

# The emerging nanomedicine landscape

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**A global survey of companies pursuing 'nanomedicine' indicates that nanotechnology is taking root in the drug and medical device industry.**

The past decade's surge in research in what has been termed 'nanomedicine' is now translating into considerable commercialization efforts around the world. Alerted by these developments, governmental agencies are planning funding programs to support this research, and roadmaps and foresight studies have been commissioned by various science administrations to analyze technological and commercial perspectives of this emerging field. The European Science Foundation's report *Scientific Forward Look on Nanomedicine*, the culmination of a two-year study completed in 2005, warns that nanomedicine benefits will be lost without major investment and calls for a coordinated European strategy to deliver new nanotechnology-based medical tools for diagnostics and therapeutics<sup>1</sup>. However, because of a lack of primary data on scientific and business activities in the field, discussions up until now have been largely qualitative. For this reason, the European Science and Technology Observatory (ESTO), a network of organizations operating under the European Commission's leadership and funding, carried out a study focusing on gathering data<sup>2</sup>.

This article presents data from the above study showing that commercialization efforts are significant, with more than 150 startups and small and medium enterprises (SMEs) pursuing focused nanomedicine R&D projects and 38 nanotechnology-enabled products

currently on the market with total sales valued at \$6.8 billion. Drug delivery applications currently dominate nanomedicine, accounting for three-quarters of the research activity and of the nanomedicine market. Commercialization efforts in Europe in this area are relatively

weak, with only half as many companies as in the United States.

## What is nanomedicine?

The term nanomedicine can be traced back to the late 1990s; according to the Science Citation

### Box 1 Healthcare applications of nanomedicine

We present below the definitions used within this article for the different applications of nanomedicine within healthcare.

**Drug delivery.** Nanoscale particles/molecules developed to improve the bioavailability and pharmacokinetics of therapeutics. Examples are liposomes (and virosomes), polymer nanoparticles, nanosuspensions and polymer therapeutics. Drugs in which a protein is combined with a polymer nanoparticle or chemical nanostructure to improve its pharmacokinetic properties would be classified as nanomedicine-based drug delivery.

**Drugs and therapy.** Nanoscale particles/molecules used in the treatment of diseases that according to their structure have unique medical effects and as such differ from traditional small-molecule drugs. Examples include drugs based on fullerenes or dendrimers.

**In vivo imaging.** Nanoparticle contrast agents, particularly for MRI and ultrasound, that provide improved contrast and favorable biodistribution. For example, superparamagnetic iron oxide nanoparticles for use as MRI contrast agents.

**In vitro diagnostics.** Novel sensor concepts based on nanotubes, nanowires, cantilevers or atomic force microscopy applied to diagnostic devices/sensors. The aim of these sensors is to improve the sensitivity, reduce production costs or measure novel analytes (e.g., Alzheimer plaques) that until recently could not be detected. For example, Nanomix (Emeryville, CA, USA) develops carbon nanotube-based sensors for monitoring respiratory functions and Bioforce's Virichip (Ames, IA, USA) uses atomic force microscopy for the detection of whole viruses for early diagnosis of viral infections.

**Biomaterials.** Self-assembling particles or other types of nanomaterial that improve the mechanical properties and the biocompatibility of biomaterials for medical implants. Examples include nanocomposite materials used as dental fillers and nano-hydroxyapatite used for implant coatings and bone substitutes. Also decoration of implant materials with biologically active signal molecules that stimulate, for example, cell growth or differentiation.

**Active implants.** Particles/materials that improve electrode surfaces and biocompatibility of device housings. Examples include Biophan's (Henrietta, NY, USA) magnetic nanoparticle-based coating that makes medical implants safe for use with MRI imaging and nanomaterials used for retina implants to improve the charge transfer at the electrode tissue interface (Retina Implantat AG, Tübingen, Germany). To address single cells on a submicron level is currently not an area of R&D at medical device companies.

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## Box 2 Methodology of data collection

Currently, there is no generally agreed upon definition of nanomedicine, and comprehensive information resources are not yet available that allow quick and efficient data retrieval with regard to technological and commercial information. Therefore, we used a diverse set of information sources, such as internet forums, patent databases, business databases, proceedings of business conferences.

Publications were searched in the Science Citation Index database (<http://scientific.thomson.com/products/sci/>), using discrete key words indicative for each of the defined nanomedicine application sectors (see **Supplementary Methods** online). A patent search was conducted by the European Patent Office using EPODOC, the internal European Patent Office Documentation database, which covers patents worldwide, using a combined keyword and patent classification search. Because industry codes for the classification of nanotechnology companies are not yet available in business databases, we identified nanomedicine companies using various internet nanotechnology databases

(<http://www.nanoforum.org/>, <http://www.nanovip.com/>, <http://www.nano-map.de/>), booklets of nanotechnology fairs, agendas of business conferences and patent data. Companies were then profiled on the basis of publicly available information, such as web presentations, press releases and Security and Exchange Commission (SEC) filings.

From an initial list of 400 companies, 207 were selected that have visible and openly communicated activities in the field of nanomedicine as we define it. Data on products on the market and in clinical trials were retrieved by analyzing review papers and business press as well as by searching in medical databases such as the Adis Newsletter and the Pharmaprojects Drug Development Status File. Information on product sales were retrieved by SEC filings, the Creditreform database and by expert interviews. In total, 46 questionnaire-guided interviews were conducted with scientists from academia, CEOs of startups and R&D managers of pharmaceutical and medical device companies, to provide more detailed insights into the structure of the emerging nanomedicine industry.

Index (Institute for Scientific Information, Thompson, Philadelphia, PA, USA) the first research publications that use this term appeared in the year 2000. With research programs, conferences and journals focusing on nanomedicine for a number of years now, it has become clear that nanomedicine is more than a semantic fashion, though it was difficult to find a precise definition for this field with its blurred borderlines encompassing biotech and microsystems technology.

In general, two concepts can be distinguished. Some experts define nanomedicine very broadly as a technology that uses molecular tools and knowledge of the human body for medical diagnosis and treatment<sup>3</sup>. Others prefer an emphasis on the original meaning of nanotechnology as one that makes use of physical effects occurring in nanoscale objects that exist at the interface between the molecular and macroscopic world in which quantum

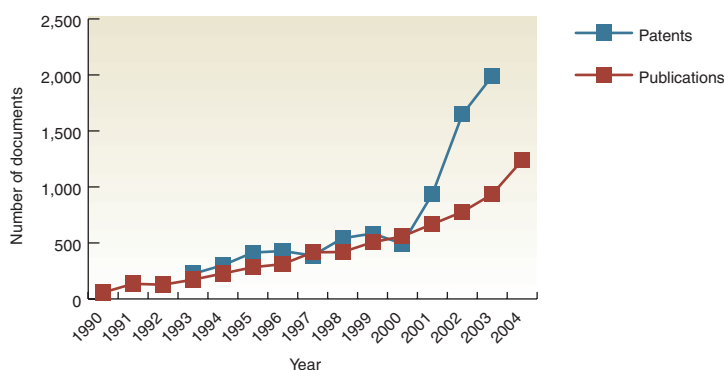
mechanics still reigns<sup>4</sup>. We adopted the second concept and define nanomedicine as the use of nanoscale or nanostructured materials in medicine that according to their structure have unique medical effects (see **Box 1**), for example, the ability to cross biological barriers or the passive targeting of tissues. Such medical effects are not strictly limited to a size range below 100 nanometers. Therefore, unlike the physical definition of nanotechnology, which is restricted to objects with dimensions in the range of 1 nm to 100 nm, we include structures and objects up to 1,000 nm in size. Such a definition also seems to be justified from a technical point of view because the control of materials in this size range not only results in new medical effects but also requires novel, scientifically demanding chemistry and manufacturing techniques. This definition does not include traditional small-molecule drugs as they are not specifically engineered on the

nanoscale to achieve therapeutic effects that relate to their nanosize dimension.

### Nanomedicine research

A bibliometric analysis of documents (see **Box 2** for methodology) in the Science Citation Index shows that nanomedicine has seen a surge in research activity over the past decade, with publication numbers rising from some ten articles per year in the late 1980s to more than 1,200 in the year 2004 (**Fig. 1**). Patenting activities have skyrocketed since the beginning of the decade: a search by the European Patent Office reveals 2,000 patent filings in the nanomedicine sector in the year 2003, up from 220 in 1993. Drug delivery is the dominant research field with a share of 76% of the scientific papers and 59% of the patents (**Figs. 2 and 3**).

In the field of nanomedicine research, the United States is leading, accounting for 32% of the publications and 54% of the patent filings. The EU country with the strongest nanomedicine activities is Germany, contributing 8% of the publications and 12% of the patent filings. Further, Japan has an internationally strong position with a share of 9% of the publications and 5% of the patents. A comparison between Europe as a whole with the United States shows that Europe is at the forefront of research with a publication share of 36%, compared with the United States' share of 32%. However, the United States leads in the number of patent filings, with 54% compared with 25% from Europe. The strong patenting activity of US scientists and companies indicates a more advanced commercialization status in the United States. This contradicts the claim that nanomedicine is more advanced in Europe



**Figure 1** Nanomedicine publications and patents worldwide. Sources: Science Citation Index, VDI Technologiezentrum GmbH, Düsseldorf, Germany and EPODOC patent database, European Patent Office, Rijswijk, The Netherlands.

than in the United States, as made in ref. 1 and elsewhere.

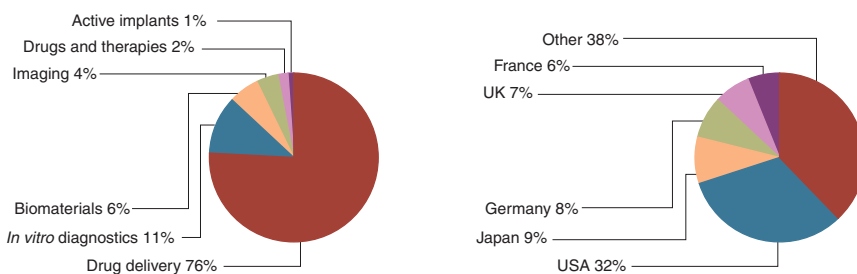
A comparison of numbers of publications in nanomedicine with nanotechnology (about 34,300 documents in 2004) suggests that nanomedicine as defined here currently accounts for about 4% of nanotechnology research worldwide. Analyzing the geographical distribution of nanomedicine research shows that the largest research clusters are in the Boston area, San Francisco, Tokyo, Berlin and South East England.

### Nanomedicine market

Commercialization efforts in nanomedicine are picking up worldwide. We identified about 207 companies that visibly pursue nanomedicine activities—158 SMEs and startups that devote either all or a significant share of their business to the development of nanomedicines. We believe this is an underestimate of the true number, as a detailed analysis of patent data for liposomes—the area of nanomedicine with one of the longest development histories—shows that the number of companies that have filed three or more patents relating to healthcare applications of liposomes, is twice as high as the number of companies that openly communicate their involvement in this technology (e.g., on their webpage or in press releases). Therefore, we assume that the 207 companies reviewed in our study that all openly communicate their nanomedicine activities are just the tip of the iceberg.

A characterizing feature of nanotechnology is its enabling function to add new functionality to existing products, making them more competitive. As measuring the added value of nanotechnology to a product is not possible, it has become common praxis in nanotechnology business studies to take the total sales of nanotechnology-enhanced products as a measure of the economic importance of nanotechnology in an industrial sector. For example, Ambisome (Gilead, Foster City, CA, USA), a liposomal formulation of the fungicide Fungizone (Bristol-Myers Squibb, New York) that shows reduced kidney toxicity, had total sales of \$212 million in 2004. For calculating the market size, we used this figure. After this procedure, we estimated the total sales of the 38 identified nanomedicine products from all sectors of nanomedicine as defined in our study to \$6.8 billion in 2004 (Tables 1 and 2).

Taking into account the pipeline of nanomedicine products that are in an advanced development stage (Table 3), we predict the market will grow to ~\$12 billion in the year 2012. Currently, nanomedicine is dominated by drug delivery systems, accounting for more than 75% of the total sales. Twenty-three



**Figure 2** Sectorial and country breakdown of nanomedicine publications. Source: Science Citation Index, 1984–2004, VDI Technologiezentrum GmbH, Düsseldorf, Germany.

nanoscale drug delivery systems are on the market, but within this group, three polymer therapeutics alone account for sales of \$3.2 billion: (i) Neulasta (pegfilgrastim; recombinant methionyl human granulocyte colony stimulating factor and monomethoxypolyethylene glycol (PEG)), (ii) Pegasys (PEGylated interferon  $\alpha$  2a) and (iii) PEG-Intron (PEGylated interferon  $\alpha$  2a), all protein therapeutics to which nanoscale polymer strings of PEG have been attached to reduce immunogenicity and to prolong plasma half-life.

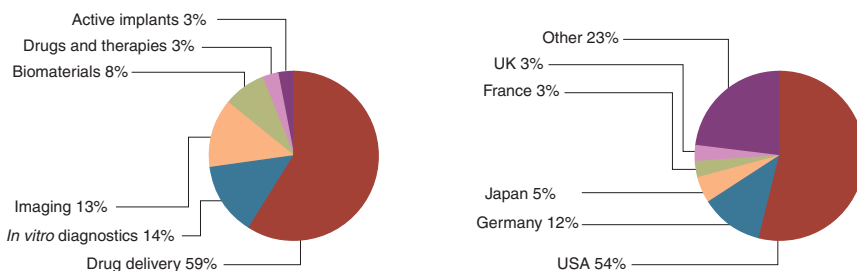
The most widely used nanotechnology product in the field of *in vitro* diagnostics is colloidal gold in lateral flow assays, which is used in rapid tests for pregnancy, ovulation, HIV and other indications. These tests are based on an immunoassay in which a dye molecule or a nanoparticle is conjugated to an antibody that is specific for the analyte. Gold nanoparticles were introduced into these tests in the late 1980s because the gold conjugates have particularly high stability that is critical for avoiding false positives. Further magnetic nanoparticles are used for cell sorting applications in clinical diagnostics.

In the field of biomaterials, the commercial status of nanotechnology-based dental restoratives is most advanced. Filtek Supreme (3M Espe; Seefeld, Germany) was the first product introduced in 2002. Furthermore, nanohydroxyapatite-based products for the repair

of bone defects, such as Vitoss (Orthovita, Malvern, PA, USA) have been successfully commercialized. A commercial success story was the launch of Acticoat in 1998, a silver nanoparticle-based wound dressing (Nucryst, Wakefield, MA, USA), with sales of \$25 million in 2004.

Nanotechnology-based contrast agents, albeit often cited as important examples for nanomedicine, are a niche market with estimated sales of about \$12 million. All of the marketed contrast agents consist of superparamagnetic iron oxide nanoparticles for magnetic resonance imaging. Advanced Magnetics' (Cambridge, MA, USA) Gastromark (ferumoxsil) was the first product of this class, approved in 1993 in Europe and 1996 in the United States. The only other company to have brought a superparamagnetic contrast agent to the market is Schering (Berlin) with Resovist (ferucarbotran), approved in 2000 for liver imaging in the European market.

Nanotechnology applications for active implants is probably the nanomedicine sector most misunderstood by the wider public. Futurists envision many nanotechnology engineering feats, such as implants restoring neurological functions or acting as computer brain interfaces. In fact, active implants is the medical sector for which experts predict the least impact of nanotechnology. The core functions of such implants are mere microtechnology; nanotechnology is used only as enabling technology for optimizing certain components. Examples are



**Figure 3** Sectorial and country breakdown of nanomedicine patent filings worldwide. Source: EPODOC database, 1993–2003, European Patent Office, Rijswijk, The Netherlands.

**Table 1 Commercial efforts in nanomedicine<sup>a</sup>**

Healthcare sector	Number of products	Sales (\$ billions)	Product pipeline		
			Total	Advanced stages <sup>b</sup>	Companies
Drug delivery	23	5.4	98	9	113
Biomaterials	9	0.07	9	6	32
<i>In vivo</i> imaging	3	0.02	8	2	13
<i>In vitro</i> diagnostics	2	0.78	30	4	35
Active implants	1	0.65	5	1	7
Drugs & therapy	0	0	7	1	7
<b>Total</b>	<b>38</b>	<b>6.8</b>	<b>157</b>	<b>23</b>	<b>207</b>

<sup>a</sup>Sales numbers of nanomedicines are estimates for the year 2004. <sup>b</sup>Drugs where the product is in clinical phase 2/3 or 3 and for all other products where market introduction is expected within two years.

Source: VDI Technologiezentrum GmbH, Düsseldorf, Germany.

nanostructured electrodes for improving the electrode tissue contact or the use of nanomaterials for increasing the biocompatibility of implant housings. Pacemakers with nanostructured (fractal) electrodes are the only active implants currently on the market that contain a nanotechnology-enabled component.

Nanotechnology has in most application areas of medicine an enabling function. This is not the case, however, when nanomaterials are used to develop novel therapies or drugs

in which the nanomaterial plays the pivotal therapeutic role. A prominent example for such a nanomedicine is nanoparticle-based magnetic hyperthermia being developed for the treatment of cancer by the startup Magforce (Berlin). In this treatment, aminosilane-coated nanoparticles are injected into the tumor and subsequently heated with a newly developed magnetic field applicator. Nanoparticles coated with aminosilane are taken up faster by tumor cells than by normal cells by an as-yet

undetermined mechanism. The tumor cells are destroyed by the heat. Because of their properties, the nanoparticles form stable deposits within the tumor, thus allowing repeated treatments. Another example is a dendrimer gel-like microbicide to prevent HIV infections, under development at Starpharma (Melbourne, Australia). Dendrimers are a new class of highly branched tree-like polymers with a precisely defined molecular structure. They are of general interest to the drug industry, as

**Table 2 Nanomedicine products on the market**

Healthcare application <sup>a</sup>	Composition/nanotech component	Indication	Company <sup>b</sup>
<b>Drug delivery</b>			
Abelcet	Amphotericin B/lipid complex	Fungal infections	Enzon (Bridgewater, NJ, USA)
Amphotec	Amphotericin B/lipid colloidal dispersion	Fungal infections	InterMune (Brisbane, CA, USA)
Ambisome	Liposomal Amphotericin B	Fungal infections	Gilead (Foster City, CA, USA), Fujisawa (Osaka, Japan)
DaunoXome	Liposomal daunorubicin	Kaposi sarcoma	Gilead
Doxil/Caelyx	Liposomal doxorubicin	Cancer, Kaposi sarcoma	Ortho Biotech (Bridgewater, NJ, USA); Schering-Plough (Kenilworth, NJ, USA)
Depocyt	Liposomal cytarabine	Cancer	SkyePharma (London), Enzon
Epaxal Berna	Virosomal hepatitis vaccine	Hepatitis A	Berna Biotech (Bern, Switzerland)
Inflexal V Berna	Virosomal influenza vaccine	Influenza	Berna Biotech
Myocet	Liposomal doxorubicin	Breast cancer	Zeneus Pharma (Oxford, UK)
Visudyne	Liposomal verteporfin	Age-related macular degeneration	QLT (Vancouver, Canada), Novartis (Basel)
Estrasorb	Estradiol in micellar nanoparticles	Menopausal therapy	Novavax (Malvern, PA, USA)
Adagen	PEG-adenosine deaminase	Immunodeficiency disease	Enzon
Neulasta	PEG-G-CSF	Febrile neutropenia	Amgen (Thousand Oaks, CA, USA)
Oncaspar	PEG-asparaginase	Leukemia	Enzon
Pegasys	PEG- $\alpha$ -interferon 2a	Hepatitis C	Nektar (San Carlos, CA, USA), Hoffmann-La Roche (Basel)
PEG-Intron	PEG- $\alpha$ -interferon 2b	Hepatitis C	Enzon, Schering-Plough
Macugen	Pegylated anti-VEGF aptamer	Age-related macular degeneration	OSI Pharmaceuticals (Melville, NY, USA), Pfizer (New York)
Somavert	PEG-HGH	Acromegaly	Nektar, Pfizer
Copaxone	Copolymer of alanine, lysine, glutamic acid and tyrosine	Multiple sclerosis	TEVA Pharmaceuticals (Petach Tikva, Israel)

Table 2 (continued)

Healthcare application <sup>a</sup>	Composition/ nanotech component	Indication	Company <sup>b</sup>
Renagel	Crosslinked poly(allylamine) resin	Chronic kidney disease	Genzyme (Cambridge, MA, USA)
Emend	Nanocrystalline aprepitant	Antiemetic	Elan Drug Delivery (King of Prussia, PA, USA), Merck & Co. (Whitehouse Station, NJ, USA)
MegaceES <sup>c</sup>	Nanocrystalline megesterol acetate	Eating disorders	Elan Drug Delivery, Par Pharmaceutical Companies (Woodcliff Lake, NJ, USA)
Rapamune	Nanocrystalline sirolimus	Immunosuppressant	Elan Drug Delivery, Wyeth Pharmaceuticals (Collegeville, PA, USA)
Tricor <sup>c</sup>	Nanocrystalline fenofibrate	Lipid regulation	Elan Drug Delivery, Abbott (Abbott Park, IL, USA)
Triglide <sup>c</sup>	Nanocrystalline fenofibrate	Lipid regulation	SkyePharma, First Horizon Pharmaceuticals (Alpharetta, GA, USA)
Abraxane	Paclitaxel protein bound nanoparticles	Cancer	Abraxis BioScience (Schaumburg, IL, USA), AstraZeneca (London)
<b><i>In vivo</i> imaging</b>			
Resovist	Iron nanoparticles	Liver tumors	Schering (Berlin)
Feridex/Endorem	Iron nanoparticles	Liver tumors	Advanced Magnetics (Cambridge, MA, USA), Guerbet (Roissy, France)
Gastromark/Lumirem	Iron nanoparticles	Imaging of abdominal structures	Advanced Magnetics, Guerbet
<b><i>In vitro</i> diagnostics</b>			
Lateral flow tests	Colloidal gold	Pregnancy, ovulation, HIV, among others	British Biocell (Cardiff, UK), Amersham/GE (Little Chalfont, UK), Nymox (Hasbrouck Heights, NJ, USA)
Clinical cell separation	Magnetic nanoparticles	Immunodiagnosics	Dynal/Invitrogen (Oslo, Norway), Miltenyi Biotec (Bergisch Gladbach, Germany), Immunicon (Huntingdon Valley, PA, USA)
<b>Biomaterials</b>			
Ceram X duo	Nanoparticle composite	Dental filling material	Dentsply (Weybridge, UK)
Filtek Supreme	Nanoparticle composite	Dental filling material	3M Espe (Seefeld, Germany)
Mondial	Nanoparticle-containing dental prosthesis	Dental restoration	Heraeus Kulzer (Hanau, Germany)
Premise	Nanoparticle composite	Dental repair	Sybron Dental Specialties (Newport Beach, CA, USA)
Tetric EvoCeram	Nanoparticle composite	Dental repair	Ivoclar Vivadent (Schaan, Liechtenstein)
Ostim	Nano-hydroxyapatite	Bone defects	Osartis (Obernburg, Germany)
Perossal	Nano-hydroxyapatite	Bone defects	aap Implantate (Berlin)
Vitoss	Nano-hydroxyapatite	Bone defects	Orthovita (Malvern, PA, USA)
Acticoat	Silver nanoparticles	Antimicrobial wound care	Nucrust (Wakefield, MA, USA)
<b>Active implants</b>			
Pacemaker	Fractal electrodes	Heart failure	Biotronik (Berlin)

G-CSF, granulocyte colony-stimulating factor; hGH, human growth hormone; PEG, polyethylene glycol; VEGF, vascular endothelial growth factor.

<sup>a</sup>Definitions of nanomedicine products considered in each healthcare sector are provided in **Box 1**. <sup>b</sup>In case the product is developed by an alliance, for example, between a drug delivery company and a pharma company, both companies are listed. <sup>c</sup>These products were not included in the nanomedicine market calculation for 2004, as they entered the market later.

they allow the synthesis of drugs that show polyvalent interaction with their target. The therapeutic approaches of both Magforce and Starpharma are in advanced clinical stages, with target markets in the range of several hundred million US dollars per year.

In the global marketplace, commercialization efforts in the United States are most advanced: about 50% of all companies developing or codeveloping nanomedicines are based there, whereas 35% are in European countries. In drug delivery, the share of European companies that have brought products to the market is only about 20%. This indicates a relative weakness of the commercialization efforts in the EU in the nanomedicine

sector with currently the highest market potential.

#### Drivers of innovation

As in most areas of biotech, developments in nanomedicine are technology driven. However, the various unique properties of nanomaterials meet important medical needs. In drug delivery, the ability of nanoparticles to cross biological barriers, to accumulate at tumor sites or to increase the solubility of drugs makes them unique materials. Molecular MRI can be realized only by accumulating contrast agents on a nanoscale level to reach the necessary contrast levels. Furthermore, nanostructured materials can stimulate self-healing cell

responses or can increase the biocompatibility of implants<sup>5</sup>.

Industry embraces nanotechnology in those cases where nanomaterials have unique properties that meet medical needs and the development hurdles are manageable. For example, five products that contain nanomaterials for dental fillers to improve wear resistance and optical properties are already on the market (**Table 2**). The improvements associated with nanomaterials are persuasive and development costs and risks of these materials can be low compared with those of new drugs or drug delivery systems. Furthermore, the drug industry shows interest in the use of nanosuspensions for increasing the solubility

**Table 3 Nanosuspension-based formulations in development**

Drug	Indication	Compound/ nanotechnology	Drug delivery company	Pharma company	Status
Paliperidone palmitate	Schizophrenia	Paliperidone palmitate/ NanoCrystal	Elan Drug Delivery	Johnson & Johnson (New Brunswick, NJ, USA)	Phase 3
Propofol IDD-D	Anesthetic	Propofol/IDD technology	SkyePharma	Looking for strategic partner	Phase 3
NPI 32101	Atopic dermatitis	Silver nanoparticles	Nucryst (Wakefield, MA, USA)	Self-developed	Phase 2
Panzem NCD	Glioblastoma	2-methoxyestradiol/ NanoCrystal	Elan Drug Delivery	EntreMed (Rockville, MD, USA)	Phase 2
AI-850	Solid tumors	Paclitaxel nanoparticles	Acusphere (Watertown, MA, USA)	Looking for strategic partner	Phase 1
BioVant	Vaccine adjuvant	Calcium phosphate nanoparticles	BioSante (Lincolnshire, IL, USA)	Self-developed	Phase 1
Baxter Nanoedge <a href="http://www.omeris.org/programs/bioohio.asp">http://www.omeris.org/ programs/bioohio.asp</a>	Antiinfectives, oncologics, cardiac drugs and others	Undisclosed	Baxter BioPharma Solutions (Bloomington, IN, USA)	Undisclosed	Preclinical to Phase 2
NanoCrystal	Variety of indications	Undisclosed	Elan Drug Delivery	Roche (Basel), Merck & Co (Whitehouse Station, NJ, USA) Aventis Pharma (Frankfurt) Bristol-Myers Squibb (New York)	Preclinical and clinical phases

of certain types of small-molecule drugs. This technology is applied to drugs that are poorly water-soluble and therefore cannot be administered via the preferred route or in some cases, at all. At present about 40% of small-molecule drugs in the pipeline of pharmaceutical

companies belong to this class of so called 'brickdust candidates'. This exemplifies how nanotechnology may offer solutions to fundamental problems in the pharmaceutical industry. Here again, commercialization efforts appear promising, with five products

on the market and many more in preclinical and clinical development (Tables 2 and 3).

#### Challenges ahead

Commercialization in nanomedicine is currently driven by startups and small SMEs.

**Table 4 Alliances between nanomedicine startups and pharma or medical device companies**

Startup	Nanotechnology focus of startup	Partner	Subject of the alliance
Bio-Gate (Nürnberg, Germany)	Antimicrobial silver nanoparticles	Ciba Specialty Chemicals (Basel)	Ciba Specialty Chemicals becomes the worldwide exclusive marketer for Bio-Gate's antimicrobial silver products (December 2005)
Capsulation (Berlin)	Nanoscale capsules as packaging systems for technical and pharmaceutical applications	Schering (Berlin) and Acri.Tec (Hennigsdorf, Germany)	Codevelopment of nano-functional hydrogels for treating gynecological and eye diseases (March 2006)
Kereos (Saint Louis, MO, USA)	Nanoscale imaging agents	Dowpharma (Midland, MI, USA) and Royal Philips Electronics (Amsterdam)	Development of nanoscale MRI contrast agents for imaging tumors and atherosclerotic plaques (April 2003)
C Sixty (now Carbon Nanotechnologies, Houston, TX, USA)	Fullerene-based therapeutics	Merck & Co, Inc. (Whitehouse Station, NJ, USA)	Research license that allows Merck to develop drugs based on C Sixty's fullerene antioxidants (October 2003)
Biophan Technologies (West Henrietta, NY, USA)	Magnetic nanomaterials for medical devices, drug delivery systems and contrast agents	Boston Scientific Corporation (Natick, MA, USA)	License agreement with Boston Scientific about the use of Biophan's technology to make metal implants safe for MRI imaging (June 2005)
Nanocarriere (Chiba, Japan)	Nanoscale micellar drug delivery systems	Debiopharm (Lausanne, Switzerland)	Research collaboration to develop anticancer drug using Nanocarriere's micellar drug delivery system (April 2005)
Altair Nanotechnologies (Reno, NV, USA)	Nanoparticles and advanced ceramic nanomaterials	Spectrum Pharmaceuticals (Irvine, CA, USA)	Licensing agreement gives Spectrum Pharmaceuticals exclusive rights to market Altair's phosphate-binding drug for treating chronic kidney disease (January 2005)
Magforce (Berlin)	Nanoparticle-based hyperthermia cancer therapy	Siemens Medical Solutions (Erlangen, Germany)	Declaration of intent for the codevelopment of Magforce's magnetic field device for nanoparticle-based cancer therapy (July 2006)
pSivida Limited (Perth, Australia)	Nanoporous biosilicon for drug delivery applications	Beijing MedPharm Corporation (Plymouth Meeting, PA, USA)	License agreement for the clinical development and marketing in China of BrachySil, a porous nanostructured silicon to be used for radiotherapy of liver cancer (November 2005)
Nektar (San Carlos, CA, USA)	Drugs and novel formulations of drugs	Roche (Basel)	Codevelopment of pegylated erythropoietin for treating renal anemia (February 2004)

However, because of the high development costs of drugs and medical devices, startup companies have little chance of bringing products to the market when not receiving backing from a larger biotech, pharmaceutical or medical device corporation (Table 4). Therefore, support by big pharma is crucial to making nanomedicine a business success. Startups currently pursue a plethora of ideas on how to improve disease treatment and diagnosis with nanotechnology, but our interview survey shows that startup founders as well as industry R&D managers agree that major pharmaceutical companies are not yet ready to emphasize nanotechnology in their business strategy. In particular, startups that pursue technologies with no approved products on the market yet find it difficult to convince pharma companies to partner with them or to license their technology.

Commercial uptake of nanotechnology in the United States is progressing more quickly than in Europe, and similarities to the commercialization pattern of recombinant DNA technology two decades ago are apparent. Differences in the entrepreneurial culture and the availability of venture capital affect the progress of commercialization of nanomedicine in Europe where less venture capital is available for startups than in the United States. Furthermore, commercialization of innovative medicines is hampered because of cost-regulated healthcare markets, and this limits the development of innovative high value drugs, including nanomedicines.

There is also currently a general discussion among scientists, industry and regulators about whether new regulations are needed to account for the specific pharmacokinetic properties of nanomedicines.

Nanotechnology activities throughout the US Food and Drug Administration are coordinated by the Office of Science and Health Coordination within the Office of the Commissioner. To identify the scientific and regulatory challenges in the area of nanotechnology, the FDA has established working groups at the level of the individual centers, as well as at the level of the Office of the Commissioner. FDA has also organized a task force charged with determining if new regulations or authorities are needed for oversight of nanotechnology.

FDA regulates products on a product-by-product basis and up to now the FDA has not required special testing of products containing nanoparticles. Examples of already approved drugs with particles in the nanosize range, include (i) products using nanocrystal technology (sirolimus (Rapamune), Wyeth Pharmaceuticals, Collegeville, PA, USA; Emend, Merck, Whitehouse Station, NJ, USA), (ii) liposomal formulations of drugs (Doxil, Ortho

Biotech, Bridgewater, NJ, USA; DaunoXome, Gilead, Foster City, CA, USA) and (iii) albumin-bound nanoparticles of paclitaxel (Abraxane, Abraxis BioScience, Schaumburg, IL, USA). Safety concerns specifically related to particle size were not identified during development of these products. FDA believes that the existing rigorous battery of safety tests that is currently required by the Center for Drug Evaluation and Research (CDER) for all new drugs, should identify relevant safety concerns associated with drugs that are reviewed by CDER. Therefore, CDER is not anticipating any new preclinical or chemistry manufacturing and control (CMC) guidance documents regarding nanomaterials in the near future. However, as science progresses, and if well-designed *in vivo* studies identify safety concerns that are specific to well-characterized products containing particles in the nanosize range, appropriate regulatory measures will be taken according to Nakissa Sadrieh, Associate Director for Research Policy and Implementation in the Office of Pharmaceutical Science, CDER.

In the EU, market authorization of medicinal products and medical devices is regulated on the European level. The European Medicines Agency (EMA) coordinates the evaluation and supervision of high-technology medicinal products such as those developed by means of biotechnological processes or that constitute a significant therapeutic, scientific or technical innovation. All nanomedicine products currently on the EU market have been authorized according to present legislation. The European Commission is currently taking a look at relevant European level legislation regarding its applicability to nanotechnology and the need for adopting new regulations<sup>6</sup>.

Investors are likely to be cautious about investing in early-stage nanomedicine innovations as long as it remains unclear which route regulatory authorities plan to take.

## Conclusions

Over the past decade, the first nanomedicine products have been introduced into the market. Compared with the total pharmaceutical and medical device market, nanomedicines currently constitute a tiny niche. For the most part, nanotechnology in medicine has an enabling function. In most cases, it constitutes only a functional component of a medical product; however, its great strength lies in its versatility: nanotechnology has the potential to add innovative functionality to many pharmaceutical products and medical devices. Since the beginning of this decade, the interest of the pharmaceutical and medical device industry is slowly picking up; patent activities in particular have increased in recent years. Nevertheless, the

investment of corporations in the development of nanomedicines is still very cautious and is currently the biggest stumbling block for commercialization. Furthermore, the uncertainty of whether novel nanotechnology-specific medical regulations will be implemented that might add further requirements to the approval process for nanomedicines hampers their commercialization.

An early clarification of this issue is important for companies planning investments in nanomedicines. Notwithstanding the commercial activities, nanomedicine is still technology driven and scientific challenges lie ahead. The chemistry of nanosized molecules is not well understood, and the manufacturing of such nanomaterials as dendrimers or pharmaceutical-grade liposomes is still costly<sup>7</sup>. Furthermore, much remains to be learned about the modification of nanoscale carriers so that circulation lifetime, biodistribution and penetration of biological tissues are optimized<sup>8,9</sup>.

Note: Supplementary information is available on the Nature Biotechnology website.

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## DISCLAIMER

The views expressed here are those of the authors and do not necessarily reflect the views of the European Commission.

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