Health, Medicine & Nanobio

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The early genesis of the concept of nanomedicine sprang from the visionary idea that tiny nanorobots and related machines could be designed, manufactured, and introduced into the human body to perform cellular repairs at the molecular level\(^1\). This story is quite similar to early ideas in Microsystem Technologies. Nanomedicine today has branched out in hundreds of different research directions, each of them embodying the key insight that the ability to structure materials and devices at the molecular scale can eventually bring enormous immediate benefits in the research and practice of medicine.

Many approaches to nanomedicine being pursued today are already close enough to fruition that their successful development is almost inevitable, and their subsequent incorporation into valuable medical diagnostics or clinical therapeutics is highly likely and may occur soon. However, the market for nanomedical products is currently very fragmented and is at best a niche market when compared with the whole medical market.

An increasing interest in nanopharmaceuticals has generated a number of advancements throughout recent years with a focus on engineering novel applications\(^2\).

Nanotechnology also offers the ability to detect diseases at much earlier stages, such as finding hidden or overt metastatic colonies often seen in patients diagnosed with breast, lung, colon, prostate, and ovarian cancer. Diagnostic applications could build upon conventional procedures using nanoparticles, such as colloidal gold, iron oxide crystals, and quantum dots. Additionally, diseases may be managed by multifunctional agents encompassing both imaging and therapeutic capabilities, thus allowing simultaneous monitoring and treatment. A detailed evaluation of each formulation is essential to expand the current nanopharmaceutical repertoire. However, the safety and long-term effects of nanoformulations must not be overlooked.

To better support policy and decision makers, this economic analysis focuses on nanotechnology applications that are on or near market. This report concentrates as a first step on three different sectors: in vivo imaging, dental filling materials and bone substitute materials.

**Bone Substitute Materials**

The emergence and establishment of ortho-biologic products and solutions is expanding. Products vary from traditional metal implants, plates and screws to biologically-based products for hard and soft tissue regeneration. One product type are materials for bone replacement.

The fastest growing sector in orthopaedics is presently the market for osseous graft substitutes as part of the biomaterials market, in particular for spinal applications. According to an analysis of Frost and Sullivan, a total turnover of $39.5 million was gained in 2003 in Europe with osseous graft substitutes. Continuous innovation should allow market growth to $114.9 million until 2010.

Since 2004 three different types of nanostructured bone replacement materials are available in the marketplace, sold by two companies. The world market volume in 2007 was €31.3 million. Within the next years it is assumed that there will be a slight increase in the market volume due to new players in this field. However, the overall market volume for nanostructured bone replacement materials will not change significantly within the next few years.
Depending on the country, strong regulations and approvals are the most common main barriers to innovation.

**Dental Filling Materials**

The prosthetics, orthotics and cosmetic enhancement product industries are entering a period of extraordinary opportunities. This is due to a convergence of technological, demographic and economic factors. Advances in materials technology, miniaturisation and operative procedures are opening up many new possibilities.

The total global market size for restoratives is about $4 billion. In comparison, the US demand for general dental products in 2007 was $8.8 billion and is forecast to rise 4.5% per year to nearly $11 billion in 2012. In 2007, professional dental products accounted for 65% of total dental product demand.

Nanotechnology in the area of dental restoratives comprises organically modified ceramic nanoparticles and nanofillers. Products merge hybrid composite filler technology with advanced nanotechnology. This results in the Nano-Ceramic Technology.

Growth drivers for dental supply sales include the worldwide focus on dental prevention and aesthetics. Higher living standards particularly in developing economies such as Brazil, Russia, India and China as well as an increasing population age 65 and over with dental needs and fast-developing dental technologies are leading to a demand for improved dental care.

Nanostructured restoratives have to demonstrate that they are equivalent to the current alternatives or that they outclass them.

**In Vivo Imaging**

In vivo imaging enables researchers to view biological processes at the molecular level. In vivo molecular imaging techniques have important implications for drug discovery and development because they aid in validating drug targets and in studying the biodistribution, target binding, clinical effects, and toxicity of drug candidates. The most widely used diagnostic tool is magnetic resonance imaging (MRI).

The ability to detect, for example, cancerous growths in the body before the cells multiply and spread is critical to effective intervention. Medical technology companies are now turning to a new set of nanotechnologies which may allow detection years earlier than current methods.

The use of nanoparticles as novel amplification agents is believed to offer many advantages. The ability to functionalise polymer-coated nano-shells, dendrimers and gold nanospheres could enable specific, site-targeted delivery of agents and drugs.

Increased demand for MRI contrasting agents is primarily driving the contrast media market. MRI contrasting agents and positron emission tomography (PET) radiopharmaceuticals are showing tremendous growth potential and are helping to balance the effects of market saturation and price erosion in the overall contrast media and radiopharmaceuticals market.

There are significant changes taking place in the European contrast media and radiopharmaceuticals market as some segments experience growth while others lag. MRI
shows great scope for expansion and is already experiencing considerable growth due to its wider application and superior contrasting features than for example computer tomography.

According to a market study from Bio-Tech Systems, Inc. the MRI contrast media market will grow to about $500 million in 2013. Whereas the MRI contrast agent market is reported to be more than $1 billion annually and is currently dominated by gadolinium chelate-based agents. These are the subject of class-action lawsuit concerns due to the potential release of gadolinium into the body. Currently, total sales of all nanosized MRI contrast media are estimated to be in a few million USD range.
Health, Medicine & Nanobio

1.1 Definitions and Methodology

1.1.1 What is nanotechnology?

Nanotechnology is a very general term. Currently, there is no definition of the term “nanotechnology” that is generally accepted. This makes it quite challenging to predict “the world market” for products produced by nanotechnology or products with functional components in the nanometre range or products working with a precision in the nanometre range.

However, if the geometry size in at least one dimension is reduced to a critical value below 100 nanometers, most fundamental physical properties, depending on the material, change. Each property has a critical length scale, and with a nanoscale building block being made smaller than the critical length scale, it is possible to control the property’s internal and surface chemistry, their atomic structure and their assembly. It is further possible to engineer properties and functionalities in completely new ways. Fine adjustment is possible by altering the sizes of those nano building blocks.

Therefore, in the following the term nanotechnology product refers to this definition:

1. Products with a functional component with controlled geometry size below 100 nanometres in at least one dimension, and innovative characteristics caused by this critical dimension.

2. Equipment for analytical or manipulatory purposes that allows controlled fabrication, movement or measurement resolution with a precision below 100 nanometres.

Obviously, only in few cases does such a product consist of nanoscale building blocks alone, without any macroscopic element. Since the value of the nanotechnology contribution to such a product is difficult to estimate, it is only possible to consider the market price value of the end product. This clearly has implications for the determination of the overall market size.

Therefore, we define the smallest unit that can be commercially sold in the marketplace as a “nanotechnology product”. Consequently, the market figures in this study are based on the market price of the smallest commercially available units with functional nanotechnology components.

Characteristics of Nanomaterials

Nanotechnology is fundamentally changing the way materials and devices will be produced in the future. The ability to synthesise nanoscale building blocks with precisely controlled size and composition and then to assemble them into larger structures with unique properties and functions will revolutionise segments of the materials manufacturing industry\textsuperscript{3,4}. Fig. 1 illustrates nanomaterials and nanostructures by their reduced dimensionality.
What is nanomedicine?

Nanomedicine is defined as the process of diagnosis, treatment and prevention of illness and traumatic injuries, the decrease of pain, as well as the preservation and improvement of the human health by molecular tools and molecular knowledge about the human body. The approaches to nanomedicine range from the medical use of nanomaterials, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials.

1.1.2 Methodology for preparing the report

The market figures for the nanotechnology world market, as covered in this report, were predicted on the basis of available market data from press releases, company reports and Internet websites including so far unpublished market research studies. Market estimations of the authors are clearly marked in the text. However, it should be taken into account that the reported market figures are only estimates.

The company profiles were identified via various databases, conferences and Internet researches.

1.1.3 Methodology for market quantitative assessment

For an analysis of the present status and future visions and economic perspectives of nanotechnology, expert interviews either personally or via a fill-in questionnaire were carried out. Due to the limited number of interviewees, the results may not be representative. Nevertheless, the answers to the future visions and future products are at least regarded as a good indicator of future developments from the present point of view. The results were cross-checked at several conferences. Furthermore, the interviews and questionnaires included some open questions concerning the most important products and main innovation barriers. Naturally, the answers to this type of questions show a broader scatter that clearly reflects the difficulties to predict future developments.
1.2 General Market Description

The following decades will show that the population in many countries around the world will age due to an increasing life expectancy and a declining birth rate. At the same time, lifestyles in developed countries have become increasingly sedentary. These developments will dramatically impact on the healthcare system: certain diseases related to lifestyle will become more prevalent earlier in life, and the older generation wants to spend their additional years with a higher quality of life. Nevertheless, healthcare costs should be kept affordable which is a fundamental problem. Furthermore, the status of nanomedicine in the various European countries seems to be very different.

Nanomedicine, the application of nanotechnology to healthcare, will be an essential tool to address many unmet clinical needs of today and in the future. Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and novel physical, chemical, and biological properties of materials at the nanometric scale. Nanomedicine can have potential impact on the prevention, early and reliable diagnosis and treatment of diseases. Many of the possible developments are currently in the basic research state.

The world market for medicine products – in general – including pharmaceuticals can not be seriously predicted. The application fields are much too broad. Therefore, individual market descriptions – with a focus on nanotechnology – will be given in the following selected and individual application examples wherever possible. In general, there are many hopes but only a few products which are currently available at the market place.

Drug delivery systems dominate the nanomedicine market with 75% of total sales.

Twenty-three nanoscale drug delivery systems are on the market. The most widely used nanotechnology product in the field of in vitro diagnostics is colloidal gold in lateral flow assays, which is used in rapid tests for pregnancy, ovulation, HIV and other indications.

One indicator for future developments and commercial importance of products are patents. Fig. 2 shows the sectorial breakdown of nanomedicine patent filings worldwide.

![Fig. 2: Sectorial breakdown of nanomedicine patent filings worldwide (EPODOC database, 1993–2003)](image)

However, patenting indicators have several well-known drawbacks, including amongst others:
• Inconsistency across industries and fields. The propensity to patent and the type and intensity of R&D differ by industry and technology area. For example, pharmaceutical companies patent more heavily and engage in years of costly R&D before achieving a fundamental breakthrough.

• Varying motivations for patenting. Inventors may patent for reasons other than commercialisation or licensing, including blocking rivals from patenting related inventions, using patents as a tactic to negotiate with competitors, and helping to prevent infringement lawsuits.

Despite these drawbacks, patent filing can be used to identify potential future products in the area of nanomedicine.

According to the European Strategic Research Agenda for nanomedicine three important research areas have been identified:

• Nanotechnology-based diagnostics including imaging
• Targeted drug delivery and release
• Regenerative medicine.

1.2.1 Nanotechnology Impact

Nanomedicine has the potential to improve many medical areas, including cancer, heart disease, and stroke. However, all these options are not fully exploited yet. Some specific areas within biomedicine where nanotechnology is especially promising include:

• Imaging: New techniques for imaging open up whole new vistas for seeing the vascular system in unparalleled detail, as well as offering greater resolution of cancerous tumors. Nanomaterials that bind to specific types of cells, such as those from prostate or breast cancer, would allow doctors to identify even the smallest clusters of cancer cells that have spread to other parts of the body.

• Sensing and diagnostics: The technology offers new ways to detect organisms such as bacteria, viruses, or antibodies; it might be used, for example, to detect any of dozens of types of bacteria, nearly instantly, in a patient.

• Drug delivery: Nanomedicine extends the trend toward rational drug design, making it possible to develop even more targeted drug delivery systems designed against very specific molecules or types of molecular machinery. The more specific the target, the less the risk of unwanted side effects in, for example, a patient who has had a hip replacement, or a patient fighting an auto-immune disorder like multiple sclerosis. Nanotechnology has already given thousands of women with breast cancer a new treatment option, allowing doctors to use a compound that previously was considered too toxic for most patients.

However, also surgical tools like nanocrystalline diamond scalpels can offer several new and better options in comparison with traditional solutions. In this context, biocompatible nanocrystalline materials for dental fillers and bone substitution materials can also offer new and more effective solutions. The possible applications of nanotechnology for nanomedicine are numerous. At the end of the day price restrictions, regulations and effectiveness in
comparison with conventional solutions will decide over the market penetration for nanotechnology related products for medical applications.

1.2.2 Drivers and Barriers to Innovation

Innovations within the pharmaceutical industry are driven by the surroundings in which it acts. It can be asserted that in many countries, the government operates as the most significant purchaser of medicines. Furthermore, the industry is highly controlled. One famous example for this is the FDA (Food and Drug Administration) approval in the United States for drugs which is an extremely expensive and time intensive procedure. Consequently, government policy has a substantial impact on the industry and the fundamental business model on which it is based. Depending on the application the business models are quite different. Up to now the time-span from the first investigation in a possible drug until the market entry is on average 10 to 15 years. The development costs range between $800 million to $1.2 billion.

Despite a steady increase in R&D expenditure and application of the latest advances in science and technology within the R&D process, there is yet to be a corresponding increase in the number of new medicines being launched. During the past years, the number of new chemical entities being approved by regulatory authorities has been at a record low.

Another major challenge the pharmaceutical industry is facing is government’s application of cost-containment policies that are designed to control expenditure on medicines. This is also a certain danger because future developments of drugs and medical aids will be clearly influenced.

Depending on the application field the innovation barriers can be quite different and will be outlined in the following in more detail for specific nanotechnology related applications.

1.2.3 Relevant sector segmentation and applications

Health/Medicine in relation to nanotechnology is the process of diagnosis, treatment and prevention of illness and traumatic injuries, the decrease of pain, as well as the preservation and improvement of the human health. Therefore, an approximate segmentation in therapeutics, diagnostics and prevention can be given.

Therapeutics can be classified in biopharmaceuticals, implantable devices, implantable materials and surgical aids. Drug delivery as a part of biopharmaceuticals means nanoscale particles/molecules developed to improve the bioavailability and pharmacokinetics of therapeutics. Examples are drugs in which a protein is combined with a polymer nanoparticle or chemical nanostructure.

In general, the nanomedicine market for currently available products is very fragmented. In the following, selected examples for nanomedicine products will be highlighted.
1.3 Health, Medicine & Nanobio Application: Bone Substitute Materials

1.3.1 Market description

The amount of new products in the research pipeline for the orthopaedic biomaterials market is expanding rapidly. Important topics among others include stem cells, bone growth factors, gene therapy, synthetic bone fillers, bioactive implant coatings and biopolymers. Further market growth is expected for the next couple of years. The most important sector is orthobiologics which includes bone growth factors and the proteins segment. These products were estimated to grow from a few percent of the orthopaedic biomaterials market in 2002 to a market share between 25-30% by 2007. This product segment also brings many new players to the market, namely pharmaceutical and biotech companies\(^{13}\).

High quality standards in manufacturing processes and professional marketing and sales are key elements to increase market shares and penetration for the leading orthopaedic companies. However, they also need a strong pipeline of new technologies and products. Therefore a close co-operation with the biotech industry could be of advantage. The biotech industry and small orthopaedic technology companies do not have the market presence to compete with the leaders in the orthopaedic industry. Therefore, the both sectors need each other.

Presently the market for osseous graft substitutes as part of the biomaterials market, in particular for spinal applications, is the fastest growing sector in the orthopaedic area. According to an analysis of the management consultancy Frost and Sullivan a total turnover of $39.5 million was gained in 2003 in Europe from osseous graft substitutes\(^{14}\). Continuous innovation should let the market grow to $114.9 million until 2010.

1.3.2 Nanotechnology Impact

The emergence and establishment of ortho-biologic products and solutions is expanding. Products vary from traditional metal implants, plates and screws to biologically-based products for hard and soft tissue regeneration. This new generation of products is fast gaining acceptance and offers the potential to improve patient quality of life and reduce health costs.

Hydroxyapatite, unlike polymer coatings, is derived naturally and found in bioceramic materials such as human bone and teeth. It is a bioactive porous material that makes up the bone mineral and matrix of teeth and is widely used today as a bone substitute material and for coatings on implantable fixation devices in orthopaedic, dental and other applications.

1.3.3 Drivers and Barriers to Innovation

The developments in nanomedicine are mostly technology driven. Various unique properties of nanomaterials meet important medical needs and are therefore of interest for the industry. For example nanostructured materials can stimulate self-healing cell responses or can increase the biocompatibility of implants. The industry is interested in nanomaterials when a significant advantage can be expected and if development hurdles and costs are manageable.
Normally, in orthopaedic surgery and in the traumatology, autografts from the osseous continuance of the patient or allogenic grafts from another human donor are used. Indeed, autografts count as the best solution to the treatment of musculo-skeletal defects; however, they have high costs and show a raised morbidity.

The increasing variety of bone grafts and improving procedures are providing physicians with greater flexibility and surgeons with better success rates.

Furthermore, the high costs of new therapeutics can be offset by their large clinical benefits such as lesser morbidity and duration of hospital stays, improvement in the life quality of patients, as well as reduction in healthcare costs in the long run.

In most countries official registrations and approvals are a requirement for the sale of medical products. Products intended for the European market have to undergo approvals to obtain a certificate of conformity.

To enter the North American market the manufacturer has to receive the clearance of the Food and Drug Administration (FDA). This is an extremely time-consuming process.

1.3.4 Relevant Product segments and applications
There is still a need for cheaper and more effective solutions which lead to a lower morbidity. With the currently available osseous graft substitute products, operation duration and rehabilitation time can be shortened. To maximise the product potential, however, the manufacturers must convince surgeons of the physiological resemblance of the product to the bone.

Consequently, it is a matter of developing an osseous substitute material with clinical effectiveness which corresponds to that of auto-grafts. Therefore, manufacturers stand before the task to put on the market materials that possess osteo-conductive (bone substitutes that bridge bone defects) and osteo-inductive (bone substitutes that promote bone growth) surfaces.

The three most important market segments are osseous graft substitutes, demineralised osseous matrix products and bone morphogenic protein products. Osseous graft substitutes and demineralised osseous matrix products showed a perceptible market growth in the past five years. Nevertheless, bone morphogenic protein products should receive qualification for the European market within the next time. Therefore, a serious competition might arise to the osteo-conductive and osteo-inductive surfaces.

The strongly fragmented market stamped by intensive competition shows innovations and regular breakthroughs over and over again. Up to now there were only a few overlaps between the product segments, because most enterprises offered only one product type. This has changed dramatically, after various big enterprises have developed a whole range of products for other orthopaedic segments that are sold together with osseous graft substitute products as one product line. Consequently, company takeovers also play an important role in the whole branch.

1.3.5 Short application description
Bone is a highly specified connective tissue that consists of approximately 30% organic components which give it elasticity and approximately 70% inorganic components which lead
to its stability. The form of a bone always depends on the tractive and compressive forces. If these forces are missing, the bone dwindles. Hence, it is important to fill defects with a suitable replacement material or construction material, in particular if the area is not loaded, e.g., after a resection of tumours or a dental extraction. In particular in oral surgery the treatment of osseous defects is of great interest after root point resections and dental extractions. For the actual therapy of osseous defects a substance is required which can induce osseous growth integrated in the body and which is completely absorbable.

Currently, there are three nanostructured biomaterials on the market with the goal of medical treatment of bone defects. These materials are designed on the basis of nanostructured hydroxyapatite because bones consist of 70% of it. Hydroxyapatite accelerates the proliferation rate of ossific cells and stimulates the osseous healing. The osseous construction occurs quickly. The material is already completely absorbed after a few months.

1.3.6 Functional requirements
The effectiveness of pure nano-hydroxyapatite is based on its large specific surface arising from the nanostructure and its relatively large solubility. This osseous substitute leads within a few weeks to the entire defective bridging structure with concurrent resorption.

1.3.7 Boundary conditions
Competition in the market for medical products especially for orthopaedic and biological implants will continue to increase. There is a fundamental risk for companies to react in time on market trends with new products or adaptations to existing products. That could have a negative impact on a company’s market position in relation to their competitors.

Government intervention in the healthcare system may also have a negative effect on the sales position. Decisions on purchasing have been transferred from physicians to the procurement departments, which also may effect the market position of a company.

1.3.8 Product examples

Ostim®
Ostim® is a ready to use, injectable, paste-like osseous matrix. It consists of fully synthetic, nanoparticulate and phase-pure Hydroxylapatit. Ostim® is used for the replenishment or reconstruction of osseous defects. The paste can be applied directly or by means of applicators in the bony defect. Ostim® does not harden while mixing with blood or cancellous bone and is therefore very well suited for the volume increase of autogenic or homologous material. The volume stability of Ostim® 35 allows resistance to bleeding pressure, while its viscosity allows application in close contact with the bone. Ostim® is suitable for the defective replenishment of fractures in the spongy area. After reposition of the joint surfaces and mechanical stabilisation, the defect is filled in with Ostim®. On account of its pasty consistency Ostim® is quickly converted into bone. An osseous formation is already visible after 3 months. Fig. 3 shows an application of Ostim® in dental bone replacement.
PerOssal®
PerOssal® serves the permanent filling or reconstruction of osseous defects in casualty surgery, orthopaedics and oral and facial surgery. PerOssal® is a synthetic osseous substitute material with two prominent qualities. With PerOssal® an osseous substitute material is available which can also be introduced into infected osseous defects after preceding surgical cleaning of the wound with concurrent delivery of antibiotic. The second important quality is the quick and entire absorbance of PerOssal®. The component responsible for this is nanocrystalline Hydroxylapatite. The easy use of the product and the possibility of free combination with different active substances makes it attractive from an economic point of view.17

Vitoss®
Vitoss® scaffold is a synthetic bone graft substitute for the repair of bony defects in the spine, extremities and pelvis. It is an osteo-conductive porous implant with a trabecular structure that resembles the multidirectional interconnected porosity of human cancellous bone. Vitoss® scaffold is composed of beta-tricalcium phosphate (β-TCP) and guides the three-dimensional regeneration of bone in the defect site into which it is implanted and resorbed as new bone forms. Vitoss® has a similar architecture and chemical composition to natural bone mineral. High surface area and nanoparticulate structure enhances resorption. It promotes new bone ingrowth and maturation. Vitoss® is available in two convenient forms - blocks that can be shaped with a scalpel and gently tamped into place and morsels that can be packed into irregularly shaped voids in the defect site. Fig. 4 shows an SEM-photograph of the Vitoss® bone void filler.18
1.3.9 Economic information for present products

The world market for all kinds of bone replacement materials is small and expected to be in the range of $115 Mio. in 2010. In the case of nanostructured bone replacement materials currently only three companies are serving this market segment.

Orthovita is a spine and orthopaedic bio surgery company. They reported product sales for the quarter ended March 31, 2008 which increased by 23% to $16.2 million compared to $13.2 million for the same period in 2007.

The reported sales growth for the period in 2008 was primarily attributable to increased sales of its product VITOSS® as shown in Fig. 5. In relation to Fig. 6 an overall turnover of about $44 million for the year 2007 arose for VITOSS®.

Approximately 61% of the product sales during the quarters ended March 31, 2008 and 2007 were from products based upon the VITOSS® FOAM platform co-developed with Kensey Nash Corporation. The data proves that the nanostructured medicine device has asserted itself compared with the conventional products.
Vitagel
21%
Cotoss
3%
Others
1%

Vitoss
75%

Fig. 5: Revenue by product for 2007 from Orthovita. Vitoss® is a nanostructured bone replacement material. Source: Orthovita, Inc., Annual report, 2007

Fig. 6: Net revenues for Vitoss®. Source: Orthovita, Inc., Annual report, 2007
In 2002 the osseous bone replacement material Ostim was admitted to the German market. PerOssal a synthetic antibiotic carrier came one year later. In 2005 the sales decline of the previous years in the section of biomaterials stopped and a 2% growth was achieved. The revenue amounted to €5.907 million compared to €5.790 million in 2004. The revenue for the nanoproducts can be expected to be in the range of 10 to 20%. This is in the order of about €1.160 million.

According to the European Commission, the worldwide market for biomaterials is worth €25 billion per year, and growing at an estimated 12% annually. In the United States, the market is worth €10 billion, with a growth rate of 20%.

The European market, the second biggest, is worth €7 billion. The income from aap Implantate AG in the segment of nanostructured osseous substitute materials amounts to only 0,005% of the world market for biomaterials. For that reason nanostructured osseous replacement materials are currently of low significance for the worldwide market.

The world market volume for nanostructured bone replacement materials in 2007 was €31.3 million. It is speculated that there will be a slight increase in the market volume due to new players in this field. However, the overall market volume for nanostructured bone replacement materials will not change significantly within the next few years.

1.3.10 Profiles of selected key companies

Osartis GmbH & Co KG

Osartis GmbH & Co KG was founded in 1999 as a development and manufacturing company for innovative biomaterials. The company is based in Obernburg, Germany. It is expected that the discovery of bone growth factors and the major progress achieved in implant materials will lead to a fundamental change in orthopaedics. This is especially true for the combination of osteo-inductive and osteo-conductive materials. This is a main reason why Osartis is already developing a bone replacement material with a nanoparticulate structure that is highly suitable for use as a matrix for growth factors. The effect is based on the very large surface and its relatively high level of solubility. This bone material is able to bridge bone defects within weeks and is resorptive at the same time.

aap Implantate AG acquired a 49% holding in Osartis GmbH & Co KG at the end of 2000. In 2005 Osartis GmbH & Co KG was completely acquired by aap Implantate AG. From this acquisition the resulting product range was extended in the area of osteo-synthesis, or healing of bone fractures.

aap Implantate AG

In 1990 aap Ahrens, Ahrens & Partner GmbH & Co. Betriebs KG was founded by a Management Buy Out (MBO) from parts of the Johnson & Johnson daughter company Mecron. In 1997 the form of the organisation changed to aap Implantate AG. The company headquarter is in Berlin, Germany. aap Implantate AG has subsidiaries in Dieburg and Obernburg near Frankfurt am Main, Düsseldorf as well as Nijmegen in the Netherlands. Since May, 2003 aap Implantate AG has been listed in the Prime Standard segment on the Frankfurt
Stock Exchange. In 2005 aap completed the acquisition of the German based company Osartis GmbH & Co KG.

The aap product portfolio includes implants for fracture healing and joint replacement, bone cements, bone graft substitutes and antibiotic carriers. The company also offers a complete set of tried and tested surgical instruments for safety on the operating table. Their implants support minimally invasive operating methods that are easy on the patient and help to accelerate the natural healing process\textsuperscript{22}.

Orthovita, Inc.

Orthovita, Inc. is a spine and orthopaedic bio surgery company with proprietary biomaterials and biologic technologies for the development and commercialisation of synthetic, biologically active, tissue engineering products.

They develop and market synthetic-based biomaterials, products to be used in spine surgery, the repair of fractures and a broad range of clinical needs in the trauma, joint reconstruction, revision and extremities markets. Their near-term commercial business is based on VITOSS\textregistered Bone Graft Substitute technology platforms, which are designed to address the non-structural bone graft market by offering synthetic alternatives to the use of autograft or cadaver-based bone material.

Another product is VITAGEL\textregistered Surgical Haemostat, which is an adherent matrix and an impermeable barrier to blood flow. Their long-term U.S. clinical development program is focused on their internally developed CORTOSS\textregistered Bone Augmentation Material technology platform, which is primarily designed for injections in osteoporotic spines to treat vertebral compression fractures.

They work jointly with Kensey Nash Corporation to develop and commercialise novel synthetic-based biomaterial products, they market VITAGEL\textregistered under a license granted by Angiotech Pharmaceuticals, Inc., and Orthovita continues to pursue similar relationships with other companies in biomaterials.

The company was expected to launch VITASURE\textregistered within the United States by the third quarter of 2008. VITASURE\textregistered is an absorbable Haemostat in the spine and orthopaedic field.
1.4 Health, Medicine & Nanobio Application: Dental Filling Materials

1.4.1 Market description

Dental restorative materials can be classified according to the major product categories:

- **Direct Restoratives**
  - Etchants, bonding agents, amalgams, composites, curing lights
- **Indirect Restoratives**
  - Cements, impression materials, temporary crown & bridge.

The total global market size for restoratives is about $4 billion\textsuperscript{23}. The US demand for dental products in 2007 was $8.8 billion and is forecast to rise 4.5% per year to nearly $11 billion in 2012. In 2007, professional dental products accounted for 65% of total dental product demand\textsuperscript{24}. Professional dental products will grow faster than the consumer segment and comprise two-thirds of demand in 2012. As a result, cosmetic dental products such as ceramic fillings, clear or tooth coloured orthodontic appliances and tooth coloured veneers will achieve above average revenues.

1.4.2 Nanotechnology Impact

In the section of dental restoratives, nanotechnology comprises organically modified ceramic nanoparticles and nanofillers combined with conventional glass fillers of ~1 \( \mu \text{m} \).

Products merge hybrid composite filler technology with advanced nanotechnology. This results in Nano-Ceramic Technology. Starting from modified precursors the organically modified ceramic nanoparticles are achieved via controlled hydrolysis and condensation reactions. The nanoparticles are highly dispersed due to an innovative manufacturing process. This results in dental fillings with higher fracture toughness.

1.4.3 Drivers and Barriers to Innovation

As in most areas of biotech, developments in nanomedicine are technology driven. Dental fillings represent an established procedure to treat tooth decay. Growth drivers for worldwide dental supply sales encompasses that people want to keep their natural teeth longer than in the past, an increasing population age 65 with corresponding dental needs, rapid developments of dental technologies and higher living standards in upcoming countries like Brazil, Russia, India and China.\textsuperscript{25}

However, there are some considerable disadvantages: nanostructured dental fillings may not be recommended for use on molars, the treatment requires a minimum of two appointments to be completed and their cost is similar to gold dental fillings.

Nanostructured restoratives will have to demonstrate that they are equivalent to the current alternatives or that they outclass them.
1.4.4 Relevant Product segments and applications

There is still a need for cheaper and more effective solutions within the dental restorative market segment.

In dentistry, composites consisting of inorganic fillers such as radiopaque glass, quartz or ceramic particles and an organic matrix, are used for the restoration of teeth.

The purpose of dental fillers or dental restoratives is to cover all aesthetic and practical demands in restoring natural tooth colour. The developmental goal is to provide an easy shading system for advanced aesthetic solutions as well as for fast restorations on a primary level.

In recent years, there has been a marked increase in the development of aesthetic materials made of ceramic and plastic. These mimic the appearance of natural teeth and are more aesthetically pleasing where they are visible. But the strength and durability of traditional materials still make them useful, particularly in the back of the mouth where they must withstand the extreme forces that result from chewing.

Important properties of the dental restorative materials can be improved by means of nanotechnology. Moreover, well designed nanostructured components can be used for producing protective and wear-resistant coatings for teeth, metal alloys, and glass fillers of special compositions.

1.4.5 Short application description

A dental restoration or dental filling can artificially restore the function, integrity and morphology of missing tooth structure by using dental restorative materials. The structural loss typically results from caries or external trauma. It is also intentionally lost during tooth preparation to improve the aesthetics or the physical integrity of the intended restorative material. Dental restoration also refers to the replacement of missing tooth structure by restoring dental implants.

Dental restorations can be classified into two broad types: direct restorations and indirect restorations. In the case that decay is spread beyond dentin, root canal therapy is used, and a crown is fitted. The tooth is prepared by cutting the infected tooth cavity to clean and finish it for filling. If permanent restoration cannot be carried out after tooth preparation, temporary restoration is done.

Dental restorations may be fabricated from a variety of materials. Common direct restorative materials include dental amalgam, glass ionomer cement and composite resins. Common indirect restorative materials include acrylic, porcelain, zirconia, gold and other metals.

There are a number of different filling materials that are used in modern dentistry practice. The fillings are divided into inlay (inside the tooth) and onlay (outside). Here are the different types of fillings:

Amalgam

Amaligan is the most commonly used and cheapest material for back teeth and takes only little time to insert. It roughly contains of half mercury and differing amounts of silver, tin, zinc, and copper. The disadvantage is that Amalgan looses shape over time and corrodes easily. The
The lifetime of these fillings last in average 5-10 years and in some cases longer. There was a controversy discussion about mercury and possible negative effects on the human body. However, up to now there has not been enough evidence to support this assumption.

Galloy
Galloy is a mercury-free alternative to Amalgan. It consists of silver, tin, copper, indium, and gallium.

Direct Composite
Direct composites are the most popular of all inlay fillings. It is a special plastic material that bonds to the tooth structure. The direct composites are tooth coloured and can be easily repaired. The average lifetime is between 5 and 7 years although smaller fillings can last longer. The material is more costly than Amalgan and takes longer to insert.

Indirect Composite Inlay/Onlay Filling
Indirect composites are used when ideal anatomy, fit, and durability is desired. Composite filling. Cost is approximately two to three times more than Amalgam.

Porcelain Inlay/Onlay
When cosmetics and wear resistance is most important for a patient porcelain inlays or onlays can be used. This type of filling material costs about the same as an indirect composite inlay/onlay.

Gold Inlay/Onlay
This type of filling is used when maximum strength is desired and appearance is not much of a concern. It costs three to four times more than Amalgam.

Titanium Inlay/Onlay
Titanium inlays or onlays are used when a gold alloy is not possible. The benefits are cost and time to perform. This is quite similar to gold fillings despite the fact that titanium is not a precious metal.

1.4.6 Functional requirements
The effectiveness of nano-ceramic restoratives is based on organically modified ceramic nanoparticles and nanofillers as used in adhesives like Prime&Bond® NT combined with conventional glass fillers of \(~1 \mu m\).
1.4.7 Boundary conditions

Competition in the market for medical products, especially nanomodified restorative materials, is very restricted because Dentsply International with market shares of about 70 to 80 percent has a monopoly position. This has a negative impact on other companies' market position. The Government alleged that Defendant, Dentsply International, Inc., acted unlawfully to maintain a monopoly. After a bench trial, the District Court denied the injunctive relief sought by the Government and entered judgment for defendant.

According to Heraeus Kulzer the markets in which Heraeus operates are typically well protected against major new entrants. In consideration of the high technology barriers to entry and the relatively modest size of this market, it is uneconomic for new competitors to make large investments in these markets.

1.4.8 Product examples

Filtek Supreme

Filtek Supreme™ is a new resin composite by 3M ESPE with a unique nanofiller technology. Formulated with nanomer and nanocluster filler particles, the composite is designated to combine the strength of a hybrid and the polish of a microfil. Nanomers are discrete non-agglomerated particles of 20-75 nm in size. Nanoclusters are loosely bound agglomerates of nano-sized particles.

The combination of nanomer-sized particles and the nanocluster formulations provides increased filler loading, better physical properties and improved polish retention when compared to composites containing only nanoclusters.

The composite is available in 30 different shades in 4 opacities and is purportedly suitable for anterior and posterior restorations, core build-ups, splinting, and indirect restorations, including inlays, onlays and veneers. A shade selection wheel is provided for more complex restorations and serves as a guide for placing anywhere from one to four layers of composite. Fig. 7 and Fig. 8 compare the situation before and after the treatment with Filtek Supreme.

Fig. 7: Prae operative view of the denture; ©Dr. Claus-Peter Ernst, Universität Mainz
Ceram\textsuperscript{X}™ duo

Ceram\textsuperscript{X}™ is a light-cured, dental restorative material that has been conceived for restoration of anterior and posterior teeth. The product is characterised by the combination of nanotechnology with organically modified ceramic particles. The combination leads to a Nano-Ceramic Restorative and thus, it provides natural aesthetics by a simple technique, low monomer release and simple use for dentists. Furthermore, it offers a convenient natural shade system of two shading systems in one product that satisfies all clinical and aesthetic requirements.

Ceram\textsuperscript{X}™ Mono encompasses seven shades with translucency characteristics comparable to conventional composites and a fast and easy handling.

Ceram\textsuperscript{X}™ Duo offers four dentine shades with translucencies of natural dentin and three enamel shades which emitate natural enamel. The concept for the design was to realise highly aesthetic restorations with a minimum number of shades.

Mondial®

The Mondial® tooth line was designed for patients who desire a dental prosthesis but are concerned about keeping a natural-looking smile. Mondial® is stronger and has 50% better abrasion resistance than conventional dentures that allows for a significantly longer lifespan.

Mondial® is stronger and has 50% better abrasion resistance than conventional dentures that allows for a significantly longer lifespan.

1.4.9 Economic information for present products

Dentsply UK, the British subsidiary of Dentsply International, introduced Ceram X duo to the market in 2003. In their 2007 annual report the company announced net sales of $2 billion. Sales excluding precious metal content rose 12.1% to $1.8 billion in 2007\textsuperscript{29}. About 38% of sales ($684 million) belong to consumables like sealants and restoratives.
There is no data available on their product Ceram X duo. Therefore, sales for Ceram X duo only can be estimated. Seven categories with about 25 to 30 products belong to the group “consumables”. Assuming an arithmetic average of sales, the result is about $25 million. In comparison to the total global sales for restoratives of about $4 billion the contribution of Ceram X duo to the market is about 0.6%.

3M Espe announced in its 2007 annual report that sales in their health care section rose to $1.1 billion. In relation to their nanosized dental storage product Filtek Supreme, the company mentioned that there is strong interest in the new Filtek(TM) restorative system.

1.4.10 Profiles of selected key companies

Dentsply International, Inc.
DENTSPLY is a multinational health care corporation and was founded in 1899. From the beginning in 1899, the Company has grown to become one of the largest professional dental products companies in the world. They have facilities in 22 nations on six continents and distribute their dental products in over 100 countries.

DENTSPLY, the largest manufacturer of dental prosthetics and consumable dental products in the world, possesses manufacturing plants in Europe, North and South America and Asia. Its products are sold throughout the globe.

Heraeus Kulzer GmbH
Heraeus Kulzer with its headquarters in Hanau, Germany is a private company working in the business segments of precious metals, dental health, sensors, quartz glass and specialty lighting sources.

The company can refer to revenues of more than €10 billion ($15 billion) and more than 11,000 employees in over 100 countries.

The company acts as a system provider and service partner for dental offices and dental laboratories, with more than 1,500 employees worldwide, the company grossed €327 million ($452 million) in sales in 2006.

3M Espe AG
3M founded in 1902 has its headquarters in Two Harbors, Minn. In the early 1940s, 3M was highly engaged in the defence materials market. Today, each of their businesses has earned a leading global market position.

In the 1970s and 1980s the company decided to expand into pharmaceuticals, radiology and energy control. In the 1990s, sales reached the $15 billion mark. 3M continued to develop a wide range of products from health care and highway safety to office products.

Now, 3M Espe is a company with 75,000 employees and operations in more than 60 countries. In the meantime their sales reached about $24 billion.
1.5 Health, Medicine & Nanobio Application: In Vivo Imaging

1.5.1 Market description

In vivo imaging is a scientific tool to investigate biological processes at the molecular level. The most interesting applications are drug discovery and development. Moreover, in vivo imaging techniques are a great support in validating drug targets and in studying the biodistribution, clinical effects, and toxicity of drug candidates.

Diagnostic procedures in molecular medicine include a variety of imaging techniques, all of which have one common objective. The purpose is to depict biological processes in living organisms (in vivo) on the cellular and molecular level, in high quality and in the most extensive manner possible. Traditional imaging techniques, on the other hand, depict morphological and functional changes that are not visible until the late stages of specific diseases.

The most widely used techniques for molecular imaging currently rely on positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance tomography (MRT), optical devices such as endoscopes, and high-frequency (more than 20 megahertz) ultrasound units.

The contrast media market is very dynamic. On the one hand, there is a continued development of new generations which permit easier and safer diagnosis; on the other hand, there is the high impact these techniques have on healthcare expenses. The relative toxicity of some of the contrast media raises a stirring debate in the medical profession regarding costs/benefits.

However, MRI contrast agents offer an enormous growth potential and are able to help to balance the effects of market saturation in the contrast media and radiopharmaceuticals market.

Companies that overcome the pricing threats by introducing cost-effective and enhanced imaging agents will be well positioned in the contrast agents segment. In 2007 the market for MRI contrast agents in Europe was about $320 million.

In the USA sales of MRI contrast media grew to $364 million in 2006, stimulated by increases in the proportion of enhanced studies. In 2006, 45% of MRI studies were enhanced and this proportion should increase in the future. Although sales of MRI contrast agents have been under competitive pressure, this market is stabilising. Therefore, future sales growth will be more consistent with increases in procedure volume. Also, the introduction of new products to enhance MR angiography and permit targeted imaging will favourably affect procedure growth.

As announced by frost & Sullivan, contrast media sales should show rapid growth to about $500 million by 2013 as new products are introduced.

The total MRI contrast agent market is reported to be more than $1 billion annually and is currently dominated by gadolinium chelate-based agents which are the subject of class-action lawsuit concerns due to the potential release of gadolinium into the body.
1.5.2 Nanotechnology Impact

Although the section of medical science can be characterised by a continuous progress in the treatment of most major diseases, early diagnosis of cancer, cardiovascular and neurodegenerative diseases remains the most important contributor to therapies. It is very important for an effective therapy to detect cancerous growth of cells before metastases will spread through the whole body. Medical technology companies try to apply nanotechnologies in order to develop equipments which may allow detection earlier than current methods.

Among scientists it is believed that the use of nanoparticles as novel amplification agents may offer many advantages. It is possible to functionalise polymer-coated nano-shells, dendrimers and gold nanospheres in order to enable specific, site-targeted delivery of agents and drugs. The uptake into cells of these new materials could be significantly easier due to their inherently small size. The application of such nanostructured contrast agents should lead to lower dose requirements and significant signal amplification and thus it could provide e.g. the ability to detect primary tumours at a much earlier stage of development. Currently, there are three products for MRI in vivo imaging on the market. Resovist® and Feridex®/Endorem® are specifically designed for the diagnosis of liver tumours and GastroMARK® for the imaging of abdominal structures.

1.5.3 Drivers and Barriers to Innovation

It is observed that there are significant changes taking place in the European contrast media and radiopharmaceuticals market as some segments demonstrate growth while others lag. Magnetic resonance imaging (MRI) shows great scope for expansion and is already experiencing considerable growth due to its wider application and superior contrasting features than, for example, computer tomography.

Increased demand for MRI contrast agents is primarily driving the contrast media market. MRI contrast agents and PET radiopharmaceuticals are showing tremendous growth potential and are helping to balance the effects of market saturation and price erosion in the overall contrast media and radiopharmaceuticals market.

Radiologists and technicians across Europe are always trying to identify better imaging agents that provide enhanced image quality and thereby aid in the improved detection of diseases.

As competition increases and products reach maturity, the focus on research and development is rapidly increasing. New products are expected to offer superior features while being less expensive in order to suit the needs of end users.

The production of chemical active ingredients for contrast agents generates different security and environmental risks. These risks result from dangers inherent in chemical products, their production, transport, use and elimination. Chemical active ingredients used to produce contrast agents for medical imaging are distinguished by their low toxicity and excellent level of tolerance. In contrast, certain synthetic intermediates or products used in the production of these active ingredients like raw materials, solvents, reactants, intermediates, etc. may present certain risks.

Barriers may arise from the dependency on industrial patents or licenses. Guerbet S.A. for example uses several products under license agreements:
Dotarem® is used under license from Schering AG. This product was originally discovered by Guerbet, however the patent on the nanomodified product owned by Schering requires Guerbet to licence the product for commercial use.

Like all pharmaceutical products, medical imaging contrast products may present certain risks and have undesirable side effects. While in most cases benign, they may sometimes have serious consequences.

1.5.4 Relevant Product segments and applications

Although MRI was conceived to enable the physician to provide definitive diagnoses non-invasively, in many cases it is essential to apply contrast agents to improve the sensitivity and/or specificity. In the meantime there are six groups of MRI contrast agents according to their field of application. These groups encompass gastrointestinal contrast agents, intravenous contrast agents, intravascular (blood pool) contrast agents, tumour-specific agents, liver-specific contrast agents and last but not least reticuloendothelial contrast agents.

Currently, there are only two fields of application, the diagnosis of liver cancer and metastases of the liver and secondly investigations of abdominal structures.

1.5.5 Short application description

In vivo imaging techniques were developed to receive images of the human body or parts thereof for medical purposes. As a medical discipline it comprises nuclear medicine, endoscopy, nuclear magnetic imaging, positron emission tomography, ultrasound reflection mode and near infrared imaging techniques.

The in vivo molecular cell and tissue analysis could only be facilitated by a rapid progress in the field of image generation technologies, sensor biotechnology, and computational modelling. These technologies allow to observe the detailed functions of single cells, organs, and whole organisms and to monitor i.e. tumour development or basic cell development processes.

To investigate basic questions of in vivo tumour development and progression, fluorescence based imaging techniques were developed to allow new insights into molecular targets. The design of novel fluorescent dyes emitting in the near infrared range (NIR) in combination with sensitive detector systems and monochromatic powerful NIR-lasers enables the quantification and imaging in deeper tissues. Furthermore, laser based techniques in the NIR-range (like two-photon microscopy) offer extremely high signal to noise ratios, and thus the possibility to observe molecular targets in vivo.

Currently, there are only three iron nanoparticle-containing contrast agents used in nuclear magnetic imaging on the market.

1.5.6 Functional requirements

Although magnetic resonance imaging (MRI) has been created as a useful tool for detecting tumours its ability to diagnose very small tumours is restricted by the way to detect the difference between malignant and normal tissue. To solve this sensitivity problem
nanoparticles that are targeted to tumours and loaded with magnetic metal ions such as iron are used. The metal ions act as signal amplifiers.

Resovist® consists of superparamagnetic iron oxide (SPIO) nanoparticles coated with carboxydextran, which are accumulated by phagocytosis in cells of the reticuloendothelial system (RES) of the liver. Feridex® works in the same way.

GastroMARK® is an aqueous suspension of silicone-coated, superparamagnetic iron oxide, intended for oral administration.

1.5.7 Boundary conditions

The existing products are designed for the diagnosis of liver cancer, whereas the third MRI contrast agent is conceived for the imaging of abdominal structures. Therefore, the fields of application are very restricted.

In order to develop new contrast agents scientists break new ground. For example metal ion carriers are combined with the cowpea chlorotic mottle virus (CCMV) which infects only plants and which can be produced in a cost effective way and in large quantities. The proteins on the CCMV shell are able to bind up to 180 metal atoms. Other segments of these shell proteins can additionally be used to attach molecules that could target the metal-loaded virus particles to tumours, while the empty interior of the virus particle can be used to deliver drug molecules to tumours. Such agents could be generally applied and compared to other nanomaterials. On the basis of the CCMV formulation signals that are 5 to 10 times higher than conventional signals can be realised. This tool could be capable of detecting microscopic tumours at their most treatable stage.

A study by Frost & Sullivan highlights the introduction of new diagnostic imaging technologies that require lower doses of contrast agents and therefore being key factors depressing sales.

Liver cancer the sixth most common cancer in the world leads to more than 600,000 cases of liver cancer worldwide each year. More than 400,000 patients come down with liver cancer in Asia, 54,000 in the European Union, and 15,000 in the United States. This illustrates that the market for specific contrast agents is very restricted.

1.5.8 Product examples

Resovist®

Resovist® is a liver specific MRI contrast agent, used in order to detect and characterise especially small focal liver lesions.

Resovist® consists of superparamagnetic iron oxide (SPIO) nanoparticles coated with carboxydextran a material which enables the SPIOs to be accumulated in healthy cells of the reticuloendothelial system (RES) of the liver.

Most malignant liver tumours do not contain RES cells and therefore do not uptake the iron particles. Thus, the application of coated nanoparticles leads to an improved contrast between the tumour (bright) and the surrounding tissue (dark).

Because Resovist® is injected as an intravenous bolus, an immediate imaging of the liver with a reduced examination time can be realised.
In 2001, Resovist® was approved for the European market. Currently, Resovist® is for sale in Japan, Australia and Europe. In the USA it is in Phase III clinical studies.

Feridex®/Endorem®
FERIDEX I.V.®, a ferumoxides injectable solution was introduced in 1996 as the world’s first liver specific MR imaging agent used to detect and evaluate liver lesions due to an alteration in the reticuloendothelial system (RES). FERIDEX I.V.® can be characterised as a "negative" contrast agent because the liver decreases in signal intensity, not the lesions.
FERIDEX I.V.® belongs to the product portfolio of Advanced Magnetic Industries, Inc.

GastroMARK®/Lumirem®
GastroMARK® belongs to the negative oral contrast agents (same as Lumirem®), another brand name for ferumoxsil. Suitable materials for oral contrast agents should have little or no absorption by the stomach or intestines, complete excretion, no motion or susceptibility artefacts, affordability, and uniform marking of the gastrointestinal tract. Benefits of negative oral contrast agents are the reduction of ghosting artefacts caused by the lack of signal.

GastroMARK® is an oral gastrointestinal imaging agent manufactured by AMAG Pharmaceuticals, used to distinguish the loops of the bowel from other abdominal structures. MRI images of abdominal organs and tissues without contrast agents can be very difficult to read because the abdominal organs and tissues cannot be easily distinguished from the loops of the bowel. After ingestion of GastroMARK® the contrast agent flows through and darkens the bowel.

1.5.9 Economic information for present products
According to a press release by Reuters the MRI contrast agent market is characterised to be worth more than $1 billion annually and is currently dominated by gadolinium chelate-based contrast agents.40.

According to a study of the freedonia group, the market for contrast agents will expand moderately with increasing numbers of X-ray, CT and MRI scans on body regions where visual enhancement is needed. Within this market segment nanosized compounds will show the best growth prospects because they are expected to improve the sensitivity of MRI-generated images41.

AMAG Pharmaceuticals, Inc. is a biopharmaceutical company that utilises its proprietary nanoparticle technology for the development and commercialisation of therapeutic iron compounds to treat anaemia and novel imaging agents to aid in the diagnosis of cancer and cardiovascular disease; reported unaudited consolidated financial results for the quarter and six months ended June 30, 2008. Revenues for GastroMARK® and Feridex® for the quarter ended June 30, 2008 were $0.5 million compared to revenues of $0.7 million for the same period in 200742. Revenues for the six month period ended June 30, 2008 were $1.1 million compared to $1.7 million for the same period in 2007.

Guerbet S.A. sells Feridex®/Lumirem® and GastroMARK®/Endorem® on the European and Latin American market. According to their financial report from 2006 they attained revenues of
$86.4 million for their four MRI contrast agent products. With Dotarem®, a gadolininium based formula, AMAG Pharmaceuticals solely received revenues of about $85 million. Compared with 2005 there is a change of +9.1%. For Artirem®, GastroMARK®/Lumirem®, Feridex®/Endorem® they attained $1.4 million. Benevolently estimated AMAG Pharmaceutical Inc. received profits of about $400 to 500 thousand. According to their 2006 annual financial report AMAG declared that the contribution of both nano-sized contrast agents to total Group sales is marginal.

Bayer Schering AG announced on the Bayer health care Day in 2007 sales of € 373 million for their four MRI contrast media Magnevist, Gadovist, Vasovist and Primovist but no information about their nanosized Resovist. Therefore, only marginal sales are anticipated.

1.5.10 Profiles of selected key companies

**Bayer Schering AG**

Schering AG was a research-centred pharmaceutical company founded in 1851 that merged with Bayer in December 2006. At that time the company employed more than 26,000 people in 140 subsidiaries all over the world. The company's headquarters are in Berlin, Germany. Schering's annual gross revenue was nearly €5 billion (2003).

To Schering's key businesses belong the areas of gynaecology, andrology and oncology. Their best-known products are combined oral contraceptive pills. The company was also involved in special therapeutics, diagnostic devices & nuclear medicine.

The company's founder was Ernst Schering (1824-1889). The largest German manufacturing facility is located in Bergkamen. Schering used the Berlex Laboratories brand in the USA.

On March 13, 2006, Merck KGaA announced a €14.6 billion bid for Schering. The offer document was due to be issued in early April 2006. Merck's takeover bid was surpassed by Bayer's €16.2 Billion white-knight bid for Schering on March 23, 2006. In June 2006 Bayer finally bought the majority of shares, over 90%. A domination agreement using the code name "Step One" was used for the take-over. As a result of the take, Bayer Schering Pharma is one of the ten largest specialty pharmaceutical companies in the world and the company's goal is a leading market position in each of its specialist fields. With its distinctive expertise in research, the company develops new medicines and therapies which make an essential contribution toward improving patient's quality of life.

**Advanced Magnetics, Inc.**

On 25 July, 2007 Advanced Magnetics, Inc. announced that it has changed its company name to AMAG Pharmaceuticals, Inc. The company's trading symbol will remain unchanged on the NASDAQ Global Market. The company has undergone significant evolution, and the new name reflects these developments while recognising the long-standing business presence.

AMAG Pharmaceuticals is a biopharmaceutical company that utilises its proprietary nanoparticle technology for the development and commercialisation of therapeutic iron compounds to treat anemia and novel imaging agents to aid in the diagnosis of cancer and cardiovascular disease. The core technology is based on the characteristic properties of extremely small, coated superparamagnetic iron oxide nanoparticles. The company has two
commercial products, FERIDEX I.V.® and GastroMARK®. Both are imaging agents that are approved and marketed in the United States, Europe and other countries.

Feridex® is marketed in the United States by Bayer Healthcare Pharmaceuticals, in Europe by Guerbet S.A. and in South Korea by TaeJoon.

Guerbet S.A.

Guerbet, headquartered in Paris, France, is a company holding more than 20% of the European contrast media market and 7% of the worldwide.

Guerbet’s product portfolio is sold in 130 countries worldwide and contains contrast agents for X-ray and MRI diagnostic interventions. Oxilan®, Hexabrix®, Dotarem®, Lumirem® and Endorem® are the company’s key products. Guerbet currently has multiple agents in Phase III clinical trials.

Guerbet S.A. purchased the assets of Oxilan® from Cook®, one of the leaders in the medical device industry. This was the starting signal in 2002 for its US subsidiary GerbetLLC. Currently Guerbet LLC is responsible for the marketing, sales and distribution of Oxilan®. Currently the company tries to receive approval for new extra cellular MR agent and an MR blood pool agent products in the U.S. market.
This report was peer reviewed by experts with a significant experience in the fields of Nanotechnology, medicine, biology, and materials. The experts are

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Prof. Dr. Roland Lauster
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Technical University of Berlin
Germany
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