiezentrum GmbH, 2005.

Table 4.1 Publications (1980-2004) and patents (1993-2003) in nanomedicine: Breakdown for medical sectors

	Publications	%	Publications Share of EU25	Patents	%	Patents Share of EU25
Drug Delivery	6332	76.3	37 %	5884	58.8	23 %
Drugs & Therapies	150	1.8	32 %	342	3.4	32 %
In vivo Imaging	352	4.2	39 %	1267	12.7	29 %
In vitro Diagnostics	915	11.0	29 %	1400	14.0	26 %
Biomaterials	487	5.9	28 %	801	8.0	35 %
Active Implants	52	0.6	27 %	319	3.2	22 %
Sum /average	8288	100	36 %	10013	100	25 %

Source: VDI Technologiezentrum GmbH

Fig. 4.3 shows publication and patent activity since the 1990s for the 15 EU countries with the highest research activity. The three leading countries with regards to publications and patents are Germany, the UK, and France with more than 400 publications each. Within Europe the nanomedicine patent activity of Germany is outstanding with more than 700 filed patents in the period between 1993 and 2003. Although the publication activity in the UK and France is comparable to Germany (87% and 72%, respectively), patent numbers are about a factor of three lower. In addition to Germany, Sweden and Denmark show high patent activities compared to the publication output, indicating commercially highly relevant research activities.

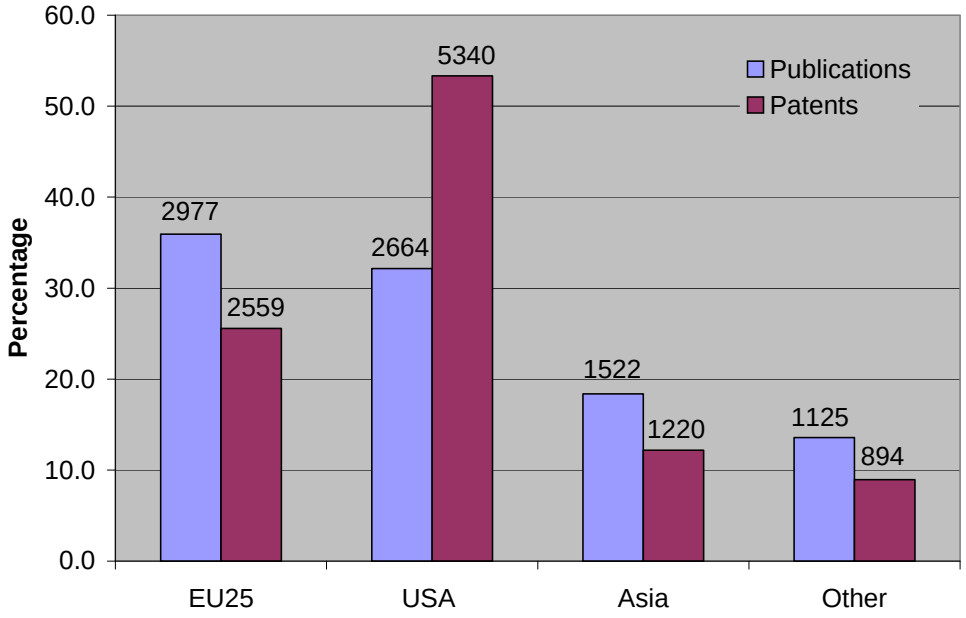

Figure 4.2 Area breakdown for nanomedicine publications (1980-2004) and patents (1993-2003)
Asia includes Japan, China, South Korea, Taiwan, Singapur and India.
Source: EPO, VDI Technologiezentrum GmbH

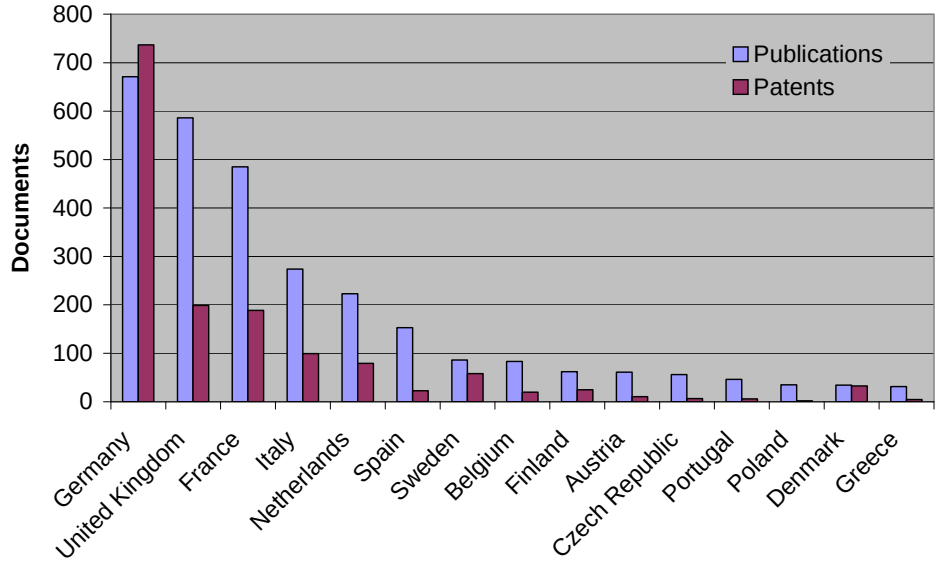

Figure 4.3 Nanomedicine in Europe: Publications (1980-2004) and patents (1993-2003) for the top 15 EU25 countries

Source: VDI Technologiezentrum GmbH, EPO

To obtain some information on the relative importance of nanomedicine research in EU25 countries we have calculated the share of nanotechnology publications that focus on medicine out of all nanotechnology publications since the 1970s. The results (Fig. 4.4) show that The Netherlands, Portugal, the UK, Finland and the Czech Republic have a comparatively strong focus on nanomedicine with more than 7% of their nanotechnology publications covering medicine related research whereas for countries such as France, Germany and Sweden, the share of nanomedicine publications is only about 4%. On average 5.2% of EU25 nanotechnology publications cover nanomedicine topics, te share is 6.3% for the USA and 4% for Japan.

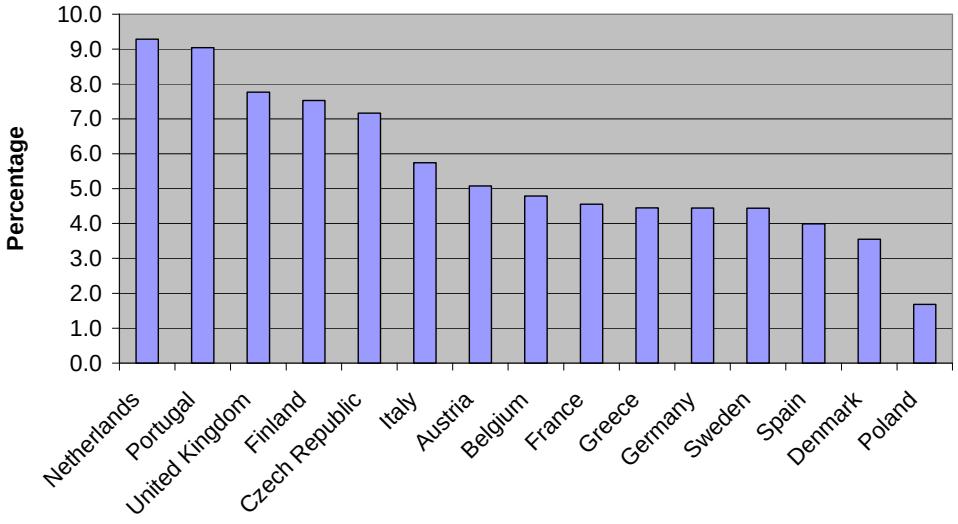

Figure 4.4 Share of nanotechnology publications since the 1970s that focus on nanomedicine for the top15 EU25 countries

Source: VDI Technologiezentrum GmbH

Figures 4.5 and 4.6 show the geographical distribution of companies and leading academic research groups as identified in this study for the USA and Europe. Though fairly crude, this provide an indication for emerging nanomedicine clusters worldwide. In the USA activities in the areas of Boston, New York, San Francisco and Los Angeles are outstanding. Furthermore, many start-ups are founded in the States in the North Eastern part of the USA such as Illinois, Indiana, Michigan, Ohio and Pennsylvania. Research activities in Houston, Austin and Dallas are also significant.

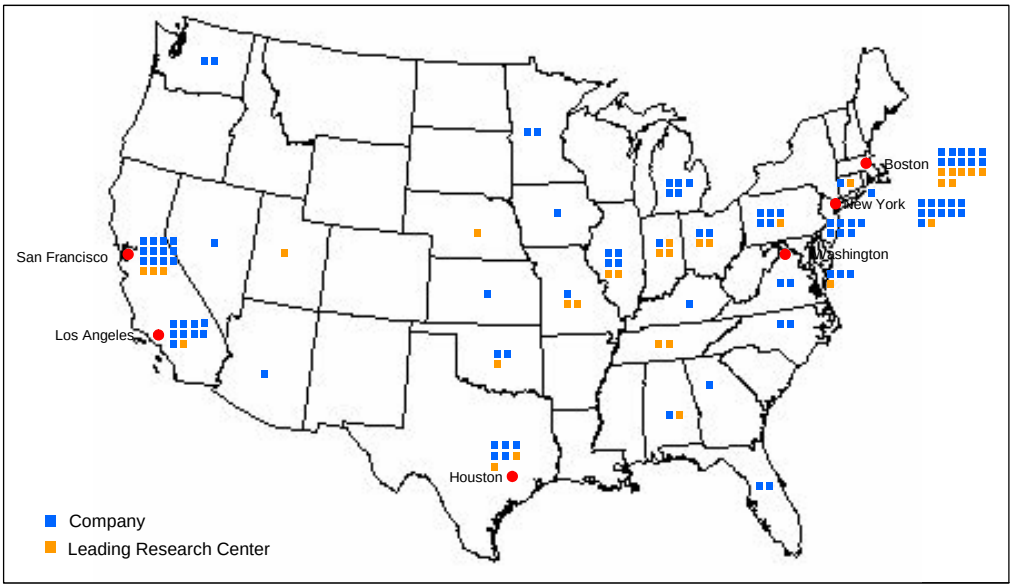

Figure 4.5 Nanomedicine companies and leading research groups in the USA identified in this study

Source: VDI Technologiezentrum GmbH

In Europe much of the activity is centered in Germany, Switzerland, France and the UK. Remarkable is the concentration of start-up companies in Berlin, South East England (London, Oxford and Cambridge) and the Paris area.

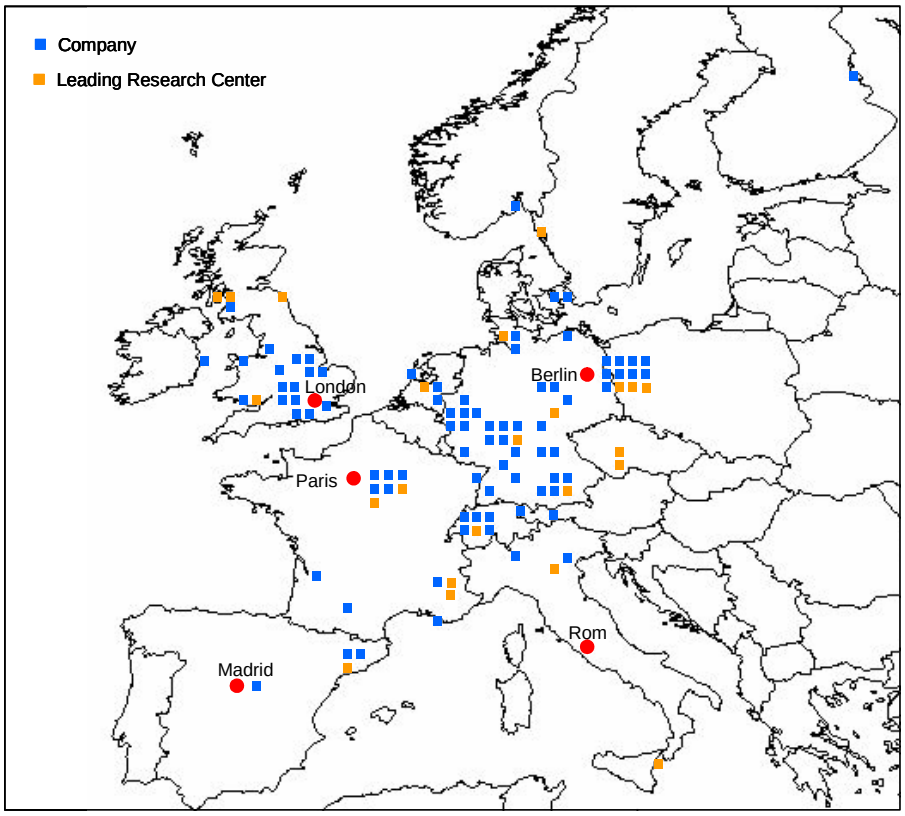

Figure 4.6 Nanomedicine companies and leading research groups in the EU identified in this study
Source: VDI Technologiezentrum GmbH

4.2 Public Funding and Strategic Initiatives

Nanotechnology has become one of the most heavily funded research areas, receiving about EUR 3 billion per year worldwide. In recent years the USA has run the biggest nanotechnology research programme funded with EUR 740 million in 2004, followed by Japan with EUR 480 million. The European Commission in 2004 spent about EUR 370 million on nanotechnology research and the EU25 countries all together EUR 960 million. In the EU25, the biggest governmental nanotechnology programmes are currently run by Germany (EUR 293 million), France (EUR 224 million), The Netherlands (EUR 120 million) and UK (EUR 100 million) (Fig. 4.7).

Interviews with representatives from funding agencies have revealed, that there are no data available on public funding of nanomedicine research for any of the major players in this field such as the USA, Germany, the UK, and France. As nanotechnology is a cross-cutting technology, obtaining detailed data on governmental funding is already very difficult for most countries. A detailed breakdown of funding with regards to nanotechnology sectors seems to be an even more daunting endeavour that is not pursued by any of the countries reviewed in this report.

However, as an indicator the share of nanotechnology publications that focus on medical applications can be used. Based on this it is estimated that on average in the EU25 about 5% of the nanotechnology funding is spent on medicine-related research projects. A further 15% is probably funneled into other areas of nanotechnology such as biomedical research and related fundamental research so that life sciences related research is likely to account for about 20% of nanotechnology activity and funding [Paschen, 2003].

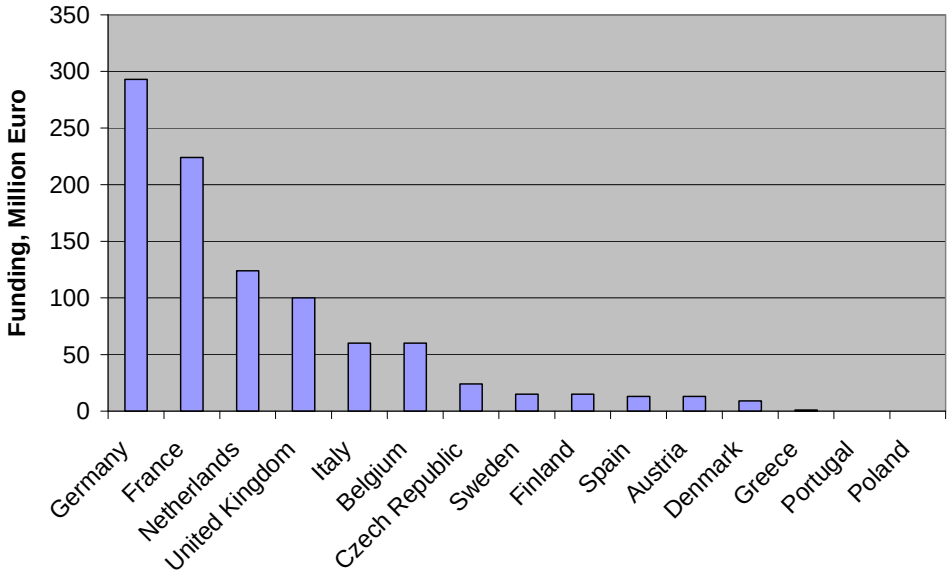

Figure 4.7 Nanotechnology public funding of EU25 countries in 2004
Source: [European Commission 2005]

While concrete figures on the public spending on nanomedicine do not exist for the major nanomedicine players in the EU25, there is information available on research programmes and funding initiatives that reflects the governmental funding activities in this field:

France: The investment of INSERM (the French national medical research institute) into nanotechnology, that might be indicative for the French nanomedicine funding, was EUR 6.5 million in 2004. Further, in 2005 a decision was taken to create a center dedicated to micro- and nanotechnologies for health and biology in Grenoble that will be supported with EUR 23,5 million public funding for new equipment and facilities.

Germany: The German Federal Research Ministry supports a specific nanobiotechnology research programme including nanomedicine projects since 2000 over a period of six years with a total of EUR 50 million. To specificly promote R&D activities in nanomedicine (drug delivery, molecular imaging, and medical implants/regenerative medicine) the lead innovation initiative "NanoforLife" was established in 2004, a funding programme for four to five years that started end of 2005. Total funding will be up to EUR 30 million intended to leverage a similar amount of money from industry. Nanobiotechnology clusters were established in Rhineland-Palatinate/Saarland and Munich to tighten contacts between research groups and companies.

United Kingdom: Nanotechnology research funded by UK Research Councils (the Biotechnology and Biological Sciences Research Council, BBSRC; the Engineering and Physical Sciences Research Council, EPSRC, and the Medical Reserach Council, MRC) includes two Interdisciplinary Research Collaborations (IRC) that focus on research in nanotechnology and life sciences and that are supported by EUR 56 million over a period of six years. As the UK biotechnology and pharmaceutical sector enjoys internationally a very strong position combined with a strong medical and science base, nanomedicine is anticipated to have a particular great synergy potential in the UK. Therefore, it is planned that future phases of the Department of Trade and Industry funded Micro- and Nanotechnology Initiative (MNT, about EUR 40 million per year) have a strong focus on nanomedicine.

The European Union: Within The Sixth EU Framework Programme for Research and Technological Development (FP6, 2002-2006) an expected average spending on nanotechnology related projects is EUR 250 million per year. Of those 129 FP6nanotechnology projects on which information is publicly available there are seven that can be classified as nanomedicine. At present several initiatives are on-going to strengthen European nanobiotechnology and nanomedicine research:

> **Nano2Life** is a network of excellence funded via FP6 with the objective to coordinate and bring together existing European expertise and knowledge in the field of nanobiotechnology in order to make Europe a leader in commercialising nanobiotechnology research in 5 years time. Nano2Life aims to develop the basis for a virtual European Nanobiotechnology Institute. Research of this virtual institute is targeted at nanotechnology applications in the areas of sensor technology, health care, pharmaceuticals, environment, defence and food safety.
>
> A **European Technology Platform (ETP) on NanoMedicine** was launched in autumn 2005. It aims to bring together stakeholders to develop a long-term vision for nanomedicine that should result in a strategic research agenda. It further aims to identify priority research areas, to mobilise public and private investment and to overcome fragmentation in the European nanomedical research community. The ETP will focus on the following three topics: drug delivery, regenerative medicine and nanodiagnostics including sensors and medical imaging [ETP Nanomedicine, 2005].

The European level initiative, **Forward Look Nanomedicine**, a foresight process conducted by the European Science Foundation, brought together over a period of 2 years (2003-2004) over 100 international experts from academia, industry and governmental agencies to review the field and to deliver recommendations regarding funding priorities and organisational and research infrastructures needed in Europe. The report was recently published [ESF, 2005].

USA: In the USA the multiagency efforts in nanotechnology research are coordinated by the National Nanotechnology Initiative (NNI). The US Department of Health and Human Services (HHS) contributed EUR 62 million (8%) to the total budget of the NNI. Though there is normally considerable thematic overlap between different funding domains, this could be an indication for the share of the budget that is spent on nanobiotechnology/nanomedicine research. The field of nanobiotechnology has been further strengthened by the US National Science Foundation that increased the budget for biological sciences within the NNI from EUR 4 million in 2004 to EUR 36 million

in 2005. Additionally, the National Institutes of Health (NIH) made three major commitments to a focused support of health related nanotechnology research in the year 2004/2005:

The National Cancer Institute's **Alliance for Nanotechnology in Cancer,** a EUR 112 million five-year initiative to develop and apply nanotechnology to cancer, that was launched in September 2004 [NCI, 2005].

The **Program of Excellence in Nanotechnology** of the National Heart, Lung and Blood Institute to fund four research centers (EUR 42 million between 2005-2009) that develop nanotechnology solutions for the diagnosis and treatment of cardiovascular, pulmonary, blood and sleep disorders [NHLBI, 2006].

The **Nanomedicine Roadmap Initiative,** a broad programme that seeks to measure and characterise molecules and use this data to understand molecular pathways and networks [NIH, 2005].

China: Within the five-year plan 2001-2005 China spent EUR 150-230 million on nanotechnology research. It is estimated that about five percent of the funding is spent on nanobiotechnology and nanomedicine related research projects [RAM, 2004; ATIP, 2003].

Japan: Japan pursues an ambitious research programme “Nanotechnology & Material Science” with a total funding of EUR 600 million in 2004, of which about 80% (EUR 480 million) are earmarked for nanotechnology. About 16% (EUR 100 million) of the budget is spent on the priority life sciences. In the year 2002 the Ministry of Health, Labour and Welfare initiated a Nano Medicine Research Project that provides funding of about EUR 7 million per year for 23 projects between 2002 and 2006. Thematically the projects cover a broad range of technologies including drug delivery, molecular imaging, biosensors and medical implants.

5 Impact of Nanomedicine Applications on Health Care Costs[15]

In most industrial countries today, rising health care expenditures are a major concern for health care sytems. The most prominent explanations for this development are demographic changes and high costs of health care innovations. Thus future health care innovations will not only be required to be of high quality, safety and efficacy – they will, in addition, be assessed with respect to the costs at which they deliver health benefits. Consequently, high costs are likely to increasingly impede the diffusion of health innovations in the market. Against this background, nanomedicine innovations were analysed regading potential impacts on future health care costs and their cost-effectiveness.

5.1 Trends in Health Care Systems

In the past, health innovations were mainly assessed with respect to efficacy and improved quality of life of patients, whereas cost considerations were not of prominent importance. Nowadays, the situation has changed: health care costs do matter. National health care expenditures are expected to increase significantly if the current practice is also pursued in the future: while in 2002, EU15 member states spent 6.2% of their gross domestic product on health care, this share is likely to rise to 8.9% in 2050 [Surcke et al., 2005]. The main drivers are demographic changes towards an ageing society (decreasing birth rates, increasing life expectancy), and medical innovations which alter the patterns of the most prevalent diseases towards an increase of complex and chronic diseases.

The changing age structure of the society together with an increase in health care expenditure challenges the sustainability of the health care systems, because most of these systems are based on a pay-as-you-go financing mode. Population ageing unbalances the relation between health care expenditures and health care contributions, as fewer people of working ag will have to support those in retirement. This is reflected by the indicator of old-age dependency ratio, which is expected to rise in EU15 from 24.3 in 2000 to 53.2 in 2050 [European Commission, 2006].

Therefore, present health care systems will no longer be affordable in the medium to long term and require significant changes. Several options can be taken into consideration, among them

- Structural reforms such as a change in the financing mode, reduced coverage, or a reduction in institutional inefficiencies in health care delivery,
- Investments into the health of the population,
- Cost reduction in sectors identified as main cost drivers.

With respect to health innovations, it can be concluded that efficacy and improved quality of life will remain a necessary prerequisite, but will no longer be sufficient. In addition, health innovations will increasingly be assessed with respect to the costs at which the improvements come. For this reason, cost aspects of nanomedicine are considered in the following paragraphs.

[15] This chapter is based on Work package 3 - Potential socio-economic impacts of medicinal nanobiotechnology applications, B. Hüsing and S. Gaisser, Fraunhofer Institute for Systems and Innovation Research, 2005.

5.2 Cost Considerations for Nanomedicine Applications

Based on model calculations for Germany performed by Farkas et al. [2004], major drivers for future health care costs were identified: In addition to demographic changes, cancer, cardiovascular, neurodegenerative and musculo-sceletal diseases are expectd to be the major cost-causing diseases. Further, personnel-intensive care (e.g. days in hospital) is very cost intensive. Taking this into account, nanomedicicine innovations are likely to reduce future health care costs if they

- Aim at major cost-causing diseases, and at the same time,
- Reduce personnel costs, for example by reducing the required days of inpatient care,
- Contribute to "healthy ageing" via raising the health status of the population.

On the other hand, nanomedicine innovations are likely to have no major effect or even increase future health care costs if they

- Aim at diseases of minor cost relevance such as infections or diseases with low prevalence and incidence, or
- Come as add-on technology, which offers only a small health effect at significant costs so that the cost-benefit-ratio is unfavourable, or
- Result in additional procedures without substantial health effects (e.g. more diagnostic procedures).

For the major cost-causing disease groups cancer, cardiovascular, neurodegenerative and musculo-skeletal diseases, technology dependent costs account for a maximum of 20% of the total costs [Farkas et al, 2004]. Thus nanotechnology innovations are likely to have a particularly strong impact on health care costs if they reduce personnel costs by reduction of the number of days in hospital. Other savings may be realised in ambulatory care costs, i.e. for diagnostic tests or for pharmaceutical therapies. In the following, examples are given how nanotechnology could impact future health expenditures:

Cardiovascular disease is with 30% of the projected deaths the leading cause of death worldwide. Due to the high number of patients with cardiovascular diseases, even small cost effects (positive or negative) on an individual case basis will result in large cost impacts, if the whole affected population is taken into consideration. Main cost drivers are intensive care for chronic patients and rehabilitation for stroke patients. Some nanotechnology-based diagnostic tests may offer a potential for cost reductions. An example for nanotechnology innovations with potentially high impact in this field are contrast agents developed by Kereos, USA, in cooperation with Bristol-Myers Squibb Medical Imaging, USA. These are developed to detect unstable plaques with MRI to early identify those patients at high risk of heart attack. Effective prevention strategies for these high risk patients could result in reduced costs for intensive care and rehabilitation for stroke patients. The contrast agent is based on nanoscale perfluorocarbon emulsion particles and is currently in a preclinical development stage.

Diseases of the nervous system: In the diagnostic group of nervous system diseases, nanotechnology-based drug delivery systems (NDDS) are in development that are able to transport drugs across the blood-brain barrier. Furthermore, novel nanoscale materials

are developed that possess much stronger antioxidant properties than any of the traditionally drugs for treatment of neurodegenerative diseases. However, none of the these products has reached late stage clinical trials so that possible cost impacts are difficult to assess. In conjunction with an early detection of neurodegenerative diseases before the onset of clinical symptoms, it is hoped that the period without the need for - expensive - custodial care can be prolonged and that the savings in care exceed the costs for additional diagnostics and medication.

Cancer therapy requires an average stay in hospital of 10 days in Europe. For cancer diagnostics and treatment, novel nanotechnology-based in vivo diagnostic approaches and NDDS are under development. For example, nanotechnology-based cancer diagnostics are developed that aim at monitoring the therapeutic effects of drugs. Such a therapy-specific monitoring is expected to prove the efficacy of a drug within days compared to weeks or months with currently available diagnostic methods. As cancer therapies cost up to several thousand euros per month and it often takes several months until an effective drug treatment is found, nanotechnology-based molecular diagnostics are expected to improve the efficiency of disease treatment. Another important research direction in nanomedicine is the development of NDDS for anticancer drugs that result in drug accumulation at the tumour site and in that way reduce side effects. In case a reduction of treatment costs due to less side effects overcompensates the additional costs for the drug delivery system, an overall reduction in treatment costs could be achieved (see also below case study on liposomal doxorubicin). Furthermore, novel nanotechnology-enabled therapies are developed, such as iron nanoparticle-based hyperthermia, that are expected to have the same efficacy as traditional therapies but at significantly lower costs. Therefore experts expect these methods to have great potential to reduce health care costs.

However, there is an important general consideration that is relevant for all life-prolonging anticancer medicines. A global cost calculation has to take into account that tumour patients who survive their first tumour might require additional treatments due to the occurrence of secondary tumours. This scenario would eventually result in higher health care costs for any anticancer drug that is not able to eradicate cancer completely.

Infectious diseases currently do not present a significant economic problem for the health care systems of industrialised countries. However, as the number of opportunistic infections increases due to the rising number of aggressive tumour therapies and transplantations (both are therapies that weaken the immune system), the spectrum of morbidity could change in the future. A certain improvement of drug therapies can be expected as nano-encapsulated drugs could be applied site directed and in higher concentrations. The case study of liposomal amphotericin B will describe this in more detail (see below).

Musculo-skeletal diseases: Model calculations based on data for Germany show that this diagnostic group will cause the highest health care costs due to high costs for personnel in care and physiotherapy but also for drugs and implants [Farkas et al., 2004]. A nanotechnology-based increase of the lifespan of implants from 15 years to 25 years could be beneficial particularly for younger patients. However, in Germany only 12% of all patients that undergo hip replacement are younger than 55 years. Therefore the potential of implants with longer lifespans to reduce treatment costs seems to be

limited. However, this situation might change taking into account the steadily increasing life expectancy and the high costs of revisions.

The number of studies that cover economic aspects of nanomedicine products is very small. Up to now only for liposomal amphotericin B, an antifungal drug, and pegylated liposomal doxorubicine, an anticancer drug, sufficient data is available that allows a first analysis of cost-effectiveness.

Case Study: Liposomal Amphotericin B (AmBisome®)

Amphotericin B is an antifungal drug which is mainly used against fungal infections in transplant recipients, patients suffering from HIV/AIDS or in cancer patients. The major drawback of this drug is its kidney toxicity. To reduce the nephrotoxic side effects the company Gilead (USA) has developed AmBisome®, a liposomal formulation of amphotericin B. Several clinical studies came to the conclusion that AmBisome® has a higher efficacy than conventional amphotericin B [Sharon et al., 2002; Hann and Prentice, 2001; Cagnoni et al., 2000]. The costs of AmBisome® are substantial: A standard therapy against aspergillosis with AmBisome® costs EUR 26.000 to EUR 53.000, whereas a standard therapy with amphotericin B costs EUR 107 to EUR 214. Depending on the infection, the high cost of AmBisome® may be counterbalanced by reduction of hospitalisation duration and absence of side effects. Owing to the much lower price amphotericin B is used as a standard therapy for treating fungal infections. Only if kidney problems occur, or if the patient is at high risk for developing severe kidney damage, AmBisome® is recommended as first-line therapy [Sharon et al., 2002; Dupouy-Camet 2004]. For these reasons sales of AmBisome® are moderate with EUR 164 million in 2004. There is no information available about the price strategy of Gilead. However, experts assume that the high costs do not reflect the production costs but more the medical value of the drug. AmBisome® is a first generation liposomal product and it is assumed that the development and production costs of liposomal formulation will decrease with further scientific progress.

Case Study: Pegylated liposomal Doxorubicin (Doxil®/Caelyx®)

To reduce the cardiotoxic effects of the anti-cancer drug doxorubicin, pegylated liposome formulations (Doxil®/Caelyx®) were developed and launched beginning of the 1990s. They are used to treat HIV/AIDS related Kaposi sarkoma or ovarian carcinoma. First-line therapy against ovarian carcinoma are platinum based drugs. In case patients do not respond to this therapy, the gold standard for the second-line therapy is topotecan. Approximately 150 clinical studies have been performed worldwide in order to assess the cost-effectiveness of liposomal doxorubicin in comparison with topotecan [Forbes et al. 2002; Thigpen et al. 2005; NICE 2005]. Both, topotecan and liposomal doxorubicin show similar clinical effectiveness in the treatment of ovarian cancer, but differ significantly in their pattern of side effects and incidence of adverse events. Treatment costs of liposomal doxorubicin tend to be slightly lower owing to a different pattern in side effects [Capri et al., 2003; Ojeda et al., 2003], but its overall cost-effectiveness in terms of quality-adjusted life-years still remains to be established [Forbes et al. 2002]. Currently, treatment with liposomal doxorubicin costs 20 times more (about EUR 10.000 per treatment) than standard doxorubicin. Therefore liposomal doxorubicine is only administered to risk patients that suffer from cardiac diseases and

drug sales are moderate (EUR 112 million in 2004) with European uptake of less than three percent.

Both drugs show similar or better clinical effectiveness and less side effects than the gold standard treatment, but differ in the cost at which this health benefit comes. They are cost-effective only for the small group of risk patients and are recommended only for this group. Therefore market uptake of these drugs remains low.

Apart from the technological development, the future framework for approval and reimbursement is a key issue for the economic impact of nanotechnology on health care systems. The extent to which innovative technologies are added to the list of reimbursement by insurances or the national health care systems is a political question; facing the financial shortage in the health care systems, prices and cost-effectiveness ratios will be very crucial. Only cost-effective health technologies are likely to be reimbursed. This is a chance to focus nanomedicine research on medical technologies that aim at reducing health care costs.

Looking at the multitude of options to apply nanotechnology to medicine, it becomes clear that at present no general assessment can be given, in which way nanotechnology will eventually impact health care costs. Generally, the development of novel pharmaceuticals with added functions such as drug delivery systems will be more costly than the drug alone, though eventually indirect cost reduction, such as less side effects, shorter recovery times and less costs for patient care (particularly regarding neurodegenerative diseases) will be decisive for the overall cost effect. With regards to analytical methods there are nanotechnology-based applications in the pipeline that promise early detection of diseases. Should this make an earlier and more effective intervention possible, costs could be reduced.

According to experts, nanomedicine indeed has the potential to reduce health care costs, provided that the proper incentives to exploit these potentials are effective in the health care systems. One prerequisite would be the integration of health technology assessments in the development process of nanomedicine products. However, many more nanotechnological products and analyses of their cost-effectiveness are needed to be able to deliver a general assessment of the impact of nanomedicine on future health care costs.

6 Social and Ethical Issues in Nanomedicine[16]

It has been widely recognised that there is a need to address social and ethical issues of nanotechnology in addition to scientific, economic and political issues [e.g. European Commission 2004, 2005]. Moreover, the ethical and sociological reflection should rather not be considered as an "add-on" which follows scientific-technological research and development, but should accompany it as an integral part (Schummer, 2004). It is hoped that a better understanding of the interaction and mutual interdependence of science, technology and society could lead to better informed decisions about how to shape the development of nanotechnology, and that mistakes that have been made with other technologies, such as biotechnology and genetic engineering, might be avoided by dealing proactively with the social and ethical embedding of nanotechnology [see e. g. Lewenstein 2005; Macnaghten et al. 2005].

However, the systematic exploration of social and ethical issues of nanotechnology started a few years ago. Due to the early stage development of nanotechnology, these are mainly deliberations about possible social and ethical issues for nanotechnology in general. The majority of these analyses relates to nanotechnology in their entirety, the differentiated analysis of certain application areas or subfields of nanotechnology (e.g. to nanomedicine) or of specific product lines (e.g. drug delivery) has only started recently (e.g. within the FP6 funded network of excellence Nano2Life the Ethics Board works on a wider assessment of ethical and social implications on new nanotechnology applications in addition to the ethical evaluation of research projects; Bruce, 2006). Moreover, because the development of nanotechnology applications is a rather long-term endeavour, the exploration of social and ethical issues is hampered by the inherent uncertainty of this process and by the uncertainty about the future social contexts into which the use of the respective applications might be embedded.

Issues raised by nanotechnology applications have, in part, been dealt with in depth in other technological contexts, so that the analysis of ethical and social issues of nanotechnology can establish links with this work [MacDonald, 2004]. For example, nanotechnology-enabled diagnostics may have close links with aspects of genetic testing, and enhancement of body functions raise similar issues as performance enhancing drugs in sports [UNESCO 2006]. But even if the ethical and social issues are not genuinely new or exclusively specific for nanotechnologies, this does not render them less valid. Rather, due to the enabling nature of nanotechnology some issues may become (even) more critical, and there may be shifts in emphasis. In addition, new and specific issues may arise [Baumgartner 2004]. Moreover, many potential applications and visions explicitly refer to the convergence of nanotechnologies, biotechnology, ICT and cognitive sciences [National Science Foundation 2002; Roco 2003], which seems to be a specific feature of the nanotechnology discourse.

The expectation that nanotechnology applications in medicine will lead to positive health impacts for individual patients as well as the public is a major driving force for this field, and also characterises the prevailing view in the general public. However,

[16] This chapter is based Work package 3 - Potential socio-economic impacts of medicinal nanobiotechnology applications, B. Hüsing and S. Gaisser, Fraunhofer Institute for Systems and Innovation Research, 2005.

possible health benefits must be carefully balanced against possible adverse health effects and social and ethical issues need to be addressed.

6.1 Health risks of nanoparticles

It is known that the exposure to ultrafine dust particles poses health risks for humans. This implies that exposure to engineered nanoparticles could pose health risks too. Particularly because of their mobility across biological barriers, size related chemical activity effects and their ability to penetrate cells, nanoparticles show properties that could result in increased toxicity compared to bulk materials. Nanoparticle sources are natural (e.g. salt spray from the ocean), unintentionally produced (e.g. cooking, material fabrication, diesel exhaust) or, relatively new, engineered nanoparticles. Presently, it is not known how significant the increase in exposure due to these engineered nanoparticles is and will be in the future [European Commission, 2006a]. Generally two forms of application of nanoparticles need to be distinguished with respect to exposure and possible health risks:

- Nanoparticles bound into a chemical matrix, such as a polymer or a metal. Unless nanoparticles are released due to chemical processes or wear, these materials are generally considered as safe.
- Free nanoparticles in the air or in fluids that can be taken up by the body via the lung, skin or the intestinal tract.

Nanoparticle emission, intentionally or unintentionally, can occur during research and development activities, manufacturing, use, and after use/during disposal, and after their dispersion in the environment. Potentially exposed groups comprise staff in R&D, manufacturing, diagnosis and treatment, disposal, recycling, remediation and cleaning, transport and trade, and accidents, patients, and the general population. Additionally, ecosystems might be affected. Therefore toxicologists warn that health and environmental effects of nanoparticles and exposure of workers need to be investigated. There is consensus among stakeholders that the present level of knowledge is insufficient for risk assessments. The need to

- Develop harmonised nomenclature and criteria for nanoparticle characterisation,
- Develop methodologies for routine measurements,
- Develop equipment and methods for the determination of the environmental fate of nanoparticles and for the detection in the environment, and for exposure assessment to nanoparticles,
- Understand toxicity and ecotoxicity of nanoparticles,
- Conduct epidemiological studies

is broadly recognised [European Commission, 2006a].

6.2 Changes in health care delivery

Several changes in health care delivery can be expected from the scientific-technological developments outlined in Chapter 2:

- *Personalised medicine.* By providing diagnostic systems (e. g. for screening), nanotechnology will be an enabler for extended risk specifications on the level of the individual, which may open up the possibility to adopt preventive risk management strategies and to choose the most appropriate intervention for the affected individual. Therapeutic interventions (e.g. dosing of drugs) could be tailored to the individual response, if nanotechnology-enabled monitoring of disease progression and of effects of therapeutic interventions could be applied. This trend towards personalised medicine could increase the available options for patients to exert more self-determination and self-responsibility on their health, but on the other hand this option may also turn into a duty.
- *Convergence with ambient intelligence.* The applications of nanotechnology are expected to support the introduction of telemedicine into health care delivery through nanotechnology-enabled devices such as sensors, which include ICT components. These devices will increasingly be interconnected, leading to a convergence of telemedicine/e-health with ambient intelligence. This will lead to changes in work and information flow in health care, and in the tasks that have to be performed by medical staff.
- *Shift of (chronic) diseases to older age.* Earlier diagnosis and risk specification before clinical symptoms become manifest, coupled with preventive measures and improved therapies are expected to shift chronic disease states to older age. This should allow a higher quality of life until older age, but could have significant impacts on demographic development, and the need for social support systems for the elderly.
- *"Exchange of spare parts".* Nanotechnology is seen as an enabler for the provision of interventions which compensate disabilities and impaired motor, sensory and cognitive functions. This could lead to a notion of medicine as providing "spare parts" which are exchanged in case of disease or accident in order to "repair" defects, with significant impacts on the role of the body for personal identity, and also on our understanding of health and disease (see also Chapter 6.4).

6.3 Access to and availability of nanomedicine

Fairness is one of the key principles of biomedical ethics which translates into the goal that there should be equal access to nanotechnology-enabled medical diagnostics, therapies and services for all those in need of it. However, the concern is often brought forward regarding the danger of inequal access to nanotechnology and a resulting "nano-divide". This term implies that there are winners with access to nanotechnology and losers who lack this access. This divide can take shape on different levels [Mnyusiwalla et al, 2003; Baird and Vogt, 2004; Invernizzi and Foladori, 2005]:

- Between developed and developing countries in the way that the unequal access to scientific-technological know-how and use of nanotechnology is further increasing the wealth gap between these two parts of the world. The priorities of R&D efforts play a major role for realising the benefits of nanomedicine while avaoing the risks. Furthermore, research agendas of developed countries could also be targeted at developments beneficial for developing countries (see e.g.

Global Dialogue on Nanotechnology and the Poor: Opportunities and Risks[17]). Nanomedicine products could also be so expensive that poorer countries could be prevented from access to much needed medication.

- On a company and cluster level, e.g. through the development of patent monopolies which allow the patent owner significant influence over certain trajectories of nanomedicine developments, and hinder the market entry of other players.
- On a health care level in case nanomedicine products are so costly that they are not covered by health insurances and only the privileged get access to them. A just allocation of resources in health care requires the integration of health technology assessments and cost-effectiveness studies in the development of these new interventions.

6.4 Specific characteristics of nanotechnology-based diagnostics

In the following specific features of nanotechnology-base diagnostics will be analysed in more detail, also taking into account that thse applications seem to be comparatively close to the clinical application.

It is expected that nanotechnology-enabled diagnostics will enable a significant extension in various dimensions of present capabilities to analyse and diagnose. These features, in their sum, can only be achieved by a convergence of nanotechnology with biotechnology and ICT:

- *Range of testable conditions*. It is expected that the range of testable conditions (e.g. body functions and states, diseases or disease predispositions) will significantly expand, and that tests at the cellular or molecular level will become available.
- *Time and frequency.* Testing will become possible at earlier disease states (i.e. before clinical symptoms become manifest) and even before an elevated individual risk is suspected (i.e. screening), resulting in an increase in predictive testing. It is likely that also the frequency of testing will increase, in order to monitor the progression of disease or the effects of therapeutic or preventive interventions, and even continuous surveillance and control can be expected.
- *Occasions for testing.* New occasions for testing are likely to emerge: general screening for preventive purposes, for specification of individual risk, for monitoring of health status if a higher individual risk has been identified, and continuous surveillance.
- *Sites of testing.* In addition to specialists, testing will also be performed by non-specialist doctors and laboratories, by the care staff or the patient himself, with an increase in point-of-care and home testing.
- *Populations tested.* Broader segments of the population will be subjected to testing, e. g. healthy people without clinical symptoms, children, newborns and unborns, but also tissues and gametes.

[17] http://www.meridian-nano.org/

- *Data acquired.* Both the quantity of data acquired will increase, but also the quality will change including data on behaviour, activity profiles and life style. Moreover, the risk of incidental findings, i.e. information about conditions where there was no intention to obtain them, will increase [see e.g. Illes et al. 2002, 2004].
- *Linking diagnostics to intervention.* Especially in surveillance applications, deviations from normal conditions will trigger interventional procedures.

Overview of relevant privacy issues and measures to guarantee privacy

The issue of privacy is especially relevant for nanotechnology applications in medical diagnostics (*in vivo* imaging and in vitro diagnostics). With respect to social impacts and ethical deliberations, one can build on an extensive analysis in the genetic testing and pharmacogenomics/pharmacogenetics field [see e.g. CIOMS Working Group on Pharmacogenetics 2005; The Royal Society 2005; Kollek et al. 2004] as well as the telemedicine/ambient intelligence field [see e.g. Friedewald and Da Costa 2004; Friedewald et al. 2005]. Despite these links, a nano-specific analysis is nevertheless desirable for the following reasons:

- The nanotechnologies community is – at least in part – not fully aware of and familiar with the debate in the above-mentioned fields,
- Nanotechnologies-enabled diagnostics have specific features and imply both a new quality as well as new contexts of diagnostic procedures, which make certain social implications and ethical consideration even more important and/or mean a shift in emphasis.

The major concern regarding privacy is the potential misuse of the very sensitive and personal data obtained by diagnostic procedures. The increase in quantity and quality of highly sensitive personal data that can be expected due to improved and new diagnostic possibilities and the increasing abilities to interlink and process them makes the need for privacy and data protection even more pressing.

The main issues are

- Free and informed consent before a diagnostic procedure is performed. However, the scope and use of the data the consent relates to should be clear. The case of genetic testing showed that although extensive information and counselling of the person to be tested is required, the provision very often is of substandard quality and quantity [Ibarreta et al. 2004]. Patients could see themselves exposed to perceived or factual social pressure and discrimination if they wish to make use of their right not to know and do not make use of the predictive testing and risk specification options available.
- *Purpose of tests*. Nanotechnology-enabled diagnostic procedures bear the potential to be used for a broad variety of purposes, including defined medical purposes, research involving human beings, criminal investigations as well as national security, surveillance and control, testing for workplace and for insurance purposes. Against this background, there is a clear need for political control and legitimation for which purposes personal data may be collected and analysed in order to avoid discrimination, social control and to ensure civil rights.

- *Data access and use*. Data access and use should be appropriately confined, especially if personal data can be increasingly interlinked. There is concern that information may be concentrated in the hand of those with the resources to develop, run and control such networks.

There may be a requirement to establish whether current regulatory frameworks and institutions provide appropriate safeguards to individual or group privacy [The Royal Society & The Royal Academy of Engineering 2004].

Quality assurance of tests and related counselling

Given the likely rapid expansion of testable conditions and diagnostic test systems, there is a clear need for validation and quality assurance of the diagnostic tests, especially if they will increasingly be applied outside specialists' facilities and increasingly provide predictive information. This does not only relate to genetic testing, but also to the testing of disease conditions in presymptomatic stages of the disease. Moreover, medical staff must be qualified to appropriately understand and interpret the results of the tests, which often only give a probability for a disease condition, in terms that are understandable by the patients and can be transformed into appropriate (changes of) behaviour.

Dealing and coping with information from diagnostic procedures

Many concerns related to expanded options for diagnosis are not directed at the testing procedures themselves, but relate to the knowledge that is acquired in this way:

- *Gap between diagnostic and therapeutic capabilities.* While the diagnostic capabilities expand, this is not necessarily the case for the abilities to treat and cure the respective disease or disorder. In case of herediatary disorders, the diagnosis might also affect family members.
- *Interpretation of test results.* Many diagnostic tests, especially if they are of predictive character, only give a specification of the individual risk in terms of increased probabilities. Whether the increased risk will, in the future, become manifest as clinical symptoms in the individual case, has inherent prognostic uncertainties. If a predisposition for a severe disorder or disease is diagnosed, this also bears the risk of (perceived or factual) discrimination, even if the disorder never becomes manifest in the individual case.
- *Predictive testing information*. Nanotechnology-enabled diagnostic and therapeutic interventions will provide extended options for self-determination with respect to one's health, especially through predictive testing and risk specifications in early, asymptomatic stages of disease. In order to use these options for one's benefit, certain skills and abilities will be required [Rohr and Schade, 2000] such as the willingness and means to care for one's future life.
- *Right not to know.* The more diagnostic tests are performed, the more the notion could prevail that people have a duty to perform (predictive) diagnostic tests, resulting in social pressure or discrimination if such tests are refused. Against this background, a broader debate is required about the question to which extent man

can be held responsible for his own life and health, and how this responsibility can in practice be balanced with the right not to know and with patient's autonomy.

- *Incidental findings.* The more diagnostic tests are performed, the higher the probability of incidental findings, i.e. information about conditions where there was no intention to obtain them, and, because of the unintentional character, there are often no appropriate structures and provisions available or consistently enforced to deal with these findings, thus increasing the risk that privacy, patient autonomy and the right not to know, as well as access to counselling and psychosocial support, and other interests of the patient are at risk.
- *Medicalisation of deviations from normal status.* The more diagnostic tests are performed, the higher the likelihood that any deviations from a "normal" status are seen as pathologic and as requiring medical treatment. This poses the question what – in the light of the wide variability in living organisms – constitutes a "normal" condition and by whom and on what empirical basis this has been established, bearing also in mind that the definition of "normal status" has a clear cultural component.

6.5 Human Enhancement

Biomedical applications of nanotechnology can not only be used to treat and restore impaired body functions, but also for enhancing them. Enhancement is understood as interventions which aim at an improvement of human abilities and performance beyond "normal" levels - also in an excessive and undesired manner [Friele and Fulford 2004]. Enhancement is not at all new or specific to nanotechnology. Examples can be found in e.g. the use of growth hormones in paediatrics, plastic and cosmetic surgery, doping in sports, or genetic engineering [Fuchs et al. 2002], and it is also discussed in neuroscience for cognitive, motor and sensory enhancement [Kennedy 2004; McGuire and McGee 1999; Wolpe 2002; Farah et al. 2004; Chatterjee 2004; Hüsing et al. 2005]. Nevertheless, nanotechnology, especially in the convergence with biotechnology and ICT, are often seen as powerful potential enablers to perform such interventions into a broad variety of motor, sensory and cognitive functions with unprecedented precision [see e.g. National Science Foundation 2002]. A latent societal demand for enhancement of certain human functions (e.g. cognitive performance, alertness, mood, endurance) is not unlikely. Against this background, ethical deliberations and social debates are required whether there is a difference between helping someone whose capacities are below average to reach the average, and helping someone already above average to reach a still higher level of functioning [Friele and Fulford 2004].

However, there is no fixed and clear definition of what can be considered as "healthy" or "normal", because of broad biological variation of human functions, abilities and performance, and social, cultural and subjective elements in the perception of what is "normal". As a consequence, the borderline between "health/enhancement/illegitimate" and "disease/treatment/legitimate" is blurred. This could also lead to the medicalisation of an increasingly wide range of aspects of human life. Interventions with an enhancement purpose also raise the health economic questions whether and under which conditions health care systems should provide and pay such interventions.

It is likely that nanotechnology-based enhancement would not be confined to the health care systems, and that access to enhancing interventions will not be equal, so that certain segments of the population will be favoured over others, thus leading to a further widening of socio-economic divide ("nanodivide"). This does not rule out the possibility that enhancement could be used by individuals to compensate for existing inequalities, and to narrow the socioeconomic gap that way. In this context, it is also argued that some forms of enhancement are not only chosen in order to achieve a competitive advantage, but for the sake of non-competitive, intrinsic benefits. If enhancement were rejected in order to avoid socio-economic inequalities, the achievement of intrinsic benefits would also be ruled out.

6.6 Blurring the borderline between humans and technical artefacts

The use of technical artefacts or interventions for restoring or substituting impaired functions of the human body is an integral part of human culture, as exemplified by glasses for impaired vision, limb prostheses, dental implants, pacemakers and organ transplants. Against this background, the use of nanomedicine applications poses the question whether such applications bring about a new quality in the foreseeable time which might push the – culturally defined – borderline between humans and technical artefacts further.

Among the technical trends with the potential to blur the borderline between humans and technical artefacts are

- Devices as replacements for or complementation of biological components, e.g. retinal or cochlear implants, artificial organs,
- Intimate integration of miniaturised devices into the human body (e.g. sensors, pacemakers, artificial organs),
- Interlinkage of humans with internal or external devices (e.g. remote surveillance and control, brain-computer interfaces), also hybrid systems of distributed action, i.e. interaction of humans with intelligent technical artefacts,
- "Humanisation" of devices (e.g. "intelligent" devices, autonomously acting systems, futuristic visions of self-replicating and autonomous nanorobots).

A new quality which may challenge human dignity, fundamental rights, integrity of the human body and non-instrumentalisation is especially seen in nanotechnology-enabled interventions if [EGE, 2005]

- the devices cannot be removed easily (implants),
- they influence, determine or change cognitive and psychic functions, thus influencing human identity as a species as well as individual subjectivity and autonomy,
- they could be misused, due to their network capability, for all kinds of social surveillance and manipulation,
- they serve military applications,
- no clear distinction between therapeutic intervention and enhancement can be drawn,

- if technology by-passes normal sensory experience,
- if implants influence future generations, biologically and/or culturally.

In addition to earlier discussed concerns related to privay, informed consent, human enhancement, access and availability, technical artefacts raise furher issues [Baumgartner, 2004]:

- *Possible impacts on our understanding of what makes humans human (conditio humana).* What makes humans human is a central question in philosophy and religion. It also comprises the question against what humans can be distinguished in order to define their identity. The technical trends described above could lead to the requirement to redefine the borderline between man and machine/technical artefacts.
- *Personal identity*. Basic to personal identity is the intimate relationship between bodily and psychical functions. This personal identity may be challenged if a major proportion of bodily or psychical functions is performed or supported by technical artefacts. Autonomy is also considered a central characteristic of personal identity which would be, in hybrid systems of distributed action, be (partly) delegated to "intelligent" technical artefacts which act autonomously and adaptively, perhaps leading to emergent behaviour of the systems with properties that no individual component of the system has.
- *Free will*. Our concept of a human being as well as human societies are based on the notion that human beings have a free will, a view that is currently being challenged by some in the view of recent findings from brain imaging studies [see e.g. Wegner 2002; Singer 2003] and is very controversially being discussed [see e.g. Pauen 2004; Raeymaekers et al. 2004]. If technical devices would interfere with the free will, then our ways of thinking about responsibility and blame would be challenged, with possible, yet disputed impacts on criminal law and justice [Hüsing et al. 2005]. This discussion from the neuroscience/philosophy-field could also extend to nanotechnology.
- *Moral status of "made" artefacts.* The question is also raised whether "made" artefacts which fulfil important criteria of known forms of living organisms can claim the moral and normative status that is currently assigned to humans, animals or other life forms.

6.7 Military Use

Biomedical applications of nanotechnology bear the potential to be used both for civil as well as military purposes. In the USA, the Department of Defence funds major nanotechnology research projects that have a clear focus on military applications. The application of nanobiotechnology for military purposes includes [Paschen et al. 2003]

- nanoscale encapsulation systems for the improvement of chemical and biological weapons
- the enhancement of soldiers' performance in battles, e.g. by implants with nanotechnology components, or antimicrobial battle-suits,

- the development of nanosensors to detect biological and chemical weapons.

Against this background, a US citizens' jury on nanotechnologies has recommended "that nanotechnology should not be used to develop weaponry" [Kleinman, 2005]. There are concerns that nanotechnology could trigger new forms of an arms race, and that new types of weapons could be developed which are not covered by existing arms control frameworks. As military nanotechnology projects are secret, they could spark and fuel public's distrust in military nanotechnology R&D which might also extend to civil developments.

7 Public Debate[18]

7.1 Public Perception of Nanotechnology and its Applications in Medicine

Mass media play a significant role in the shaping of public attitudes towards nanotechnology because they are a major source of information for the general public. Moreover, they have a role as agenda-setters for public discourse and as gatekeeper that confer status on issues, stakeholders, and policy makers. At present no studies have been carried out about the media coverage of nanomedicine. Therefore, studies on nanotechnology were analysed that represent the field as a whole including nanomedicine [Anderson et al., 2005; Gaskell et al., 2004, 2005; Gorss and Lewenstein, 2005; Faber 2005; Stephens, 2005; Schummer 2004, 2005]. From these studies, mainly focussing on the USA and UK print media, the following general conclusions can be drawn:

- Media interest in nanotechnology has grown significantly since 1999. In 2003, it began to spread from the opinion-leading elite press to the general press, thus addressing a wider public.
- Media coverage of nanotechnology throughout the entire period analysed (1986 – 2004) is overwhelmingly positive. Though there are articles about nanotechnology risks that are clearly negative in tone, they are less prevalent.
- The media, in the majority of articles, present nanotechnology in terms of progress and economic prospects.

Media coverage of nanotechnology follows very similar pattern in terms of salience and framing, as was the case for biotechhology in its early stages. However, biotechnology was presented even more positive and progress-oriented, as nanotechnology is presented today. This might reflect a learning process ("avoid the same mistakes"), the current public climate which could be more sensitive to possible impacts of new technologies, or just an inherent feature of nanotechnology.

Since 2002, several surveys have been completed which aimed at elucidating the public's knowledge of and attitudes towards nanotechnology [Gaskell et al., 2004, 2005; Eurobarometer 224 and 225; The Royal Society & The Royal Academy of Engineering 2004; komm.passion GmbH 2004; Bainbridge 2002; Cobb and Macoubrie 2004; Cobb 2005; Sheetz et al., 2005; Scheufele and Lewenstein 2005; Lee et al., 2005]. All in all, the combined findings from the surveys show that the public's awareness of nanotechnology and their factual knowledge are very low. Nevertheless, in the absence of relevant scientific or policy-related information, people form opinions and make judgements about nanotechnology. Their opinions are currently influenced by factors other than factual and nanotechnology-specific information. Among these influencing factors are attitudes towards science and technology in general, scientific literacy, emotions, and cognitive shortcuts (e.g. personal predispositions, such as religion, ideology) and heuristics which are often provided by the mass media. Overall, benefits and positive emotions prevail, in particular expected benefits of nanotechnology relate

[18] This chapter is based on Work package 3 - Potential socio-economic impacts of medicinal nanobiotechnology applications, B. Hüsing and S. Gaisser, Fraunhofer Institute fore Systems and Innovation Research, 2005.

to medical progress, environmental protection and economic growth. Metaphors such as "grey goo" have not been taken up widely and significantly by the general public. Whether public perception will remain that positive depends strongly on the social and regulatory context in which nanotechnology is embedded.

Public workshops and focus groups are sources that give further information about genuinely considered beliefs of the public towards nanotechnology instead of (currently) uninformed opinions as via surveys [The Royal Society & The Royal Academy of Engineering, 2004; Macoubrie 2005, 2006; Meridian Institute 2005; Nanojury 2005; Kleinman and Powell 2005; Katz et al. 2005]. These activities addressed nanotechnologies in their entirety and have not been specifically devoted to nanomedicine. They took place mostly in the USA and the UK[19] with the following findings: All in all, assessments of nanotechnology are positive, and major benefits are anticipated, especially from health applications of nanotechnology. Aspects which are of concern for the layman are, among others, 1) how to deal with the inherent uncertainty regarding potential impacts and future developments, 2) low trust in governmental bodies as well as industry to take decisions for the benefit of the general population, 3) the potential risks of nanotechnology, particularly from nanoparticles, which the public believes should be proactively addressed. Against this background, there is a high demand by these groups for effective regulation and control. In addition, governance issues are stressed and transparency of and public involvement in technology decision-making are called for. Citizens' juries are an instrument for public engagement in decision-making. Up to now one citizens' jury took place in the EU, the NanoJury UK[20].

7.2 Non-Governmental Organisations – Involvement and Positions

At present only few non-governmental organisations (NGOs) have actively contributed to the public debate about nanotechnology. Greenpeace and the etc group have taken the most prominent and visible role in this debate [e.g. etc group 2003a, 2003b; Arnall, 2003; Parr 2005]. The majority of potentially affected NGOs in the field of nanomedicine are still in an earlier stage of engagement: while the importance and relevance of nanotechnology and its possible impacts are acknowledged, many NGOs still concentrate on monitoring developments in nanotechnology[21]. Noteworthy is the early and prominent engagement of insurance companies, documented by several studies and position papers [Munich Re Group 2002; Swiss Re 2004; Allianz and OECD 2005].

The etc group has gained public awareness after publishing the report "The Big Down. From Genomes to Atoms" [etc group, 2003b] that called for a moratorium on commercial production of nanomaterials. In contrast to the etc group, Greenpeace takes a much more balanced position. In the report "Future Technologies, Today's Choices -

[19] Additional dialogues will be performed in EU countries within recently started EU-funded projects, e.g. Nanologue (www.nanologue.net), Nanobio-RAISE (http://nanobio-raise.org/), and NanoDialogue (www.nanodialogue.org).

[20] http://www.nanojury.org/

[21] This relates mainly to consumer organisations, environmental organisations, civil society groups, and industry unions. No patient organisations was identified which had genuinely engaged in nanotechnology issues.

Nanotechnology, Artificial Intelligence and Robotics" [Arnall 2003] and subsequent publications [Arnall and Parr 2005; Parr, 2005], the potential of nanotechnology to be used for both, beneficial and detrimental purposes is acknowledged and a differentiated opinion is advocated, depending on the applications and taking the present uncertainties into account. Against this background, the process and the knowledge base, on which decisions about future trajectories of technology development are taken, are emphasised. There is a call for more research to investigate environmental and toxicological effects of nanoparticles and for upstream stakeholder and citizens' involvement in political decisions. As a consequence, Greenpeace UK has been one of the major initiators and supporters of the NanoJury UK. A moratorium is not supported by Greenpeace.

According to the experts interviewed, other NGOs, if monitoring nanotechnologies at all, have not yet formed or published an "official" opinion, but may be in the process of doing so. The publications and positions by the etc group and Greenpeace are used as a major input in this process.

7.3 Debate about Health and Environmental Impacts of Nanoparticles

In the last years, a debate about possible health and environmental risks of engineered nanoparticles has developed. It is mainly an expert debate in which the relevant professionals such as toxicologists as well as representatives from industry, regulatory and governmental bodies as well as insurance companies are involved, both on national as well as international (EU, OECD) levels. Consumer and environmental groups monitor the debate, but have not yet taken an active part in it.

According to the experts interviewed, there is consensus among the different players in both national as well as the international debate with respect to the following aspects:

- Acknowledgement of both chances and risks of nanotechnology,
- Need for action regarding standardisation, common nomenclature, and availability of reference materials,
- Need for further research into potential risks of nanoparticles and exposure along all stages of the life cycle of products including the development of suitable test systems.

However, different views prevail regarding the question whether and to what extent this requries regulation. Moreover, only few stakeholders know and reflect the interests of the other parties. In the following the main positions of the different stakeholders are summarised:

- **Industry:** The main interest is the development and commercial exploitation of new nanotechnology products and services. Product and process safety in relation to liability claims play an important role for investments in R&D. Existing regulatory regimes are deemed sufficient. Transparency is supported as long as protection of economically important know-how is guaranteed.
- **Governmental agencies** are in the process of defining their responsibilities and tasks with respect to nanoparticles and start developing strategies. They aim at supporting the further development of nanotechnology.

- **Environmental, consumer and civil society groups** aim at preventing or reducing risks for the environment, consumers and workers. They want to critically monitor the developments. They support the intensification of research into the identification and assessment of risks. Environmental and consumer groups aim at increasing the transparency for consumers and citizens and therefore support measures such as product labelling.
- **Academic scientists** see themselves as service providers in order to close knowledge gaps. Moreover, they hope for more research funding.
- **Unions and occupational health professionals** want to examine whether the existing precautionary and protective measures and regulations need amendment and adaptation.

8 Regulatory Issues[22]

In the EU, medicinal products and medical devices are not allowed to enter the market unless their compliance with regulatory requirements has been shown convincingly. For medical devices, the regulatory requirements are laid down in three European Directives: Directive on Medical Devices 93/42/EEC[23], Directive on Active Implantable Medical Devices 90/385/EEC[24], and Directive on In Vitro Diagnostic Medical Devices 98/79/EC[25]. For medicinal products, the Directive on Medicinal Products for Human Use 2001/83/EC[26] and the Directive on Clinical Trials on Medicinal Products for Human Use 2001/20/EC[27] apply.

Nanomedicine products are regulated as medicinal products or as medical devices and there is currently no specific regulatory framework for nanotechnology-based products neither in the EU nor in the USA. NDDS are always approved in combination with the drug they deliver and they are regulated as drugs because the delivery system interacts with the drug and can change its efficacy and safety profile. Some therapies in which nanoparticles have no direct therapeutic effect are regulated as medical devices. Examples are hyperthermia with iron nanoparticles or cell therapy using nanoparticles for cell sorting. Nanoparticle-based contrast agents that are administered intravenously, on the other hand, are regulated as drugs.

Additionally to the above-mentioned regulations, also principles of biomedical ethics require a careful balancing of the benefits of a medical intervention or diagnostic procedure with the risks, not only when placing such products on the market, but also in the research phase. This is especially important in the case of nanomedicine, because not all risks may be known or deducible from existing therapies. It cannot be ruled out that medical interventions based on nanotechnology could have unprecedented biological and adverse effects, which have not been encountered before due to the novelty of these interventions. This is due to the lack of knowledge regarding the behaviour of nanoparticles in the human body, due to the inherent properties of some drug delivery systems to move across biological barriers, if new therapeutic principles are to be established (e.g. gene therapy), and if complex systems which e.g. comprise biological, nanotechnological and IT components and/or for which not all relevant parameters of safety and quality can reasonably be tested beforehand (e.g. long-term effects, interference with other components or systems).

8.1 Toxicological Aspects

At present, possible health and environmental risks of nanoparticles are debated. In the directives which regulate market access for medicinal products and medical devices in the EU, a risk assessment and management is already required in order to obtain market approval. However, it may be challenging to carry out this assessment in practice,

[22] This chapter is based on Work package 2 - Challenges and drivers for medicinal nanobiotechnoloy and its impact on the medical sector, V. Wagner, VDI Technologiezentrum GmbH, 2005 and 2) Work package 3 - Potential socio-economic impacts of medicinal nanobiotechnology applications, B. Hüsing and S. Gaisser, Fraunhofer Institute for Systems and Innovation Research, 2005.
[23] Official Journal L 169 12/07/1993, p. 1-43
[24] Official Journal L 189, 20.7.1990, p. 17–36
[25] Official Journal L 331, 7.12.1998, p. 1–37
[26] Official Journal L 311 28/11/2001, p. 67-128
[27] Official Journal L 121, 1.5.2001, p. 34–44

because the required knowledge about the behaviour and biological effects of nanoparticles is presently too patchy and assessment schemes are not specifically tailored to assess nanoparticle-specific questions and might require amendment in order to take the specificities of nanotechnologies into account appropriately. A dedicated nanotoxicological risk assessment might be necesssary for novel nanomedicine products which should take into account

- The biological fate of nanoparticles inlcuding distribution, accumulation and metabolism,
- Medication-specific uptake routes related to the different routes of administration and the types of nanomaterials used,
- Possible side effects, caused by the interaction of nanoparticles with living matter or their transport across biological barriers [De Jong et al, 2005].

The SCENIHR[28] in its opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnlogies, came to the conclusion that appropriate and nano-specific test systems and assessment schemes still have to be developed. It also stated, that depending on results of future research on the toxicological potential of nanoparticles, regulation might need to be adapted [European Commission, 2006a]. This also implies the development of specific guidance documents at a European level for the safety evaluation of nanotechnology products applied in medical technology and the need for an appropriate labelling and safety sheets [De Jong et al., 2005].

With respect to the production process of nanomedicine products, new workplace standards might be required, taking into account the specific toxicological relevant properties of nanoparticles. Because classical toxicity testing does not account for nanoparticle specific properties it has been questioned whether nanoparticulate materials should fall within chemicals legislation, such as REACH[29] [European Commission, 2006a; The Royal Society & The Royal Academy of Engineering, 2004]. So far, the chemicals legislation does not have specific provisions or testing requirements for substances on a nanoscale. In March 2006, the European Commission's Directorate General Environment requested the SCENIHR to assess the current risk assessment methodology, as laid down in the Technical Guidance Documents of the chemicals legislation, to provide an opinion on their appropriateness and to make suggestions for improvements where appropriate[30]. The assessment is due at the end of 2006.

The European medicines Agency (EMEA) recently published a reflection paper on nanotechnology-based products for human use, outlining the currnet thinking and initiatives by EMEA related to nanotechnology. An Innovation Task Force was created that coordinates EMEA-wide scientific and regulatory competence for emerging therapies and technologies, including nanotechnology. EMEA encourages potential

[28] SCENIHR is the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks

[29] REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals, COM(2003) 644

[30] See European Commission, DG Health and Consumer Protection, Public Health, http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_q_008.pdf

applicants to contact the agency early on in the product development process [EMEA, 2006]. Also in the USA, the appropriateness of current legislation for nanotechnology is being discussed. Recently, the US Food and Drug Administration (FDA) set up an internal Nanotechnology Task Force to identify and recommend ways to address any existing knowledge or policy gaps with the aim to enable FDA to evaluate possible adverse health effefts of FDA-regulated nanotechnology products [FDA, 2006].

8.2 Classification of Nanomedicine products

"Borderline products" which do neither clearly fall into the scope of the medicinal products nor the medical devices regulation are known e.g. from the field of tissue engineering [Bock et al. 2003, 2005]. Nanotechnology-enabled products combining diagnostic and therpeutic activities, so-called theranostics (e.g. implantable drug delivery systems that release a certain amount of a drug according to specific body signals), or cell-free scaffolds for tissue regeneration, that release pharmaceutically active substances) could be difficult to categorise. Other cases could be nanotechnology-based cosmetic or functional food products with health claims. Against this background, "clearing house mechanisms" in regulatory authorities may be required in order to properly deal with such "borderline products" and which may involve nanotechnology in their manufacturing. However, the "borderline character" is inherent to these specific products, but is not specifically conveyed to them by nanotechnology.

8.3 Regulation versus innovation

Only if nanomedicine products are available and commercially viable, their potential health benefits can be realised. However, the higher the requirements to prove safety, quality, efficacy, and possibly also superiority over existing products and services in terms of costs or quality of life gains, the higher the barriers are for innovative products and services. Many of the more innovative NDDS and nanoparticle contrast agents focus on diseases that occur in comparatively small patient groups, e.g. brain or liver cancer. The regulatory requirements for these novel therapies are the same as for conventional drugs. According to experts, many novel therapeutic products based on NDDS will not enter the market simply because the costs for achieving regulatory approval are too high compared to expected sales. Other hurdles relate to the development of nanomedicine by relatively resource-poor SMEs, or the difficulty to prove superiority in certain characteristics, such as long-term effects (e.g. avoidance of frequent relapse). In the regulatory approval of medicinal products, provisions are established to reduce these barriers, e.g. the orphan drug regulation[31] granting market exclusivity for a duration 10 years for treatments for rare diseases, or according to the Directve for Medicinal Products, possibilities for reduced fees and administrative assistance for SMEs, or conditional marketing authorisations. It might be necessary to evaluate the performance and appropriateness of these provisions with respect to nanomedicine products.

Further, many experts anticipate that regulatory authorities might adapt the approval process for nanomedicine products due to safety concerns and e.g. request a more rigorous testing of the potential toxicity of nanoparticles. The ESF nanomedicine report

[31] Official Journal L 18, 22/01/2000, p. 1-5

[ESF, 2005] comes to the conclusion that with an increasing number of nanotechnology-based drugs there is also a need to review or define appropriate regulatory guidelines for each new class of nanomedicine products. It further states that there is a need for preclinical and clinical test standardisation and an evaluation of the environmental impact of these products in the context of academic research and industrial development. According to expert opinion a more vivid and close information exchange between the scientific community and the regulatory authorities would be helpful to reach soon clarification whether regulation needs to be adapted. This could start with an open exchange of views at conferences and workshops. European scientists also point to the USA where regulatory authorities join the discussion process earlier and also attend conferences and workshops more frequently than their European colleagues. Experts believe that many pharmaceutical companies will be cautious with investments in nanotechnology-based medicines as long as it remains unclear to which extent the regulatory framework will be adjusted for nanomedicine products. Once this point is clarified industry can take strategic decisions and decide which nanomedicine products might be economically viable under the specific regulatory regime. Experts also see two important issues that should be addressed by regulatory authorities with regards to nanomedicine products:

1) For nanotechnology-based drugs for small patient groups, scientists suggest the option of a conditional approval for drugs after clinical trial phase II so that they can be applied by trained experts to informed patients.

2) Particularly for nanoscale imaging agents experts suggest to create a regulatory framework that supports the development of nanoscale delivery platforms. They believe that in many cases where novel products are just combinations of an already approved delivery system and an approved contrast agent, the approval process should be less rigorous than for new substances. Such a procedure would reduce the development costs and make the development of nanoscale contrast agents economically more viable and interesting for the pharmaceutical industry.

8.4 Reimbursement

In most health care systems, reimbursement by statutory and private health insurances plays a major role for market access of medical products. Health economic assessments will play an increasingly important role in reimbursement decisions. Many experts also see price controls as an important parameter in nanomedicine commercialisation. In the USA prescription drug prices are largely unregulated. That differs from most other countries, where prices are regulated either directly through price controls (e. g. France and Italy) or indirectly through limits on reimbursement (e. g. Germany and Japan). Particularly for drug delivery systems that are likely to increase the cost of a drug, reimbursement regulation is an important issue. Whereas US companies see little problems getting their more expensive nanotechnology-enabled drugs placed on the US market, companies that focus on the European market have a competitive disadvantage and less incentives for investment in the costly development of NDDS. Particularly American experts interviewed for this study state that the more cost regulated European pharmaceutical markets are an important reason for the widening innovation gap between the European and American pharmaceutical markets.

9 Conclusions

In recent years nanomedicine has emerged as one of the most prominent application fields of nanotechnology, although publication-wise it currently accounts only for 5% of nanotechnology publications worldwide. It still is at an early stage development with few products on the market. Also the large share of start-up companies and SMEs (80%) within the companies worldwide that openly develop nanomedicine products reflects the early development stage of nanomedicine. However, not all large pharmaceutical and medical device companies make their engagement in nanomedicine R&D public.

Table 9.1 shows a qualitative comparison of key aspects of the different nanomedicine application fields that were covered in this study. The application fields are in different development stages regarding research activity, patenting and products.

Table 9.1 Qualitative comparison of nanomedicine applications in different medical sectors
(■■■■ = very high, ■■■ = high, ■■ = medium, ■ = low)
[a)] "Share of nanotechnology" assesses how much of the system actually consists of nanotechnology.
Source: VDI Technologiezentrum GmbH

	Drug Delivery	Drugs & Therapies	In vivo Imaging	In vitro Diagnostics	Bio-materials	Active Implants
Research activity	■■■■	■	■	■■	■■	■
Commercialisation efforts	■■■■	■■	■	■■■	■■	■
Development status	■■■	■■	■	■	■■	■
Target market	■■■■	■■■	■■	■■	■■	■
Importance of nanotechnology for the sector as a whole	■■■■	■■	■■■	■■■	■■■	■■
Share of nanotechnology [a)]	■■■■	■■■■	■■■	■■	■■	■
EU25 competitiveness, science	■■■■	■■■	■■■	■■■	■■■	■■■
EU25 competitiveness, commercialisation	■■	■■■	■■	■■■	■■■	■■■

Nanotechnology-based drug delivery is by far the most advanced field of nanomedicine. More than 50% of research activities and commercialisation efforts as well as companies are targeted at NDD. The importance of nanotechnology for drug delivery is expected to increase in the future: Two thirds of the experts surveyed in the NanoRoadMap project[32] agreed that nanotechnology will impact 25-50% of the drug

[32] NanoRoadMap is a FP6 project funded by the European Commission. Its main objective is to produce a long term (10 years) forecasting exercise aiming to highlight the applications of nanotechnology in three important industrial fields: Materials, health and medical services, and energy (www.nanoroadmap.it).

delivery market until 2015 [Hartwig, 2005]. One of the drivers is the extension of a drug's patent life cycle by a new drug delivery approach. Interestingly, Europe holds the leading position with regards to scientific output (37% of drug delivery publications compared to 30% of the USA), but has failed to translate this strength into products. This trend is documented by a lower number of patents than the USA (23% compared to 55%), less companies involved in developing nanotechnology-based drug delivery systems (23% compared 52%) and less products on the market (29% compared to 74%). The position of the EU is below average compared to other nanomedicine application fields, however, the NDDS field is the most advanced regarding commercialisation. In general, the USA accounts for higher shares of patents, companies, products on the market and in development (45-55%) compared to the EU (35%). One reason for this could be the more restricted private funding situation in Europe.

Nanotechnology-based drugs and therapies is probably the technology field that is most genuinely nanotechnolgy, as the therapies are based on the use of nanoparticles or nanoscale molecules. In all other sectors, nanotechnology has more of an enabling function. However, research activity is comparatively low and the impact of nanotechnology on the pharmaceutical sector as a whole will be small for the foreseeable future.

The use of nanotechnology for in vivo imaging is still in a very early development stage. Most of the engineered nanoparticle contrast agents are currently developed by US companies. For in vitro diagnostics nanotechnolgy plays mainly an enabling role and most of the sensor systems that are under development for clinical applications are considered microsystem technology. Implant materials are a further field in which research activity and commercialisation efforts of nanotechnology-based devices are still in a fairly early stage. Particularly the market for orthopaedic implants is very mature and leaves only little room for innovation. Nanotechnology is of least importance for active implants. If at all, nanotechnolgy will only be used for the improvement of certain components such as implant housings or electrode surfaces.

Within the EU, Germany, the UK and France are the countries with the highest research and commercial activity in nanomedicine. Noteworthy is the large difference between Germany, France and the UK regarding the number of patents in relation to publication numbers: France and the UK have much less patents than publications, whereas Germany has slightly more patents than publications.

Development and commercialisation of nanomedicine products is faced with a number of challenges:

- Pharmaceutical and medical device industry shows still a very moderate interest in this emerging technology. Start-ups currently pursue a plethora of ideas how to improve disease treatment and diagnosis with nanotechnology, but it seems to be difficult for them to find major pharmaceutical or medical device companies that licence their technology or partner with them to bring their novel nanomedicine products or diagnostic methods through the regulatory approval process.
- Due to safety concerns regarding nanoparticles, the need for new or adapted regulation is currently discussed in the EU but also worldwide. This seems to create uncertainty concerning future regulatory requirements and results in a current cautiousness by the companies regarding investments in nanotechnology.

- Nanotechnology-based diagnostics and therapies are expected to address smaller patient groups, due to targeting less frequent diseases (e.g. liver or brain cancer), risk patients (e.g. the anticancer drug pegylated liposomal doxorubicin is applied to patients suffering from cardiac diseases), and due to the possibility of targeting subtypes of diseases (e.g. cancer tissue exhibiting specific marker proteins). This follows the trend of "personalised medicine" which is currently discussed in the context of pharmacogenetic approaches[33]. Therapies are expected to be more focussed on specific patient groups, implying smaller markets and resulting in a challenge for the blockbuster business model, which is currently followed by the pharmaceutical industry. A similar issue exists for the diagnostics industry, as more specific diagnostic approaches also meet a smaller market which might lie well blow the estimated EUR 80 million market size that is deemed necessary to receive a positive return on investment for a new diagnostic test [Batchelder and Miller, 2006]. This dilemma can only be solved if development costs can be reduced [FDA, 2004]. Nanotechnology-based diagnostics could play a role in cost reduction by supporting the R&D process and the establishment of faster and safe regulatory approval protocols (e.g. real-time assessment of the efficacy of therapeutic regimens by in vivo molecular imaging, better patient stratification for clinical trials based on detection of also low levels of specific biomarkers [Ferrari, 2005; Ferrari nad Downing, 2005]).
- Already today there are some companies that have a strong patent portfolio and consequently broad claims for certain applications of nanomaterials. There is a risk, that broad claims on nanomaterials result in a monopol, as seen for Affymetrix and high density DNA chips.
- Nanotechnology applications in medicine include only few applications with breakthrough potential. Nanotechnology rather has the function of an enabling technology, which, however, has the potential of contributing considerably to meet medical needs and improved health care. However, the increasing cost pressure of health care systems will emphasise cost-effectiveness considerations in the future and might limit reimbursement. Currently, cost-effectiveness of nanomedicine products cannot be judged, as only few products are on the market and even fewer have been evaluated in this respect. Nevertheless, there are indications that nanomedicine approaches could result in cost-effective treatments with a potential to decrease health care costs, which to a significant extent are personnel costs.

It has been widely recognised that there is a need to address social and ethical issues of nanotechnology early in the process, involving the public in an informed and interdisciplinary debate. Additionally, these reflections should not be considered as an "add-on" but rather as an integral part of scientific-technological research and development. Initiatives to explore and discuss social and ethical issues of nanotechnology have only begun recently, and most of the initiatives focus on nanotechnology in general. Lately, initiatives targeting for example nanobiotechnology

[33] Pharmacogenetics is based on the observation that genetic factors can modify drug action. A prominent example is the breast cancer drug Herceptin for individuals which tumours overexpress the human epidermal growth factor receptor HER2. The drug use is linked to HER2 testing [The Royal Society, 2005].

have emerged, amongst other several EU-funded projects such Nano2Life, where an Ethics Board is analysing ethical issues relating e.g. to medical applications of nanobiotechnology and respective research projects, or NanoBioRAISE, a project aimed at involving the public in the discussion on ethical and social issues.

Many of the ethical and social issues raised in the context of nanotechnology and nanomedicine are not genuinely new, but known from other contexts (human enhancement – doping in sports, nanotechnology-based clinical diagnostics and monitoring – privacy and predictive diagnoses in genetic testing). However, nanotechnology might introduce a different or stronger emphasis on certain aspects. For example, the abundance of data that could be collected in the future through nanotechnology-based sensors facilitating continuous monitoring of the body, poses serious questions regarding data handling, data access, informational self-dertemination, and the “medicalisation” of life.

Social and ethical analyses of nanotechnologies also deal to a substantial extent with the potentially disruptive character of nanotechnology, among them also futuristic visions of nanotechnology-enabled autonomous systems capable of replication and of nanotechnology-enabled human enhancement (e.g. through "intelligent implants") which are seen as "unrealistic" by the scientific community in the foreseeable future. As a consequence, the challenge should be met by the ethics and social sciences in the coming years, and initiatives are already emerging, to complement the necessary analysis of the potential disruptive character of nanotechnologies by a differentiated view for nanomedicine where the majority of innovations "in the pipeline" will most likely not be disruptive and revolutionary (but could nevertheless have disruptive aspects), but will predominantly lead to stepwise and incremental innovations.

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Appendix

Methodology Applied

Nanomedicine R&D - Literature and Patents: Publications were searched in the Science Citation Index database, using discrete key words indicative for the Nanomedicine subtechnologies as they are presented and described in this report (see Box 12.1). Data is statistically analysed to retrieve rankings by country and number of publications per year. The patent search was conducted by the European Patent Office using the EPODOC database which covers patents worldwide. Nanomedicine patents were identified with a combined key-word and patent classification search. A crosscheck of the publication and patent analysis for this report with publicly available bibliometric and patent data in the field of nanobiotechnology show reasonable consistency, so that we are confident that the patent and literature data in this report is conclusive.

Box 1 Search fields and terms for literature and patent search

Drug Delivery:

Liposomes
Polymeric Drugs
Drug Polymer Conjugate
Protein Polymer Conjugate
Pegylated Proteins
Nanoparticles
Nanocapsules
Nanosuspensions
Nanocrystals
Solid lipid nanoparticles
Dendrimers
Gold nanoparticles
Colloidal gold
Silicate nanoparticles
Calcium nanoparticles
Biosilicon
Titanium dioxide nanoparticles

Drugs and Therapy

Fullerene drugs
Dendrimer drugs
Nanoshells and phototherapy and hypothermal therapy
Magnetic nanoparticles and hyperthermal therapy

In vivo Imaging

Superparamagnetic iron oxide
Ultrasmall superparamagnetic iron oxide
Monocristalline iron oxide nanoparticles
Cross-linked iron oxide nanoparticles
Liposome and ultrasound
Nanoparticles and nuclear imaging
Nanoparticels and optical imaging
Nanoshells and optical imaging
Quantum dots and optical imaging

Medical Biosensors

Surface plasmon resonance
Cantilever biochips
DNA Chips and electrical detection
Nanoarrays
Quantum dots and diagnostics
Gold nanoparticles and diagnostics
Magnetic nanoparticles and diagnostics

Biomaterials

Bone cements and nanostructures
Dental implants and nanocomposites
Orthopedic implants and nanostructures
Cardiovascular implants and nanostructures
Tissue engineering and nanostructures
Silver nanoparticles and implants and wound dressings

Intelligent Implants/ Neural Prothesis

Electronic drug delivery systems and nanotechnology
Neural prothesis and nanotechnology

Cosmetics

Sunscreens and nanoparticles
Nanoparticles
Nanocapsules
Lipid nanoparticles
Liposomes

Structure of the Industry: The analysis of industrial development of Nanomedicine is based on expert interviews and the collected bibliometric and business information. 46 questionnaire guided interviews were conducted with leading experts from academia and industry. The interview partners were either professors or group leaders at universities (30 %) or management staff of companies (44 %) or start-ups (26 %). 52 % of the interviews were conducted with European experts, 33 % with experts based in the USA and 15 % of the interviewees came from other countries such as Australia, Canada and Israel.

Companies, Products and Market Data: The most direct strategy to identify companies that produce a certain class of products are searches in company and product databases, that cover business activities worldwide. Unfortunately, in the case of nanomedicine, this is not a feasible strategy as the product classification schemes in these databases do not include nanotechnology or nanomedicine products. Therefore, currently it is not possible to get a complete survey of business activity in the field of nanomedicine by the usage of business databases.
In order to compile a list with companies worldwide that work in the field of nanomedicine other sources than business databases were analysed for this report such as: business reports, various internet data bases and fora, including Nanovip and Nanoforum, patent data and interviews with experts. With this strategy we expect to cover about two third of the business activities in the field of nanomedicine. Data on products on the market and in clinical trials was retrieved by analysing review papers and business press. Further, expert interviews and searches in the Pharmaproject database provided valuable information. Sales numbers for products were taken from business press, company reports, and business databases or are estimates based on experts interviews. Comprehensive lists of nanomedicine products on the market and nanomedicine companies can be found in the appendix. Foreign currencies are calculated into Euro taking the following exchange rates:

1 USD = 0.772 EUR
1 GBP = 1.47 EUR
1 RS = 0.0177 EUR
1 FRF = 0.156 EUR
1 CHF = 0.661 EUR
1 GBP = 1.477 EUR

Methodology Chapter 5

Literature Review: To identify cost effectiveness, cost benefit studies and general cost analyses in the field of nanobiotechnological applications literature searches were carried out in the MEDLINE database, in the Scopus database, in the Cochrane Library, the NHS Centre for Reviews and Dissemination Database (NHS CRD), and the database of the German Agency for HTA.
In MEDLINE, a total of 717 articles were identified. Because this number was too high to be scanned manually, only the most recent articles, published between 2000 and 2005, were analysed (346 articles). In the Cochrane Library 167 articles had to be

scanned manually. After reviewing the abstracts, 23 articles from MEDLINE, 10 from the Cochrane Library and a few from the other sources were analysed in depth. 10 articles dealt with pegylated liposomal doxorubicin, six with liposomal amphotericin B, 10 articles dealt with other cases, especially drug delivery and microarrays. The two cases with a significant number of detailed publications (pegylated liposomal doxorubicin, liposomal amphotericin B) were chosen as case studies, the results of the remaining publications were integrated in the overall description of the indications.

Expert interviews: In order to validate the results from our literature analysis, 25 experts with a health economy background from 10 European countries were chosen to comment on the results of the literature survey. Addressing the experts via email and personal communication, they were asked to comment on the results of the German analysis as presented by Farkas et al. 2004, on the results of the literature analysis and to compare the described effects with their national situation and personal assessment of the European situation. Helpful comments were received from four experts from the Netherlands, Switzerland, Ireland and Italy. Seven did not feel competent to answer the questions, four were under time restrictions that hindered them to answer, 10 did not at all reply to the questionnaire. The poor response rate shows the difficulty in gathering health economic data in the very early stage of development in which Nanotechnology in the medical sector still is.

Methodology Chapter 6

As an emerging technology, the discussion about social and ethical issues in the context of Nanotechnology is just emerging. Reports that focus on ethical issues do not yet discuss single application fields of Nanotechnology, such as Nanomedicine. A further difficulty is, that a definition of Nanomeidicine has just been emerging over the past couples of years and it becomes clear that Nanomedicine is largely an enabling technology that is more part of than driver of trends in medicine. We have analysed reports covering ethical issues of Nanotechnology and extracted those issues that are of relevance for Nanomedicine. Reports analysed include Paschen et al. 2003; The Royal Society & The Royal Academy of Engineering 2004; Malsch et al. 2004; Wood et al. 2005; Türk et al. 2005a and Türk et al. 2005b. A further source of information are interviews conducted with 13 interview partners from NGOs, Unions, environmental and health administrations, insurances and consumer associations.

Research and Commercialisation Efforts in Nanomedicine

	Publications (cumulative until 2004)	Publications %	Patents (1993-2003)	Patents%	Companies	Companies %	Products	Products %
Drug Delivery	6332	76.3	5884	58.8	113	56.5	23	60.5
Drugs & Therapies	150	1.8	342	3.4	7	3.5	0	0.0
In vivo Imaging	352	4.2	1267	12.7	11	5.5	3	7.9
In vitro Diagnostics	915	11.0	1400	14.0	33	16.5	2	5.3
Implants	487	5.9	801	8.0	30	15	9	23.7
Active Implants	52	0.6	319	3.2	6	3.0	1	2.6
Sum	8288	100	10013	100	200	100	38	100

	Products in Pipeline	Products in Pipeline %	Market Nanomedicine 2004, Billion €	Market %
Drug Delivery	98	61.9	4.2	77.7
Drugs & Therapies	7	4.5	0	0.0
In vivo Imaging	8	5.8	0.015	0.2
In vitro Diagnostics	30	18.7	0.6	11.3
Implants	9	5.8	0.05	0.9
Active Implants	5	3.2	0.5	9.9
Sum	157	100	5.4	100

Nanomedicine Products on the Market.

NA means that information is not publicly available. Sales numbers for many products were estimated based on information from experts and companies and can not be shown owing to data confidentiality. However estimates of total sales for Nanotechnology based products in the different medical sectors are calculated based on this information (see Tab 3.3).

Therapeutic agent/Medical Device	Nanotechnology component	Indication	Company	Country	Sales 2003/2004 million $	Medical Sector	Available in at least one EU25 country
Drug Delivery							
Abelcet	Liposomes	Fungal infections	Enzon	USA	58	Drug Delivery	Yes
Ambisome,	Liposomes	Fungal infections	Gilead, Fujisawa	USA/Japan	212	Drug Delivery	Yes
Amphotec, Amphocil	Liposome	Invasive pulmonary infection	InterMune	Australia	NA	Drug Delivery	Yes
DepoCyt	Liposomes	Cancer	SkyePharma, Enzon	UK/USA	5	Drug Delivery	Yes
Doxil/Caelyx	Liposomes	Cancer (Kaposi's sarcoma, Ovarian)	ALZA, Schering Plough	USA	145	Drug Delivery	Yes
Daunoxome	Liposomes	Cancer (Kaposi's sarcoma)	Gilead	USA	2	Drug Delivery	Yes
Epaxal Berna	Liposomes	Vaccine against Hepatitis A	Berna Biotech AG	Switzerland	NA	Drug Delivery	Yes
Estrasorb	Liposomes	Hormone Therapy	Novavax	USA	2	Drug Delivery	N.A
Inflexal Berna	Liposomes	Vaccine against Influenca	Berna Biotech AG	Switzerland	NA	Drug Delivery	Yes
Myocet	Liposomes	Cancer (Breast)	Elan	Ireland	NA	Drug Delivery	Yes
Visudyne	Liposomes	Wet macular degeneration in conjuction with laser treatment	QLT, Novartis	Canada/ Switzerland	445	Drug Delivery	Yes
Adagen	Polymer-Protein Conjugate	Immunodeficiency disease	Enzon	USA	16	Drug Delivery	N.A.
Macugen	Pegylated-Aptamer	Age-related macular degeneration (eye diseases)	Eye Tech Pharmaceuticals, Pfizer	USA	Approval End 2004	Drug Delivery	No
Neulasta	Polymer-Protein Conjugate	Febrile Neutropenia	Amgen	USA	1600	Drug Delivery	Yes
PEGASYS	Polymer-Protein Conjugate	Hepatitis C	Hoffmann-La Roche,	Switzerlan/ USAd	1000	Drug Delivery	Yes

Therapeutic agent/Medical Device	Nanotechnology component	Indication	Company	Country	Sales 2003/2004 million $	Medical Sector	Available in at least one EU25 country
			Nektar				
PEG-Intron	Polymer-Protein Conjugate	Hepatitis C	Enzon, Schering-Plough	USA	570	Drug Delivery	Yes
Oncaspar	Polymer-Protein Conjugate	Leukemia	Enzon, Sanofi-Aventis	USA/ France	8	Drug Delivery	Yes
Somavert	Polymer-Protein Conjugate	Acromegaly	Nektar, Pfizer	USA	5	Drug Delivery	Yes
Copaxone	Polymeric Drug	Multiple Sclerosis	TEVA Pharmaceuticals	Israel	940	Drug Delivery	Yes
Renagel	Polymeric Drug	Kidney Failure	Genzyme	USA	350	Drug Delivery	Yes
Rapamune	Nanosuspensions	Immunosuppressant	Elan/Wyeth	Ireland/USA	240	Drug Delivery	Yes
Emend	Nanosuspension	Anti-emetic	Elan/Merck & Co., Inc	Ireland/USA	29	Drug Delivery	Yes
Abraxane (ABI-007)	Nanoparticle (Albumin)	Cancer	American Pharmaceutical	USA	23	Drug Delivery	No
Imaging							
Feridex/Endorem	Iron Nanoparticles	Liver tumors	Advanced Magnetics/Guerbet	USA/France	NA	Imaging	Yes
Gastromark/Lumirem	Iron Nanoparticles	Abdominal diseases	Advanced Magnetics/Guerbet	USA/France	NA	Imaging	Yes
Resovist (Ferucarbotran)	Iron Nanoparticles	Liver tumors	Schering	Germany	NA	Imaging	Yes
In vitro Diagnostics							
cellsave/celltracks	Magnetic nanoparticles and instrumentation	Clinical cell separation	Immunicon	USA	NA	IVD	N.A.
CliniMacs	Magnetic nanoparticles and instrumentation	Clinical cell separation	Milenyi Biotec	Germany	NA	IVD	Yes
Colloidal Gold	Gold nanoparticles for lateral flow tests	e. g. pregnancy	British Biocell	UK	NA	IVD	Yes
Collloidal Gold	Gold nanoparticles for	e. g. pregnancy	Amersham	UK	NA	IVD	Yes

Therapeutic agent/Medical Device	Nanotechnology component	Indication	Company	Country	Sales 2003/2004 million $	Medical Sector	Available in at least one EU25 country
	lateral flow tests						
Colloidal Gold	Gold nanoparticles for lateral flow tests	Alzheimer	Nymox	USA	NA	IVD	N.A.
Dynabeads	Magnetic nanoparticles	Clinical cell separation	Dynal/Invitrogen	Norway/USA	NA	IVD	Yes
Biomaterials							
Acticoat (TM)	Silver Nanoparticle based wound dressing	Antimicrobial wound care	Nucryst	USA	25	Implants	Yes
Ceram X duo	Nanoceramic restorative	Dentistry	Dentsply	UK	NA	Implants	Yes
Filtek Supreme	Nanocomposite dental restorative	Dentristy	3M Espe	Germany/ USA	NA	Implants	Yes
Mondial	Nanoparticle containing dental prosthesis	Dentistry	Heraeus Kulzer	Germany	NA	Implants	Yes
Ostim	Nano-hydroxyapatite	Bone defects	Osartis	Germany	NA	Implants	Yes
PerOssal	Nano-hydroxyapatite based bone substitute	bone defects	Coripharm	Germany	NA	Implants	Yes
Premise	Nanocomposite dental restorative	Dentistry	Sybron Dental Specialities	USA	4	Implants	N.A.
Tetric EvoCeram	Nanocomposite denta restorative	Dentistry	Ivoclar Vivadent	Liechtenstein	NA	Implants	Yes
Vitoss	Nano-hydroxyapatite	Bone defects	Orthovita	USA	7.8	Implants	Yes
Active Implants							
Fractal Electrodes	Fractale electrodes for pacemaker	Heart failure	Biotronik	Germany	NA	Active Implants	Yes
Cosmetics (Examples)							
Capture	Liposomes	Anti-Aging	Christian Dior	Frnace	NA	Cosmetics	Yes
Dermo-Expertise	Liposomes	Anti-Aging	L'Oreal	France	NA	Cosmetics	Yes
Hydra Zen	Liposomes	Anti-Aging	L'Oreal	France	NA	Cosmetics	Yes
Hydrazone	Liposomes	Anti-Aging	Guinot	France	NA	Cosmetics	Yes
Liftosome	Liposomes	Anti-Aging	Guinot	France	NA	Cosmetics	Yes
Liposome Lotion	Liposomes	Anti-Aging	Cali	USA	NA	Cosmetics	Yes
Nanobase	Solid Lipid Nanoparticles	Moisturiser	Astellas	Japan	NA	Cosmetics	N.A.

Therapeutic agent/Medical Device	Nanotechnology component	Indication	Company	Country	Sales 2003/2004 million $	Medical Sector	Available in at least one EU25 country
			(Yamanouchi)				
Plentitude	Nanocapsules	Anti-Aging	L'Oreal	France	NA	Cosmetics	Yes
Primordiale Intense Eye	Nanocapsules	Anti-Aging	L'Oreal	France	NA	Cosmetics	Yes
Re-Surface	Nanocapsules	Anti-Aging	L'Oreal	France	NA	Cosmetics	Yes
Extra Protective	TiO2, ZnO	Sunscreen	Beiersdorf	Germany	NA	Cosmetics	N.A.
Sun Age Defence	TiO2	Sunscreen	Beiersdorf	Germany	NA	Cosmetics	N.A.
Sunblock SPF 15	TiO2	Sunscreen	Pevonia Botanica	USA	NA	Cosmetics	N.A.
Suncare	TiO2	Sunscreen	Cellex-C	Canada	NA	Cosmetics	N.A.
Ti.Silc SPF45	TiO2	Sunscreen	Sheer	Spain	NA	Cosmetics	N.A.

Companies with Nanomedicine Activities

Explanation of abbreviation and categories:
1) Company size: Start-ups = spin-offs from universities or companies; SME = companies with less than 500 employees mostly profitable at least mature status of product development; Corporation = companies with more than 500 employees.
2) Development status of most advanced Nanotechnology enhanced product: M = Market, CP = Clinical Phase, PC = Preclinical Phase, Dev = Development status for sensors
3) Nanomedicine involvement: Core = company focuses on Nanomedicine applications, Partly = company pursues several business segments including Nanomedicine, Peripheral = Company has minor activities in the field of Nanomedicine that are of little or peripheral importance for its business activities
4) IVD = In vitro Diagnostics, NA= Not available

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Drug Delivery								
Access Pharmaceuticals	Dallas, TX	USA	Start-up	Drug Delivery	Polymer-Drug Conjugates	CP	Partly	Drug Delivery
Activery	Barcelona	Spain	Start-up	Drug Delivery	Development of nanostructured DDS	NN	Core	Drug Delivery
Acusphere	Watertown, MA	USA	Start-up	Speciality Pharmaceuticals	Drug Nanoparticles	CP	Partly	Drug Delivery
Advanced Magnetics	Cambridge, MA	USA	SME	Biopharmaceuticals	Iron Nanoparticles	M	Core	Drug Delivery
Alnis Biosciences	Emeryville, CA	USA	Start-up	Biopharmaceuticals	Polymer Nanoparticles	NN	Core	Drug Delivery
Altair	Reno, NV	USA	Start-up	Nanotechnology	Inorganic Nanoparticles	PC	Partly	Drug Delivery
ALZA	Mountain View, CA	USA	Corporation	Drug Delivery	Liposomes, Doxil, Caelyx	M	Partly	Drug Delivery
American Pharmaceutical Partners	Los Angeles	USA	Corporation	Pharmaceuticals	Nanoparticles, Nanosuspensions	M	Partly	Drug Delivery
Amgen	Thousand Oaks, CA	USA	Corporation	Biopharmaceuticals	Liposomes	CP	Peripheral	Drug Delivery
Anosys	Evry Cedex	Fr / USA	Start-up	Biopharmaceuticals	Dexoxomes, Vaccines	CP	Core	Drug Delivery
Antigenics	New York	USA	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Aphios	Woburn	USA	SME	Biopharmaceuticals	Polymer Nanospheres	NN	Partly	Drug Delivery
Baxter	Deerfield, IL	USA	Corporation	Pharmaceuticals, Medical Products	Nanosuspensions	CP	Peripheral	Drug Delivery
Bayer Healthcare	Lerverkusen	Germany	Corporation	Pharmaceuticals	Liposomes	CP	Peripheral	Drug Delivery
Berna Biotech AG	Bern	Switzerland	Corporation	Biopharmaceuticals	Liposomes	M	Partly	Drug Delivery
Bioalliance Pharma	Paris	France	Start-up	Biopharmaceuticals	Polymer Nanoparticles	CP	Partly	Drug Delivery
Biodelivery Sciences	Newark, NJ	USA	Start-up	Speciality Biopharmaceuticals	Phospholipid Nanotubes	NN	Partly	Drug Delivery
Biofontera	Lerverkusen	Germany	Start-up	Speciality Pharmaceuticals	Nanocolloids, Phototherapy	CP	Partly	Drug Delivery
Biomira	Edmonton	Canada	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery
Biosante	Lincolnshire, IL	USA	Start-up	Biopharmaceuticals	Nanosuspensions, Inorganic Nanoparticles	CP	Partly	Drug Delivery
Callisto Pharmaceuticals	New York	USA	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery
Capsulution	Berlin	Germany	Start-up	Polymer Capsules	Polymer Nanocapsules	NN	Core	Drug Delivery
Cell Therapeutics	Seattle	USA	SME	Pharmaceuticals	Polymer-Drug Conjugates	CP	Partly	Drug Delivery
Celltech	Slough	UK	Corporation	Biopharmaceuticals	Polymer-Protein Conjugates	CP	Peripheral	Drug Delivery
Celmed	Saint-Laurent	Canada	SME	Biopharmaceuticals	Drug Nanoparticles	CP	Partly	Drug Delivery
Celsion	Columbi, MD	USA	Start-up	Pharmaceuticals, Medical Equipment	Liposomes	CP	Partly	Drug Delivery
Chugai	Tokyo	Japan	Corporation	Pharmaceuticals	Liposomes	CP	Peripheral	Drug Delivery
Copernicus Therapeutics	Cleveland	USA	SME	Biopharmaceuticals	Gene delivery with liposomes	NN	Partly	Drug Delivery
CritiTech	Lawrence, KN	USA	Start-up	Drug Delivery	Submicron drug nanoparticles	NN	Core	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Cytimmune	Rockville, MD	USA	Start-up	Biotechnology, DDS	Gold Nanoparticles	NN	Core	Drug Delivery
Cytokine PharmaSciences	King of Prussia, PA	USA	Start-up	Biopharmaceuticals, DDs	Nanosuspensions	PC	Partly	Drug Delivery
Dabur Pharma	New Delhi	India	SME	Pharmaceuticals	Polymeric Micelles	CP	Partly	Drug Delivery
Daiichi Pharmaceutical	Tokyo	Japan	Corporation	Pharmaceuticals	Liposomes	NN	Peripheral	Drug Delivery
Delex Therapeutics	Mississauga	Canada	Start-up	Biopharmaceuticals, DDS	Liposomes	CP	Partly	Drug Delivery
Dendritic Nanotechnologies	Mount Pleasant, MI	USA	Start-up	Nanotechnology	Dendrimers	PC	Partly	Drug Delivery
Do-Coop Technologies	Or-Yehuda	Israel	Start-up	Life Sciences	Hydrated Nanoparticles	NN	Core	Drug Delivery
Eiffel Technologies	North Ryde	Australia	SME	Drug Delivery	Drug Nanoparticles	NN	Partly	Drug Delivery
Elan	Dublin	Ireland	Corporation	Pharmaceuticals / Biotechnology	Liposomes, Nanosuspensions	M	Partly	Drug Delivery
Endovasc	Montomery, AL	USA	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery
Enzon	Bridgewater, NJ	USA	SME	Biopharmaceuticals	Liposomes, Polymer-Drug Conjugates	M	Partly	Drug Delivery
Esteve	Barcelona	Spain	Corporation	Pharmaceuticals/Chemicals	Polymer Nanoparticles	PC	peripheral	Drug Delivery
Eurand	Milan	Italy	SME	Drug Delivery	Polymer-Drug Conjugates	NN	Partly	Drug Delivery
EyeTech Pharmaceutical	New York	USA	Start-up	Biopharmaceuticals	Polymer-Aptamer Conjugates	CP	Partly	Drug Delivery
Flamel	Venissieux	France	SME	Biotechnology, DDS	Poly-aminoacid Nanoparticles	CP	Partly	Drug Delivery
Fujisawa	Osaka	Japan	Corporation	Pharmaceuticals	Liposomes	M	Peripheral	Drug Delivery
Genzyme	Cambridge, MA	USA	Corporation	Biotechnology	Polymeric Drugs	M	Peripheral	Drug Delivery
Gilead	Foster City, CA	USA	Corporation	Biopharmaceuticals	Liposomes	M	Peripheral	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Hoffmann-La Roche	Basel	Switzerland	Corporation	Pharmaceuticals	Polymer-Protein Conjugates	M	Peripheral	Drug Delivery
IDEA	München	Germany	Start-up	Biopharmaceuticals	Transfersomes	CP	Core	Drug Delivery
INEX Pharmaceuticals Corp	Burnaby	Canada	SME	Drug Delivery	Liposomes	CP	Core	Drug Delivery
Insert Therapeutics	Pasadena, CA	USA	SME	Drug Delivery	Polymer-Drug Conjugates	NN	Core	Drug Delivery
Intermune	Brisbane	Australia	SME	Biopharmaceuticals	Liposomes	M	Partly	Drug Delivery
Intradigm	Rockville, MD	USA	Start-up	SiRNA Therapeutics	Synthetic Nanoparticles	PC	Partly	Drug Delivery
Introgen	Austin, TX	USA	SME	Biopharmaceuticals	Nanoparticle DDS	CP	Partly	Drug Delivery
Labopharm	Laval, Quebec	Canada	SME	Speciality Pharmaceuticals	Polymer Micelles	PC	Partly	Drug Delivery
LiPlasome Pharma	Lyngby	Denmark	SME	Biotechnology, DDS	Lipid Based Nanocarriers	PC	Core	Drug Delivery
Liquids Research Limited	Bangor	UK	SME	Ferrofluids	Magnetic nanoparticles as DDS	NN	Partly	Drug Delivery
MaganMedics	Aachen	Germany	Start-up	Speciality Pharmaceuticals	Iron Nanoparticles	PC	Partly	Drug Delivery
MAP Pharmaceuticals	Mountain View, CA	USA	Start-up	Drug Delivery	Nanoparticle DDS	CP	Partly	Drug Delivery
Medigene	Martinsried, San Diego	Ger/USA	SME	Biotechnology	Liposomes	CP	Partly	Drug Delivery
Medinova (Nanopharm)	Magdeburg	Germany	Start-up	Pharmaceutical Technology	Polymer Nanoparticles	PC	Core	Drug Delivery
Meiji Seika Kaisha (Tedec Meiji)	Tokyo	Japan	Corporation	Pharmaceuticals, Food, Consumer	Liposomes	CP	Peripheral	Drug Delivery
Merck & Co Inc.	Whitehouse Station, NJ	USA	Corporation	Pharmaceuticals	Nanosuspensions	M	Peripheral	Drug Delivery
Merck KGaA	Darmstadt	Germany	Corporation	Speciality Chemicals,	Liposomes	CP	Peripheral	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
				Pharmaceuticals				
Mountain View Pharmaceuticals	Menlo Park, CA	USA	SME	Biopharmaceuticals, DDS	Polymer-Drug/Protein Conjugates	CP	Core	Drug Delivery
Nanobio Corp.	Ann Arbor	USA	Start-up	Biopharmaceuticals	Nanoemulsions	CP	Core	Drug Delivery
Nanobiomagnetics	Edmond, OK	USA	Start-up	Nanobiotechnology	Magnetic Nanospheres	PC	Core	Drug Delivery
Nanocarrier	Chiba	Japan	Start-up	Drug Delivery	Polymer-Micelles	CP	Core	Drug Delivery
Nanocure	Ann Arbor	USA	Start-up	Biopharmaceuticals, DDS	Dendrimers	PC	Core	Drug Delivery
NanoCyte Inc.	Jordan Valley	Israel	Start-up	Biotechnology	Nanotubes	NN	Partly	Drug Delivery
Nanodel	Magdeburg	Germany	Start-up	Drug Delivery	Polymeric nanoparticles DDS	NN	Core	Drug Delivery
Nanomed Pharmaceuticals	Kalamazoo, MI	USA	Start-up	Drug Delivery	Nanoparticles, Nanotemplate Engineering	NN	Core	Drug Delivery
NanoMedica	Newark	USA	Start-up	Speciality Pharmaceuticals	Nanoscale DDS	NN	Core	Drug Delivery
Nanopharmacology	Plymouth, MN	USA	Start-up	Nanomedicine	Nanoshells	PC	Core	Drug Delivery
Nanotherapeutics	Alachua, FL	USA	Start-up	Nanomedicine	Nanosuspensions	NN	Core	Drug Delivery
Nektar	San Carlos, CA	USA	Corporation	Drug Delivery	Polymer-Protein Conjugates	M	Partly	Drug Delivery
Neopharm	Lake Forest, IL	USA	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery
Nippon Kayaku	Tokyo	Japan	Corporation	Chemicals/Pharmaceuticals	Polymeric Micelles	CP	Peripheral	Drug Delivery
Nippon Oils & Fats	Tokyo	Japan	SME	Chemicals	Liposomes	NN	Partly	Drug Delivery
Nippon Shinyaku	Kyoto	Japan	Corporation	Pharmaceuticals	Gene delivery with lipoplexes	NN	Peripheral	Drug Delivery
Nobex	Research Triangle Park	USA	Start-up	Drug Delivery	Polymer-Protein Conjugates	CP	Partly	Drug Delivery
Novagali	Evry	France	Start-up	Drug Delivery/Drug Development	Cationic Emulsions	CP	Core	Drug delivery
Novartis	Basel	Switzerland	Corporation	Pharmaceuticals	Liposomes	M	Peripheral	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Novavax	Malvern, PA	USA	SME	Biopharmaceuticals	Micellar Nanoparticles	M	Partly	Drug Delivery
Novosom	Halle	Germany	SME	Liposomes	Liposomes	NN	Core	Drug Delivery
Nucryst	Wakefield, MA	USA	Start-up	Pharmaceuticals	Nanosuspensions	CP	Partly	Drug Delivery
OSI Pharmaceuticals	Melville, NY	USA	SME	Biopharmaceuticals	Liposomes	CP	Partly	Drug Delivery
OZ Biosciences	Marseille	France	Start-up	Drug Delivery	Magnetic nanoparticles for transfection	M	Core	Drug Delivery
PAR Pharmaceuticals	Spring Valley, NY	USA	Corporation	Generic Pharmaceuticals	Nanocrystal	CP/ M	Peripheral	Drug Delivery
Pfizer	New York	USA	Corporation	Pharmaceuticals	Polymer-Protein Conjugates	M	Peripheral	Drug Delivery
Pharmasol	Berlin	Germany	Start-up	Drug Delivery	Nanosuspensions	CP	Core	Drug Delivery
Phoenix Pharmacologics	Lexington, KY	USA	SME	Biopharmaceuticals	Polymer-Protein Conjugates	CP	Core	Drug Delivery
pSivida	Perth	Australia/UK	Start-up	Biopharmaceuticals	BioSilicon, Nanopores	CP	Core	Drug Delivery
QLT	Vancouver	Canada	SME	Biopharmaceuticals	Liposomes	M	Partly	Drug Delivery
Regeneron Pharmaceuticals	Tarrytown, NY	USA	Corporation	Biopharmaceuticals	Polymer-Protein Conjugates	CP	Partly	Drug Delivery
Sanofi-Aventis	Strasbourg	France	Corporation	Pharmaceuticals	Polymer-Protein Conjugates, Nanosuspensions	NN	Peripheral	Drug Delivery
Savient Pharmaceuticals	East Brunswick, NJ	USA	SME	Speciality Pharmaceuticals	Polymer-Protein Conjugates	CP	Partly	Drug Delivery
Schering Plough	Kenilworth, NJ	USA	Corporation	Pharmaceuticals	Liposomes, Polymer-Protein Conjugates	M	Peripheral	Drug Delivery
Shire Pharmaceuticals	Basingstoke	UK	Corporation	Pharmaceuticals	Inorganic Nanoparticles	CP	Peripheral	Drug Delivery

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
SkyePharma	London	UK	SME	Drug Delivery	Liposomes, Nanosuspensions	M	Partly	Drug Delivery
Soliqs	Ludwigshafen	Germany	SME	Drug Delivery	Nanosuspensions	NN	Partly	Drug Delivery
Solubest	Ness Ziona	Israel	Start-up	Drug Delivery	Polymer Nanoparticles	NN	Core	Drug Delivery
Spherics	Lincoln, RI	USA	Start-up	Drug Delivery	Polymer Nanospheres	NN	Partly	Drug Delivery
Supergen	Dublin, CA	USA	SME	Pharmaceuticals	Nanosuspensions	CP	Partly	Drug Delivery
Supratek	Dorval, Quebec	Canada	Start-up	Drug Delivery	Polymer Micelles	CP	Partly	Drug Delivery
Terumo	Tokyo	Japan	Corporation	Medical Devices, Pharmaceuticals	Liposomes	NN	Peripheral	Drug Delivery
Teva Pharmaceutical Industries	Petach Tikva	Israel	Corporation	Healthcare, Pharmaceuticals	Polymeric Drugs	M	Peripheral	Drug Delivery
Transave	Monmouth, NJ	USA	SME	Biotechnology	Gene delivery with liposomes	NN	Partly	Drug Delivery
Transgenex Nanobiotech	Tampa, FL	USA	Start-up	Nanomedicine	Polymer Nanoparticles	PC	Core	Drug Delivery
Valentis	Burlingame, CA	USA	SME	Biotechnology	Gene delivery with cationic lipids	NN	Partly	Drug Delivery
Wyeth-Ayerst	Madison, NJ	USA	Corporation	Pharmaceuticals	Nanosuspensions	M	Peripheral	Drug Delivery
Xstalbio	Glasgow	UK	Start-up	Advanced Drug Delivery	Nanostructured DDS	NN	Core	Drug Delivery
Zilip-Pharma	Amsterdam	The Netherlands	Start-up	Biotechnology	Liposomes	CP	Core	Drug Delivery
Drugs & Therapies								
C Sixty	Houston, TX	USA	Start-up	Nanomedicine	Fullere Drugs and DDS	PC	Core	Drugs/Therapies
ImaRx	Tucson, AZ	USA	Start-up	Nanomedicine	Lipid Nanospheres	CP/ M	Core	Drugs/Therapies
Magforce Nanotechnologies	Berlin	Germany	Start-up	Nanotechnology	Iron Nanoparticles, Thermotherapy	CP	Core	Drugs/Therapies

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Nanobiotix	Labege	France	Start-up	Nanotechnology	Magnetic Nanoparticles	PC	Core	Drugs/Therapies
Nanospectra Bioscience	Houston, TX	USA	Start-up	Nanotechnology	Nanoshells, Thermotherapy	NN	Core	Drugs/Therapies
Starpharma	Melbourne	Australia	SME	Dendrimers	Dendrimer Drugs	CP	Core	Drugs/Therapies
Triton Biosystems	Chelmsford MA	USA	SME	Speciality Pharmaceuticals	Magnetic Nanoparticles	PC	Core	Drugs/Therapies
Imaging								
BioCrystal	Westerville, OH	USA	Start-up	Bioanalytics/Biopharmaceutics	Nanocrystal Probes, Flowcytometry	M	Core	Imaging
Chemicell	Berlin	Germany	Start-up	Magnetic Nanoparticles	Magnetic nanoparticles DDS and imaging agents	M	Core	Imaging
Ferropharm	Berlin	Germany	Start-up	Diagnostic Imaging	Nanoparticle MRI contrast agents	M	Core	Imaging
Guerbet	Roissy	France	SME	Diagnostic Imaging	Nanoparticle MRI contrast agents	M	Peripheral	Imaging
Philips Medical Systems	Best	The Netherlands	Corporation	Diagnostic Imaging	Imaging modalities/contrast agents	Dev	Peripheral	Imaging
Schering	Berlin	Germany	Corporation	Pharmaceuticals and Diagnostics	Nanoparticle MRI contrast agents	M	Peripheral	Imaging
Siemens	München	Germany	Corporation	Diagnostic Imaging	Imaging systems, Electrical Biochips	Dev	Peripheral	Imaging
Visen Medical	Woburn, MA	USA	Start-up	Diagnostic Imaging	Nanoparticle fluorescence contrast agent	PC	Partly	Imaging
Kereos	Saint Louis, MO	USA	Start-up	Nanomedicine	Perfluorocarbon Emulsions	PC	Core	Imaging
Luna Nanomaterials	Blacksburg, Va	USA	SME	Technology/Engineering	Metal Encapsulating Fullerenes	NN	Partly	Imaging
Amersham/GE	Little Chalfont	UK	Corporation	Medical Diagnostics and	Colloidal gold for diagnostic	M	peripheral	Imaging

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
				Life Sciences	applications			
In vitro Diagnostics								
Akubio	Cambridge	UK	Start-up	Nanobiotechnology	Acoustic Biosensors	Dev	Core	IVD
Ambri	Chatswood	Australia	SME	Nanobiotechnology	Biosensor, Biochips	Dev	Core	IVD
Aurion	Wageningen	The Netherlands	SME	Immuno Gold	Colloidal gold	M	Core	IVD
Bioforce Nanoscience	Ames, IA	USA	Start-up	Nanotechnology	AFM, Nanoarrayer	Dev	Core	IVD
Biogenon	Oulu	Finland	Start-up	Nanobiotechnology Sensors	Nanotechnology Biosensors	Dev	Core	IVD
Biognostic	Berlin	Germany	Start-up	Diagnostics	Nano-encapsulated dyes for immuno tests	Dev	Partly	IVD
British Biocell	Cardiff	UK	SME	Colloidal gold	Colloidal gold for lateral flow tests	M	Core	IVD
Cantion	Lyngby	Denmark	Start-up	Nanotechnology	Cantilever Biochips	NN	Core	IVD
CombiMatrix Corp	Mukilteo	USA	SME	Drugs and Diagnostics, Technology	Biochip with electrochemical detection, nanostructured	Dev	Partly	IVD
Concentris	Basel	Switzerland	Start-up	Cantilever Sensors	Cantilever Sensors for chemical and biochemical sensing	NN	core	IVD
Dynal/Invitrogen	Oslo	Norway	SME	Biomagnetic Separation Technology	Superparmagnetic particles	M	Partly	IVD
eBiochip	Itzehoe	Germany	Start-up	Biochips	Nanoelectrodes for biochips	NN	Core	IVD
Evident Technologies	New York	USA	Start-up	Nanotechnology	Quantum Dots	Dev	Partly	IVD
Evotec Technologies	Hamburg	Germany	SME	Technology Provider for Life Sciences	GMI biosensor	Dev	Peripheral	IVD

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Genefluidics	Monterey Park	USA	Start-up	Bioanalytics	Microchips with nanotech components	Dev	Partly	IVD
Immunicon	Monterey Park	USA	SME	Nanobiotechnology Microfluidics	Magnetic nanoparticles for cell separation, cancer diagnostic	M	Core	IVD
Maxwell Sensors	Santa Fe Springs	USA	Start-up	Medical Sensors	Quantum Dot beads	NN	Partly	IVD
Micromod	Rostock	Germany	SME	Bioanalytics	Nanoparticles for bioanalytics	M	Partly	IVD
Miltenyi Biotec	Bergisch Gladbach	Germany	SME	Biotechnology, Cellular Technologies	Superparamagnetic nanoparticles for cell separation	M	Partly	IVD
Nanoco	Manchester	UK	Start-up	Nanotechnology	Quantum dots for healthcare applications	NN	Partly	IVD
Nanomix	Emmeryville	USA	Start-up	Nanotechnology	CNT based Sensors for medical applications	Dev	Partly	IVD
Nanoplex	Menlo Park, CA	USA	Start-up	Nanotechnology	Nanobarcode Particles	Dev	Partly	IVD
Nanoprobes	Yaphank, NY	USA	SME	Bioanalytics	Gold Nanoparticles	M	Core	IVD
Nanosphere	Northbrook IL	USA	Start-up	Bioanalytics	Gold Nanoprobes	Dev	Core	IVD
Nomadics	Stillwater, OK	USA	SME	Sensor Technology	SPR Sensors	NN	Partly	IVD
Nymox	Maywood	USA	SME	Biopharmaceutical Company	Colloidal gold for Alzheimer diagnostic	M	Partly	IVD
Orasure	Bethlehem	USA	SME	Medical Diagnostics	Upconverting Phosphor technology	NN	Partly	IVD
QuantumDot	Hayward, CA	USA	Start-up	Bioanalytics	Qdot-Nanocrystals	Dev	Core	IVD
Ademtech	Pessac (Bordeaux)	France	Start-up	Magnetic Microbeads	Nanomagnetical materials for diagnostics	M	Core	IVD
Oxonica	Kidlington	UK	SME	Nanomaterials	Nanoparticles for diagnostics	M	Partly	IVD
Sensia	Madrid	Spain	Start-up	Life Science Analytics	SPR and cantilever sensors incl.	NN	Partly	IVD

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
					for diagnostic applications			
Solexa	Cambridge UK	UK	Start-up	Bioanalytics	Nanotechnology based DNA Biochips	Dev	Core	IVD
Sphere Medical Limited	Cambridge	UK	Start-up	Diagnostic Products	Nanoimprinted receptor materials for diagnostic sensors	NN	Partly	IVD
Implants								
MIV Therapeutics Inc	Vancouver	Canada	Start-up	Biomaterials	Nano-film Hydroxyapatite	Dev	Partly	Implant
Fidia Advanced Biopolymers	Abano Terme	Italy	SME	Biomaterials	Nanotechnology applications for regenerative medicine	NN	Peripheral	Implants
3M Espe	St. Paul, MN	USA	Corporation	Dental Materials	Nanocomposite dental restorative	M	Peripheral	Implants
Alchimer	Massy	France	Start-up	Coatings	Nanostructured (electrografted) surfaces for medical implants	NN	Core	Implants
Alcove	Gladbeck	Germany	Start-up	Surface Technology	Nanoporous coatings for stents	NN	partly	Implants
Angstrom Medica	Woburn, MA	USA	Start-up	Biomaterials	Nanocrystalline Calcium Phosphate	M	Core	Implants
Blue Membrane	Wiesbaden	Germany	Start-up	Nanostructured Composite Materials	Nanotechnology based coatings for implants and medical devices	Dev	Partly	Implants
Coripharm	Dieburg	Germany	SME	Biomaterials for Bone Repair	Bone substitute materials based on nanocrystalline hydroxyapatite	M	Partly	Implants
Debiotech	Lausanne	Switzerland	SME	Medical Devices	Nanoporous coatings for stents	NN	Peripheral	Implants
Dentsply	Weybridge	UK	Corporation	Dental Products	Nanoceramic restoratives	M	Peripheral	Implants
DePuy Orthopedics	Warsaw, Indiana	USA	Corporation	Orthopedic Care	Nanoapatite coatings for orthopedic implants	NN	Peripheral	Implants

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Erothitan	Suhl	Germany	SME	Implant Technology	Nanoparticle based HA coatings for titanium implants	Dev	Partly	Implants
GfE Medizintechnik GmbH	Nürnberg	Germany	SME	Surface Technology for Medical Implants	Nanoscale titanized plastic implants	Dev	Core	Implants
Hemoteq GmbH	Wuerselen	Germany	Start-up	Medical Devices Supplier	Nanocoatings	NN	Core	Implants
Heraeus Kulzer	Hanau	Germany	Corporation	Dental Prothesis	Nanopearls, inorganic nanomaterials for dental prothesis	M	Peripheral	Implants
Inframat Corp	Farmington CT	USA	Start-up	Nanotechnology Research	Nano-apatite coatings for implants	Dev	Partly	Implants
Ivoclar Vivadent	Schaan	Liechtenstein	Corporation	Dental Materials	Nanocomposite dental restorative	M	Peripheral	Implants
Nano Interface Technology, Inc.	Lorton, VA	USA	Start-up	Medical Devices	nano-hydroxyapatite	NN	Core	Implants
Nanomatrix	Dallas TX	USA	Start-up	Medical Devices	Collagen nanofibers	NN	Core	Implants
Nucryst	Wakefield MA	USA	SME	Medical Devices	Antimicrobial dressing based on silver nanocrystals	M	Core	Implants
Orthovita	Malvern, PA	USA	SME	Biomaterials	Nanoparticle based bone replacement	M	Peripheral	Implants
Osartis	Obernburg	Germany	SME	Biomaterials	Nanocrystalline hydroxyapatite	M	Core	Implants
PlasmaChem	Berlin	Germany	SME	Plasma Ultra-Thin Tilm Technology	Nanoscale coatings for stents	NN	Partly	Implants
QuantumSphere	Costa Mesa	USA	Start-up	Nanomaterials	Nanosilver for medical/cosmetic applications	M	Partly	Implants
Raymor Industries	Montreal	Canada	SME	Advanced Materials,	Nano-sized titanium powder for	M	Partly	Implants

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
				Nanomaterials	biomedical markets			
Stryker	Kalamazoo	USA	Corporation	Orthoaedics	Use of nano-sized titanium powder for implants	NN	Peripheral	Implants
Sustech	Darmstadt	Germany	Start-up	Nanotechnology Research Company	Nano-apatite for dental applications	M	Partly	Implants
Sybron Dental Specialities	West Collins Orange	USA	Corporation	Dental Products	Nanocomposite dental restorative	M	Peripheral	Implants
Bio-Gate	Nürnberg	Germany	Start-up	Silver Nanoparticles	Silver nanoparticles for medical devices	M	Partly	Implants
Sarastro	Quierschied-Goettelborn	Germany	Start-up	Nanocoatings	Antimicrobial nano-coatings	NN	Partly	Implants
Active Implants								
iMedd	Columbus, OH	USA	Start-up	Biomedical	Nanoporous membranes	Dev	Partly	Active Implants
Microchips	Cambridge, MA	USA	Start-up	Medical Devices	Nanomembranes	Dev	Partly	Active Implants
Biophan	West Henrietta, NY	USA	Start-up	Medical Devices	Nanoparticle Coatings,	Dev	Core	Active Implants
Biotronik	Berlin	Germany	Corporation	Biomedical Technology Company	Fractal coatings for pacemaker electrodes	M	Peripheral	Active Implants
Med-EL	Innsbruck	Austria	SME	Cochlear Implants	Nanotechnology applications in screening status	Dev	Peripheral	Active Implants
Retina Implant AG	Reutlingen	Germany	Start-up	Retina Implants	Nanoporous thinfilm electrodes	Dev	Peripheral	Active Implants
Second Sight	Sylmar	USA	Start-up	Retina Prosthesis	Nanostructured diamond coatings for retina implants	Dev	Peripheral	Active Implants
Cosmetics (Examples)								

Company	Town	Country	Size	Business Segment	Nanotechnology	Status	Nano-medicine	Medical Sector
Beiersdorf	Hamburg	Germany	Corporation	Consumer Goods	TiO2 Nanopowders	M	Peripheral	Cosmetic
BioSpectrum	Yongin City	Korea	SME	Life Science / Skin Care	Liposomes	M	Partly	Cosmetic
Cali	New York	USA	NA	Cosmetics	Liposomes	M	NA	Cosmetic
Cellex-C	Toronto	Canada	NA	Cosmetics	TiO2	M	NA	Cosmetic
Chenyin Technology	Shenzhen	China	SME	Hightech Materials	TiO2 Nanopowders	M	Partly	Cosmetics
Christian Dior	Paris	France	Corporation	Cosmetics	Liposomes	M	Peripheral	Cosmetics
Engelhard/Coletlica	Iselin, NJ	USA	Corporation	Surface and Material Science	Nanoencapsulation	M	Partly	Cosmetics
Guinot	Paris	France	Corporation	Cosmetics	Liposomes	M	Peripheral	Cosmetics
L'Oreal	Paris	France	Corporation	Cosemtics	Liposomes, Nanocapsules	M	Partly	Cosmetics
Pevonica Botanica	Daytona Beach, FL	USA	NA	Cosmetics	TiO2	M	NA	Cosmetics
Sheer	Sant Boi de Llobregat	Spain	NA	Cosmetics	TiO2	M	NA	Cosmetics
Astellas Pharma (Yamanouchi)	Tokyo	Japan	Corporation	Pharmaceutics	Solid Lipid Nanoparticles	M	Peripheral	Cosmetics

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Abstract

Nanobiotechnological applications in the medical area belong to the most advanced and promising fields. As the field of nanobiotechnology is rather young, a comprehensive picture of the state-of-the-art of research and commercial nanobiotechnology activities in Europe is still missing. Furthermore, to enable the exploitation of this technology and a proactive approach to increase European competitiveness, information is needed on future directions of nanobiotechnology applications and on possible drivers and barriers for its development.
The objectives of the study are to:
provide a comprehensive picture on nanobiotechnology R&D and commercial activities related to the medical sector in Europe
identify and analyse drivers and challenges influencing the development and implementation of nanobiotechnology applications and products
identify with a prospective view possible socio-economic impacts of nanobiotechnology applications in the medical sector.

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