National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM Report 2015-0149
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This investigation has been performed by order and for the account of the Health Care Inspectorate and the Ministry of Health, Welfare and Sport

This is a publication of:
National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Publiekssamenvatting

Nanotechnologie in medische hulpmiddelen

Nanotechnologie wordt steeds meer gebruikt voor medische hulpmiddelen. Talrijke medische disciplines profiteren van de innovaties die nanotechnologie mogelijk maakt. Ook neemt de kennis over hoe je de veiligheid van nanotechnologie moet beoordelen toe. Recente wetenschappelijke leidraden geven aan waarop moet worden gelet als nanotechnologie wordt gebruikt bij de fabricage van een medisch hulpmiddel. Kennis en leidraden vormen daarmee een goede basis om de risicobeoordeling van nanomedische hulpmiddelen uit te voeren. Dit blijkt uit een overzicht van het RIVM van het gebruik van nanotechnologie voor medische hulpmiddelen.

Een van de belangrijkste trends is het gebruik van nanocoatings op allerlei implantaten. Hierdoor integreert het implantaat beter met het omliggende weefsel, wat de kans op afstoten of complicaties verkleint. Onder andere de cardiologie (coating op stents), orthopedie (coatings op heupimplantaat) en tandheelkunde (tandheelkundige implantaten) profiteren hiervan. Verder worden antimicrobiële eigenschappen van nanomaterialen gebruikt in coatings, voor wondverzorging en medisch textiel.

Nanomaterialen kunnen ook natuurlijke weefsels nabootsen. Met behulp van nanotechnologie kunnen bij implantaten optimale biologische, fysische en mechanische eigenschappen worden gerealiseerd.

Een derde trend hangt samen met de elektrische en magnetische eigenschappen van nanomaterialen. Deze worden vooral gebruikt in medische hulpmiddelen voor neurologie en cardiologie, bijvoorbeeld om hartritmestoornissen beter te verhelpen. Ook kunnen batterijen met een langere levensduur worden ontwikkeld voor implantaten.

Een specifieke toepassing van nanotechnologie is oncologie. Voorbeelden zijn testen om kanker vroegtijdig op te sporen en hulpmiddelen om de grenzen te bepalen van tumoren of uitzaaiingen te detecteren tijdens een chirurgische ingreep. Ook kunnen nanomaterialen door lokale temperatuurverhogingen het effect van chemotherapie of bestraling versterken, of zelfs direct tumorcellen doden.

Net als bij alle medische producten moet de risicobeoordeling van nanomedische hulpmiddelen per product worden uitgevoerd. De kans dat een nanomateriaal vrij beschikbaar komt in het lichaam, bepaalt hoe diepgaand de ‘nano’ risicobeoordeling moet zijn.

Kernwoorden: nanotechnologie, nanomateriaal, medisch hulpmiddel, klinisch nut, risicobeoordeling

Synopsis

Nanotechnologies in medical devices

The application of nanotechnologies in medical devices is a growing area and numerous medical disciplines benefit from innovative features enabled by nanotechnologies. Knowledge about the safety evaluation of nanotechnology is also evolving. Recently, scientific guidance has become available, specifying considerations to be taken into account when nanotechnology is used for the manufacture of a medical device. The combination of knowledge and guidance forms a suitable basis for the risk assessment of nanomedical devices. These are the main conclusions of an overview performed by RIVM on applications of nanotechnology in medical devices.

One of the most important types of nanotechnological applications is nanocoatings, which increase biocompatibility and thus improve integration with the surrounding tissues of a variety of medical implants used, for example, in cardiology (stent coating), orthopaedics (coating on joint replacement implants) and dentistry (dental implants). In addition, antimicrobial properties of nanomaterials are used in coatings, and also in wound care and medical textiles.

Another clear trend is the use of nanomaterials to mimic naturally occurring structures. This leads to optimal biological, physical, and mechanical characteristics of implants.

A third trend of applications is related to the electrical and magnetic properties of materials on the nanoscale. This is especially relevant to medical devices used in neurology and cardiology, for instance to improve the treatment of cardiac arrhythmia. Furthermore, nanotechnologies enable the development of batteries with greatly increased lifetime for use in active implantable medical devices.

A number of nanotechnology applications are specific to oncology. Examples include diagnostic tests used in the early detection of cancer, and devices for the identification of the boundaries of a tumour or metastases during surgical interventions. Nanomaterials can also enhance the effect of therapies like chemotherapy or radiation therapy through locally increased temperature, or they can kill tumour cells directly at high temperature.

Like all medical products, the risk assessment of nanomedical devices needs to be performed on a case-by-case basis. The potential for release, leading to a higher or lower exposure to nanomaterials, is considered the most important feature driving the extent of the “nano” risk assessment.

Keywords: nanotechnology, nanomaterial, medical device, clinical benefits, risk assessment

Contents

Summary

The RIVM conducted an investigation to provide insights into and an overview of the field of medical devices using nanotechnologies, for products already on the market and for those expected within five years. This investigation was performed at the request of the Dutch Health Care Inspectorate and the Dutch Ministry of Health, Welfare and Sport.

In order to obtain an overview of medical devices using nanotechnologies, the following sources were used: scientific literature (retrieved using Pubmed and Scopus), databases on medical devices including the 510(k) Premarket Notification database of the US Food and Drug Administration (FDA) and the Health Canada Medical Device database, clinical trial databases such as ClinicalTrials.gov and the International Clinical Trials Registry Platform of the World Health Organization, and the database of the European Patent Office. In addition, European and international guidance documents of regulatory bodies on nanomaterials and nanotechnologies were consulted.

The size range of approximately 1 nm to 100 nm is commonly used to define nanomaterials and nanotechnologies. This is an arbitrary choice, with no clear scientific argumentation. In this report, the size range was not restricted to the upper limit of 100 nm, but included applications based on structures up to 1000 nm. This is in line with the approach followed by regulatory bodies like the European Medicines Agency, FDA, and Health Canada.

The application of nanotechnologies in medical devices is a growing area and numerous medical disciplines benefit from innovative features enabled by nanotechnologies.

A number of general trends can be identified with regard to the application of nanotechnologies in medical devices and their benefits. One of the most important types of applications is nanocoatings and/or surface modifications which create an increased biocompatibility and thus improved integration with surrounding tissues of a variety of medical implants used, for example, in cardiology (e.g. stents, catheter balloons), orthopaedics (e.g. joint replacement implants) and dentistry (e.g. dental implants). In addition, the antimicrobial properties of nanomaterials are used in coatings as well as in wound care and medical textiles.

Another clear trend is the use of nanomaterials to mimic naturally occurring structures. This feature is applied in dentistry and in orthopaedics for both dental and bone filler materials, but also for applications in cardiology, neurology and wound care. It yields optimal biological, physical, mechanical properties, and for dental fillers it also improves aesthetic characteristics.

Especially relevant to neurology and cardiology, a third trend of nanotechnological applications is related to the electrical and magnetic properties of materials at the nanoscale. Future nanosized applications may provide a significantly improved bioelectrical interface between a

device and the surrounding neural tissue. Furthermore, nanotechnologies enable the development of batteries with greatly increased lifetime for use in active implantable medical devices such as pacemakers and cardioverter defibrillators.

A number of nanotechnology applications are specific to oncology. Examples include diagnostic tests used in the early detection of cancer, and devices used for the identification of the boundaries of a tumour or metastases during surgical interventions. Nanomaterials can enhance the effect of cancer therapies like chemotherapy or radiation therapy when injected into a tumour and placed in an alternating magnetic field, generating an increase in temperature (hyperthermia). A high increase in temperature damages cell structures, resulting in cancer cell destruction (thermoablation).

At the moment, knowledge is evolving on the safety evaluation of nanomaterials in general, and thus also when used in medical devices. Current state-of-the-art guidance provides a suitable base for performing the risk assessment of nanomedical devices. Nanomaterials exhibit specific characteristics that may or may not lead to toxic effects. As for all medical products, risk assessment of nanomedical products needs to be performed on a case-by-case basis. The potential for release, leading to a higher or lower exposure to nanomaterials, is considered the most important feature driving the extent of the risk assessment to be performed.

1 Introduction

It is widely anticipated that innovative medical applications of nanotechnologies will have a profound impact on health care in the near future (Bleeker *et al.*, 2015). New opportunities will become available for the diagnosis, treatment, monitoring and prevention of disease. These nanotechnology applications relate to both medicinal products and medical devices. This paper focuses on nanotechnology applications for medical devices.

Nanotechnology applications in the field of medical devices span a wide range of extremely diverse products, technologies and application areas. Their intended use can be for therapy, diagnosis, monitoring or prevention of disease. Devices can be non-invasive or invasive, contacting any kind of tissue. Nanomedical devices can involve the use of nanomaterials, however, nanotechnologies also enable innovative devices without using nanomaterials, for example by applying nano-electronics or lab-on-a-chip technologies (Bleeker *et al.*, 2015). All medical disciplines are benefiting from nanomedical devices, especially orthopaedics, dentistry, oncology, neurology and cardiology. In addition, a number of innovations in clinical chemistry laboratories are enabled by nanotechnology (Hermsen *et al.*, 2013).
While the advantages are highly desirable, the emergence of innovative nanomedical products also gives rise to questions whether currently used risk assessment strategies and testing methods provide a sound scientific basis for an adequate evaluation of the quality, safety and efficacy of these products within the current regulatory framework (SCENIHR, 2015).

For the Dutch government, it is strategically important to be aware of new and emerging technologies, and the benefits as well as the risks they bring. Nanotechnologies are used in a large number of medical devices, however, there is no comprehensive overview of these products. The Ministry of Health, Welfare and Sports and the Health Care Inspectorate asked the RIVM to provide insights into and an overview of the field of medical devices using nanotechnologies, for products already on the market and for those expected within 5 years.

2 Definition of nanotechnologies in medical devices

The current regulatory framework for medical devices contains no specific provisions for nanotechnologies. Currently, a revision process of the regulatory framework for medical devices is ongoing. Partly based on recommendations made by the European Commission Working Group on New and Emerging Technologies in Medical Devices (NET WG, 2007), it was decided that specific provisions are warranted in relation to nanomaterials, but not to nanotechnologies in general. The European Commission has published a proposal for a revision of the medical devices legislation (EC, 2012) which includes a definition of nanomaterial taken from Commission Recommendation 2011/969/EU on the definition of nanomaterial (EC, 2011): 'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm.
The size range of approximately 1 nm to 100 nm is commonly used in various other working definitions or descriptions of nanotechnology proposed by the regulatory and scientific community (ISO/TS 80004-1:2010; OECD, 2011). There is, however, general consensus that the upper limit of 100 nm is not based on scientific arguments, and that size-related phenomena can also occur at sizes above 100 nm (Rauscher *et al.*, 2015; SCENIHR, 2009). At the present time, the available scientific information does not establish a uniform upper boundary above 100 nm where novel properties and phenomena similar to those seen in materials with dimensions in the nanoscale range cease to occur for all potential materials or end products. For this reason, the US Food and Drug Administration (FDA) finds it reasonable to consider evaluation of materials or end products engineered to exhibit properties or phenomena attributable to dimensions up to 1000 nm, as a means to screen materials for further examination and to determine whether these materials exhibit properties or phenomena attributable to their dimension(s) and associated with the application of nanotechnology (FDA, 2014). Also according to Health Canada's working definition for nanomaterial, the term "nanoscale" means 1 nm to 100 nm inclusive. However, individual Canadian regulatory programs may request information above the 100 nm size range to an upper limit of 1000 nm in order to maintain flexibility when assessing potential nanomaterials, including suspected nanoscale properties and phenomena (Health Canada, 2011). In Europe, the European Medicines Agency (EMA) currently states that 'nanotechnology is the use of tiny structures - less than 1000 nm across - that are designed to have specific properties'. Based on these considerations, this report is not restricted to the use of structures with an upper limit of 100 nm, but also includes applications with structures up to 1000 nm.

3 Methods

3.1 Literature study

An electronic literature search of PubMed and Scopus was performed using relevant keywords for each particular medical specialism and medical device category, combined with nano, nanotechnology and nanomaterial. Relevant reviews and research articles were used to identify current products and potential short-term future developments within the different categories. Internet searches using Google were performed to find additional information for products found using other sources, e.g. to determine whether the product was actually enabled by nanotechnologies, whether the product was on the market, or whether it was in clinical investigation. Furthermore, the internet was searched for available commercial market reports with overviews of nanomedical products. Two reports were selected and purchased based on publication date and inclusion of data on nanomedical devices in addition to nanomedicinal products.

3.2 US Food and Drug Administration and Health Canada medical device databases

The 510(k) Premarket Notification database (FDA) was accessed on April 13, 2015 to search for medical devices containing nanotechnology. Two search strategies were employed. First, a search for "nano" in the search field "Device Name" resulted in 65 hits. Second, a search for "nano" in the search field "Applicant" resulted in 45 hits. All other fields were left empty. The hits were exported to MS Excel. All hits were manually checked via internet searches to confirm the use of nanotechnology within the product. The FDA confirmed that their 510(k) Premarket Notification database is their only database that enables a broad search on nanomedical devices, and that our approach was the best method to extract data on nanomedical devices from the database [FDA, personal communication].

The Medical Device Active Licence Listing database (Health Canada) was accessed on April 14, 2015 to search for medical devices containing nanotechnology. The database was searched for "nano" in the search option "Device Name", resulting in 119 hits. The hits were exported to MS Excel. All hits were manually checked via internet searches to confirm the use of nanotechnology within the product.

3.3 Clinical trial databases

A clinical trial web search was conducted using the databases ClinicalTrials.gov of the US National Institute of Health (ClinicalTrials.gov), International Standard Randomised Controlled Trial Number (ISRCTN), and International Clinical Trials Registry Platform of the World Health Organization (ICTRP WHO). The ICTRP WHO database includes several databases, including the ClinicalTrials.gov database. All databases were accessed on April 2, 2015. The search term "nano" was used for the search in the ClinicalTrials.gov and ISRCTN databases. In the ICTRP WHO database "nano*" was used (search period 2002 - March 2015). The web search resulted in 81, 3, and 510 clinical trials in the ClinicalTrials.gov,

ISRCTN, and ICTRP WHO databases, respectively. Information on these trials was downloaded to exclude non-medical device trials such as drug trials or radiopharmaceutical trials, duplicate trials, and trials that did not actually involve nanotechnology. Using the trial identification number, each trial was retrieved from the corresponding database and the information was assessed manually. In total, 115 clinical trials were identified. Selected clinical trials were assessed to add a medical speciality, e.g. dentistry, oncology, orthopaedics etc., for each trial. Subsequently, the resulting information was analysed using IBM SPSS Statistics (IBM Corporation, USA; version 22).

3.4 Patent search

The database of the European Patent Office (Espacenet) was used to search for nanomedical device patents in the European patent (EP) collection, including full text of European published patent applications. Searching for European patents, instead of worldwide patents, was chosen because of a focus on European nanomedical devices and due to time constraints. It is likely that searching in the worldwide database (Espacenet worldwide collection of 90+ countries) would have resulted in more patents found, however this result would also include patents that are not valid in any of the European member states. The Espacenet EP collection was searched per nanomedical device category using the following four search strategies:

1. International Patent Classification (IPC) symbols for medical device category combined with IPC classification symbol for nanotechnology;
2. IPC classification symbol for nanotechnology combined with keywords of medical device category in title or abstract;
3. IPC classification symbols for medical device category combined with keywords related to nanotechnology in title or abstract;
4. keywords of medical device category in title or abstract combined with keywords related to nanotechnology in title or abstract.

IPC classification codes were obtained from the World Intellectual Property Organization (WIPO) by searching for keyword terms. A keyword search of the title and abstract, instead of full text, was used to obtain specificity. The term “medical” (in full text) was used in certain categories to obtain specificity for medical applications. Espacenet has a limit of 10 keywords and 1000 wildcard entries. Search results were exported in XLS, subsequently combined, and duplicates were removed based on publication number. Withdrawn, lapsed or non-nanomedical device category patents were removed after manual examination. Patents that fit another nanomedical device category were moved accordingly. These different strategies allowed the capture of a large number of patents related to nanomedical devices. However, as the focus was only on patents related to a medical application, more general patents that could in theory be used in nanomedical devices were excluded when this was not stated in the patent application description or claims (e.g. general material patents). Patents were included in only one category. It was difficult to determine whether patents were already being used in actual products. Manufacturers do not often state which patents are used in their products, and reversely, patent applications do not state in which products they are used. In addition, patents can be

concerned with more general technologies that can be used by a multitude of manufacturers in a different range of products.

4 Medical devices enabled by nanotechnologies

Many medical disciplines benefit from medical devices enabled by nanotechnologies, also indicated as "nanomedical devices". This chapter provides an overview of the use of nanomedical devices in cardiology, dentistry, neurology, oncology and orthopaedics. In addition, applications related to surgery as well as textiles and wound care products are included. Lab-on-a-chip devices for clinical diagnostics, which are often enabled by nanotechnology, are not included as a previous RIVM report was specifically dedicated to this category of medical devices (Hermsen *et al.*, 2013).
At the end of this chapter, analyses of the data resulting from the clinical trial databases and patent searches are included in order to provide additional insights in trends related to the various medical disciplines and recent developments.

4.1 Cardiology

Different categories of implantable medical devices contribute to the treatment of cardiovascular disease, structural heart disease, and cardiac arrhythmia. Examples of such devices that are the mainstay of (interventional) cardiology, including cardiac surgery are stents, ventricular assist devices, and pacemakers. In the following section examples of endovascular medical devices for the treatment of peripheral artery disease are also given. Treatment of peripheral artery disease is usually performed by an interventional radiologist and not by an interventional cardiologist.

Current

Stents

Coronary stents are one of the most used implantable medical devices in the USA (Allen, 2011). Coronary stents are tubular devices placed by a catheter within a coronary blood vessel for the treatment of patients with coronary artery disease. Stents support a segment of a blood vessel or any other anatomical lumen so as to preserve or regain its patency. Stents are also used for the treatment of patients with peripheral artery disease, e.g. blood vessel narrowing in the lower and upper leg. Several types of stents are currently on the market, such as bare metal, drug-eluting, and bioresorbable vascular scaffolds. Nanotechnology holds great promise for these medical devices: several nanocoated bare metal and drug-eluting stents for the treatment of patients with coronary as well as peripheral artery disease are currently available (Table 4.1.1).

Diamond-like carbon is a class of material with excellent biological, mechanical, and tribological properties. It can be deposited on many substrates such as body fluid contacting parts of implantable medical devices. Coating technologies such as Carbofilm™ (coating thickness ≤500 nm), iCarbofilm™ (also known as Bio Inducer Surface coating, <300 nm) or the diamond-like carbon coating (average thickness 35 nm) used by Japan Stent Technology Co Ltd (Japan) bring similarity to

the diamond structure of pure carbon and its exceptional biocompatibility and haemocompatibility. The haemocompatibility of diamond-like carbon coatings is attributed to their hydrophobicity and surface smoothness. A modified coating technology is the Dylyn™ technology, which is a diamond-like nanocomposite-coating containing Si:O. The major limitation of diamond-like carbon coatings is the microcracks that can form on the surface of metal substrates.
The Inert Carbon Technology (ENDOCOR GmbH, Germany) is a surface modification created by high speed bombardment of carbon ions under vacuum conditions onto the stent's surface. The carbon ions are implanted within the metal lattice under the stent surface. The depth of implantation of carbon ions is 50 nm. The Inert Carbon Technology creates a barrier for migrating heavy metal ions such as chromium, molybdenum and nickel, which would be ideal for patients suffering from metal allergy.

Polyzene®-F surface technology from CeloNova Biosciences, Inc (USA) is an advanced surface modification that is thrombo-resistant, promotes rapid endothelialisation. Polyzene®-F is a nano-thin (≤50 nm) polymer coating applied to bare metal stents, helping physicians to achieve improved efficacy without the burden of long-term anti-platelet therapy.
The Camouflage® nanocoating (100 nm) developed by eucatech AG (Germany) is a modified heparine. It is a synthetic glycocalyx covalently bonded to the stent surface. The Camouflage® nanocoating leads to masking of the stent surface which prevents pathological reactions triggered by foreign surfaces and provides biomimicry of the arterial glycocalyx.

A proprietary process has been developed by Hexacath (France) to coat titanium-nitride-oxide on the surface of the stent, based on a plasma technology using the nanosynthesis of a prespecified gas mixture of nitrogen and oxygen and metal. This plasma-enhanced vapour deposition of titanium in a vacuum chamber can be applied to different metals, for instance stainless steel, cobalt-chromium-cobalt or nickel-titanium alloys. This coating is extremely dense and hard, making titanium-nitride-oxide coated stents extremely well adapted for direct stenting.

Supercritical fluid-based techniques are applied to the production of nanoparticles, nanofibres, nanowires, nanotubes, nanofilms and nanostructured materials (Fulton *et al.*, 2003) and result in nanomaterials with potentially better performances. Supercritical fluid technology is used to apply to the electrostatic coating process, resulting in the deposition of dry powder, crystalline hydrophilic drugs, e.g. sirolimus, onto the stent surface. Because the drug is never dissolved in solvent, the crystal structure is maintained during application of the coating. Drug and polymer are layered onto the stent and each layer is sintered to fuse the coating into a smooth, conformal, well-adhered film. Maintaining the crystalline structure of sirolimus within the coating confers enhanced drug stability.
The ProPass™ stent is a bare metal coronary stent system with a platinum coating (250 nm) and is marketed by Vascular Concepts Ltd (UK). The platinum coating ensures microsmooth surface architecture.

Table 4.1.1 Cardiac medical device categories and examples of CE-marked devices utilizing nanotechnologies (non-exhaustive)

Manufacturer	Medical device	Coating	Application
Bare metal stent			
Alvimedica, Turkey[1]	Chrono	Carbofilm™	CAD
	Avantgarde	iCarbofilm™	CAD
Blue Medical Devices BV, Netherlands[2]	XTRM-FIT	Dylyn™	CAD
CeloNova Biosciences Inc, USA	CATANIA™	Polyzene®-F	CAD
	COBRA PzF™	Polyzene®-F	CAD
eucatech AG, Germany	CCFLex ProActive	Camouflage®	CAD
ENDOCOR GmbH, Germany[3]	GHOST™	Inert Carbon Technology	CAD
Hexacath, France[4]	Titan2®	PEVP technology	CAD
	Titan Optimax	PEVP technology	CAD
Japan Stent Technology Co Ltd, Japan	MOMO®	diamond-like carbon	CAD
Vascular Concepts Ltd, UK	ProPass™	platinum	CAD
Drug-eluting stent			
Alvimedica, Turkey[5]	Optima Jet	Carbofilm™	CAD
	Cre8™	Bio Inducer Surface	CAD
ENDOCOR GmbH, Germany	SEQUENCE™	Inert Carbon Technology	CAD
Micell Technologies Inc, USA	MiStent®	SCF technology	CAD
Drug-coated balloon			
Eurocor GmbH, Germany	DIOR®[6]	nanoporous shellac[7]	CAD
	MAGICAL™[8]	nanoporous shellac	CAD
Pacemaker lead			
Biotronik SE & Co KG , Germany	Safio[9]	fractal coating	CRM
Implantable cardioverter defibrillator lead			
Biotronik SE & Co KG , Germany	Linox smart	fractal coating	CRM
Cardiac resynchronization lead			
Biotronik SE & Co KG , Germany	Corox OTW BP[10]	fractal coating	CRM

Abbreviations: CAD – coronary artery disease, CRM – cardiac rhythm management, PEVP – plasma-enhanced vapour deposition, SCF – supercritical fluid.

[1] The endovascular (renal, iliac, and femoropopliteal region) portfolio of Alvimedica includes bare metal stents with Carbofilm™ coating (Radix 2) and iCarbofilm™ or Bio Inducer Surface coating (Easy HiFlype, Isthmus Logic, Easy Flype, and Inperia Advance). The Chrono and Avantgarde coronary stent systems were developed by CID Srl (Italy).

[2] Blue Medical Devices BV went bankrupt and was taken over by Wellinq Holding BV in 2013. XTRM-FIT is not available anymore on the website.

[3] ENDOCOR GmbH commercializes GHOST PV™ a balloon expandable peripheral stent system with Inert Carbon Technology.

[4] Hexacath's endovascular portfolio includes bio active stents with titanium nitride oxide coating for the treatment of peripheral artery disease (HeliFlex^{Ti}) and renal artery disease (Helios^{SD}).

[5] The Optima Jet drug-eluting coronary stent system was developed by CID Srl (Italy). The Optima Jet has reservoirs of tracolimus coated with Carboflim™. Alvimedica's endovascular portfolio (below the knee region (BTK)) includes Cre8™ BTK with Bio Inducer Surface coating.

[6] Eurocor's portfolio includes the second generation peripheral drug-eluting dilatation catheters FREEWAY™ 014 and FREEWAY™ 035.

[7] Shellac is a natural resin composed of shelloic and alleuritic acid.

[8] MAGICAL™ is a GENIUS® MAGIC CC bare metal stent delivered by the DIOR® drug-coated balloon.
[9] Biotronik's pacemaker lead portfolio includes Selox, Setrox, Siello and Solia leads.
[10] Biotronik's cardiac resynchronization lead portfolio includes Sentus OTW Quadripolar and Sentus OTW Bipolar.

Drug-coated balloons

The DIOR® coronary balloon dilatation catheter (Eurocor GmbH, Germany) is coated with a nanoporous matrix consisting of shellac, a natural resin, and paclitaxel. In contact with body liquid, i.e. blood, the hydrophilic shellac network of the nanoporous composite swells and opens the structure for pressure-induced fast release of paclitaxel on the inflated balloon. Drug-coated balloons have already proven effective in clinical trials for the treatment of in-stent restenosis. Its coronary application may potentially be widened to complex coronary *de novo* lesion subsets, such as small diameter vessels, diabetes, and diffuse lesions, where the use of stents may be hampered by suboptimal results (Loh and Waksman, 2012). Drug-coated balloons are also combined with bare metal stents. For example, the MAGICAL® drug-eluting stent system (Eurocor Gmbh, Germany) represents state-of-the-art stent technology of the GENIUS® MAGIC CC bare metal stent delivered by the DIOR® paclitaxel-eluting coronary balloon dilatation catheter.

Ventricular assist devices

Ventricular assist devices were born out of a need to support clinically deteriorating patients for whom organ shortage precludes immediate transplantation. Current implantable left ventricular assist devices support the blood stream adequately. Ventricular assist devices are now used to treat patients with terminal heart failure, not only as a bridge to transplantation, but also as a bridge to recovery or destination therapy in selected patients. The VentrAssist™ (Ventracor Ltd, Australia) is a third generation pump (i.e., magnetically-elevated pump impeller) with a diamond-like carbon coating on the blood-contacting surfaces which minimizes thrombosis. VentrAssist™ was implanted in more than 400 patients worldwide before the company collapsed in 2009. Ventracor's intellectual property was sold to Thoratec Corporation (USA). No data were identified on the structural dimensions of the diamond-like coatings. However, given the manufacturing technology, this can be considered a nanotechnology-enabled device.

Cardiac rhythm management devices

Fractal coating of implantable pacing leads (i.e. the tip of the electrode) for bradycardia therapy, tachyarrhythmia therapy, and cardiac resynchronisation optimises the electrically active surface area of the lead. The electrochemical area of the tip is dramatically increased by tissue fluid penetrating the space between the micro/nanoporous surface of the electrode, leading to lower polarization and increased sensing capabilities. In addition, a small geometric surface and therefore a low stimulation threshold can be achieved. Fractal surface coating of the tip improves its electrical sensing and pacing properties (Safak et al., 2013). The electrode is coated with a thin layer of iridium using physical vapour deposition technology creating a cauliflower-like

structure. Biotronik SE & Co KG (Germany) is the forerunner in this field, and is the only manufacturer of fractal coated leads (Table 4.1.1). Fractal-coated temporary pacing leads can be also be used for treatment and diagnosis of arrhythmias following open heart surgery procedures (Mellert et al., 2008).

St. Jude Medical, Inc (USA) has been using giant magnetoresistive-based high-speed communication systems for its pacemakers since 2001 (NVE Corporation, 2001). Giant magnetoresistive sensors are made of sandwiches of thin films consisting of alternating nanometre thick layers of magnetic and nonmagnetic layers. Giant magnetoresistive components are highly stable and sensitive magnetic sensors that replace the reeds of conventional pacemakers. Pacemakers must be tuned to the specific needs of each person's body. Physicians use magnetics to tune the pacemaker from outside the body. The device that responds to the magnetic signals is usually the reed switch. Giant magnetoresistive sensors are an order of magnitude more sensitive than reed sensors, and they are solid-state devices, not mechanical. These sensors allow the pacemaker to communicate information about heart function and to receive new instructions faster and more reliably.

Future perspectives

Stents

Technologies to modify stent surfaces can be broadly classified as nanopatterned stent surfaces/coatings, which may or may not be loaded with a drug, and nanocarriers on stents, which are based on encapsulating drugs in nanocarriers, later coated onto stents (Arsiwala *et al.*, 2014).

Microporous and nanoporous stent surfaces are intriguing because of their capacity to increase drug loading and influence drug release kinetics without the need for a polymer coating. Bare metal stents with a microporous surface are, for example, Cobal+C and Cobal+CE (Relisys Medical Devices Ltd, India) and the Yukon® Choice PC (Translumina, Germany). An example of a drug-eluting stent with microporous surface is the Yukon® Choice DES (Translumina, Germany), and an example of a nanothin microporous surface is the VESTAsync™ (MIV Therapeutics, USA). The VESTAsync™ stent is coated with hydroxyapatite (thickness 300-1000 nm) with a porosity of 40-60% in volume. The stent showed promising results in a first-in-man clinical trial (Costa *et al.*, 2009) and a randomised clinical trial (Costa *et al.*, 2014). A novel concept is the Nano+™ Polymer-free Sirolimus-eluting Coronary Stent System (Lepu Medical Technology Co Ltd, China) which utilises nano-sized pores on the stent surface. The nanoporous cavity serves as a drug carrier, and more than 80% surface porosity guarantees firm adhesion of the drug. The pore diameter is 400 nm (Suwannasom *et al.*, 2015). Currently, the Nano+™ is under clinical investigation (Table 4.1.2). The Bicare™ stent (Lepu Medical Technology Co Ltd, China) has a platform identical to the Nano+™ stent, but with a dual drug elution of sirolimus and probucol. In a first-in-man study, the Bicare™ stent demonstrated absence of early adverse safety events (Yu *et al.*, 2014). The BuMA Supreme stent (Sino Medical Sciences Technology Inc, China) is a novel (second generation) biodegradable polymer drug-eluting stent (Table 4.1.2). An electro-

grafting (eG™) base layer (poly(n-butyl methacrylate) coating) is added between the biodegradable polymer drug carrier and the metal (cobalt-chromium) stent strut. The eG™ layer (thickness 100-200 nm) secures the adhesion of the biodegradable polymer coating through interdigitation and prevents cracking and delamination upon stent expansion. It also has the benefit of supressing corrosion and ion release from metal substrates which could contribute to a lower local inflammation response *in vivo*. The patented eG™ coating technology was acquired from AlchiMedics SA (France). Currently, the BuMA Supreme stent is in clinical trial in Europe. The first generation (stainless steel) BuMA™ sirolimus-eluting stent has been approved in China.

The creation of nanotopography, such as nanopillars and nanopits, on the metal struts of the stent, using radiofrequency plasma surface texturing, influences the growth and proliferation of endothelial cells. Of note, surfaces with a defined nanopatterned grid demonstrated a higher percentage of endothelial coverage, compared to responses observed on random nanostructured surfaces. Interestingly, nanostructured surfaces, when compared to microstructured surfaces, appear to afford greater adhesion of endothelial cells, lead to higher cell densities, and to enhanced adhesion and spreading.

Table 4.1.2. Registered clinical trials on new medical devices

Product	**Company or organisation**	**Appli-cation**	**Phase**	**Reference**
Nano+ Sirolimus-Eluting Stent	Lepu Medical Technology (Beijing) Co Ltd, China	CAD	NA	http://clinicaltrials.gov/show/NCT01925027
BuMA Supreme Sirolimus-Eluting Stent	Sino Medical Sciences Technology Inc, China	CAD	NA	http://clinicaltrials.gov/show/NCT02236975
FOCUS np™ Sirolimus Based Nano Carrier Eluting Coronary Stent System	Envision Scientific Pvt Ltd, India	CAD	NA	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3165
Magic Touch™ Nano Sirolimus Drug Coated Balloon Catheter	Concept Medical Research Pvt Ltd, India	CAD	NA	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3971
Plasmonic photothermal and stem cell therapy (trial has been completed)	Ural State Medical Academy, Russia	CAD	NA	http://clinicaltrials.gov/show/NCT01270139

Abbreviations: CAD – coronary artery disease ; NA – not available

Sub-micron rough and nanometre rough stent surfaces lead to a higher endothelial cell attachment with lesser platelet adhesion compared to stents without these features. A technology like this may even bypass the need for long-term (dual) antiplatelet therapy (Arsiwala *et al.*, 2014).

Nanoparticles have been extensively applied in various drug delivery systems. However, few studies have reported the results of stent surfaces coated with nanoparticles. For example, an active coating of nanoparticles was deposited on the surfaces of metallic stents via cationic electrodeposition technology. Preclinical studies in animal models evaluated the feasibility of this nanoparticle-eluting stent system. It was concluded that the nanoparticle-eluting stent is a potential innovative platform exhibiting unique aspects in vascular compatibility and an efficient drug delivery system compared with the dip-coated polymer-eluting stent (Nakano *et al.*, 2009). Another interesting nanoparticle-mediated drug delivery system is composed of endothelial cells loaded with magnetic nanoparticles. Instead of being coated directly on the stent surface, endothelial cells were loaded first with magnetic nanoparticles and then injected into rats with stainless steel stents placed in their carotid arteries. When a magnetic field was applied, these magnetic nanoparticle-loaded cells were preferentially driven to the stented area and remained attached (Polyak *et al.*, 2008). Although promising results have been reported, further evaluation of this technology in animal studies and clinical trials is required.

A patented nanocarrier technology (Nanoactive™) developed by Envision Scientific Pvt Ltd (India) enables encapsulation of a drug at nanometre size and can be used for hydrophilic (e.g. sirolimus) as well as hydrophobic (e.g. paclitaxel) drugs. The NanoActive™ technology has been applied to a novel stent platform, the FOCUSnp™ Stent System (Envision Scientific Pvt Ltd). Phospholipid bilayer nanoparticles (mean diameter ~200 nm) containing sirolimus are sprayed on the polymer-free cobalt-chromium FOCUSnp™ stent after it has been crimped onto the balloon delivery catheter. A calcium phosphorous-based component is added to the nanoparticles, making them sensitive to subtle variations in pH, thus controlling the release of the drug content. Thus, the FOCUSnp™ Stent System delivers sirolimus through nanoparticles from the (abluminal) stent strut area and the balloon. Promising results were obtained in an animal study (Takimura *et al.*, 2015). Currently, the FOCUSnp™ is under clinical investigation (Table 4.1.2).

Using a technique called layer-by-layer (polymer) self-assembly for tunable multiple drug release in thin films (Tan *et al.*, 2013) is another way to achieve controlled and sustained drug release. The film architecture is precisely designed (up to 1 nm precision) and can be controlled through fabrication parameters. Layer-by-layer coatings on stents with both anti-proliferative and anti-thrombogenic drugs can mitigate problems like in-stent restenosis and stent thrombosis inherent to current bare metal and drug-eluting stents. The layer-by-layer coating can be fine-tuned to match blood vessel healing times. In addition, multilayers can be functionalized with bioactive molecules such as nitric oxide to reduce platelet adhesion, antibodies to encourage endothelialisation, and DNA for gene therapy. The layer-by-layer coating technique is currently in the experimental phase. No animal studies or clinical trials have yet been conducted. Issues like maintaining batch-to-batch consistency and the advantage of this technique over conventional spray coating or dip coating still has to be demonstrated.

Covered stents / endovascular stent grafts / vascular grafts

Complications associated with bare metal and drug-eluting stents, such as injury, rupture or perforation of the vessel wall and embolization of dislodged atherosclerotic plaque fragments during stent placement, have led to the development of covered stents. Covered stents usually have a (ultra-)thin (micrometre range thickness) synthetic membrane sleeve that either covers the interior lumen or the outside surface of the metallic scaffold of the stent, or completely covers the stent in a sandwich like manner (Farhatnia *et al.*, 2013). They can be used to treat perforations, heavy thrombus burden, and pathological conditions such as congenital vascular disease and fistulae. Covered stents used to treat aneurysms, a weak spot in an artery, are also known as endovascular stent grafts. Physicians typically use endovascular stent grafting to treat abdominal aortic aneurysms, thoracic aortic aneurysms and, less commonly, aneurysms at other locations.

Commonly, (ultra-)thin synthetic polymers are used as covering material, for example, polytetrafluoroethylene (PTFE), polyethylene terephthalate (PET) and polyurethane (PU). More recent developments and approaches use nanomaterials to develop synthetic nanocomposite materials. For example, polyhedral oligomeric silsesquioxane (POSS) nanoparticles (~1.5 nm diameter) can be incorporated into poly(carbonate-urea) urethane (PCU) through covalent modification (Ghanbari *et al.*, 2011). POSS-PCU nanocomposite has shown excellent haemocompatibility with anti-inflammatory and anti-thrombogenic surface properties. Incorporation of POSS nanocage structures change the morphology of the PCU polymer, and provides a surface roughness on a nanometre scale which is more favourable for endothelial cell interactions and cellular behaviour through adhesion, growth, and proliferation than is a smoother surface profile. In addition, the functional groups of the POSS nanocage structure within POSS-PCU have the potential to be further modified by incorporation of bioactive peptides, growth factors, receptor ligands and/or antibodies with the polymeric matrix.

In recent years, other nanocomposites utilising nanofibrous bacterial cellulose, silk fibroin, carbon nanotubes and iron oxide magnetic nanoparticles have been explored for cardiovascular stent and graft applications (Vellayappan *et al.*, 2015). Bacterial cellulose inclusion in a material was found to improve the mechanical strength and blood compatibility of the nanocomposite. Silk fibroin improves the mechanical strength of the matrix material. Carbon nanotube inclusion improves haemocompatibility, endothelialisation and mechanical strength. When iron oxide magnetic nanoparticles are incorporated in the matrix material, they are found to improve the antibacterial activity of the host. The company Nano4Imaging GmbH (Germany) (Nano4Imaging) has developed a proprietary technology able to modify most existing medical devices such as biopsy needles, catheters and guide wires with small markers (often metal nanoparticles), creating optimal visibility and enable navigation in multiple imaging systems including MRI, CT, X-ray, ultrasound. In 2014 they received the CE mark for an MRI-conditional guide wire which is safe to use in 1.5 and 3.0 Tesla for real-time interventions.

Electrospinning is an emerging polymer processing technique. It was discovered in the early 1900s and allows the creation of polymer nanofibres with thicknesses ranging from nanoscale to microscale. Proper selection of the processing parameters has also been shown to create polymer fibres characterised by regular structure, i.e. nanopores and nanopits (Bognitzki *et al.*, 2001). Electrospinning offers a way to form a non-woven fabric and fabrics with complex shapes. Electrospun materials have high surface-to-weight and volume ratios, which make these materials candidates for controlled biological interactions. If biodegradable materials are used, the scaffolding is eventually absorbed.

Electrospun polymeric nanofibres are promising materials for vascular grafts, as they provide topographical and biochemical cues that resemble the extracellular matrix and constitute aligned architectures that guide cell growth and spreading. In particular, aligned nanofibrous scaffolds positively affect various endothelial cell behaviours (Du *et al.*, 2011; Feng *et al.*, 2010). Combining different micro- and nanotopographic cues by complementary soft lithography and electrospinning technologies provides an interesting perspective for engineered vascular replacement constructions (Moffa *et al.*, 2014). In general, these promising strategies consist of seeding endothelial cells in the graft lumen before implantation. Thus, potential products will not be regulated as medical devices.

Drug-coated balloons

Concept Medical Pvt Ltd (India) developed the Magic Touch™ Nano Sirolimus Drug Coated Balloon Catheter based on the patented Nanoluté™ Nanocarrier Technology. The Nanocarrier term refers to a biological excipient carrier with drug, where both the components are at nanometre size range (50-300 nm). Currently, the Magic Touch™ is in clinical trials (Table 4.1.2) and is available for in-stent restenosis, small vessels, bifurcation coronary artery lesions, and other lesions difficult to treat with stent implantation.

Plasmonic photothermal therapy and stem cells

Investigators hypothesise that plasmonic photothermal therapy using gold nanoparticles with silica-iron oxide shells in stem cells can resolve coronary atherosclerosis (Table 4.1.2). Gold nanoparticles with silica-iron oxide shells promise high-energy plasmonic photothermic burning or melting effects under the near-infrared laser irradiation, and stem cells promise restoration of the vessel wall. The results of the first-in-man trial showed that plasmonic photothermal therapy using silica-gold nanoparticles was associated with significant regression of coronary atherosclerosis (Kharlamov *et al.*, 2015).

The efficacy of nanoshell technologies is limited by gaps in current understanding of the thermal interactions between nanoshell particles and laser light pulses or continuous waves in the context of complex biological environments. Irradiation, even with moderate pulses of energy, can induce melting, evaporation, and fragmentation of nanoparticles. These events can drastically alter the intended

therapeutic effects and lead to the formation of vapour bubbles (Lapotko, 2009).

Heart valves

Heart valve concepts are under development for the treatment of patients with structural heart disease. Several materials/techniques have been explored.
In situ tissue engineering is a promising route to create living heart valves within the body at the site of destination allowing integration into the body (Mol *et al.*, 2009). In this innovative approach, cell-free electrospun scaffolds gradually transform into living substitutes that replace the affected valve. Repopulation of scaffolds *in situ* is most likely to occur due to a combination of cell migration from adjacent tissues and cell capture from the blood. Compared to classical *in vitro* heart valve tissue engineering, this technology offers off-the-shelf availability at substantially reduced costs. In addition, regulatory complexity is reduced because the scaffolds can be considered as medical devices at the time of implantation (Bouten *et al.*, 2012).

Several other materials for heart valve leaflets have been explored, including POSS-PCU nanocomposite (Kidane *et al.*, 2009) and bacterial cellulose-based nanocomposite (Mohammadi, 2011). It is hypothesised that synthetic heart valve leaflets fabricated from these fibre-reinforced composite materials which mimic native valve leaflet structure, will optimise leaflet stresses and decrease tears and perforations.

Cardiac rhythm management devices

Currently, pacemaker batteries last seven to ten years on average (or three to six years for an implantable cardioverter defibrillator), requiring frequent replacements which can expose patients to potential risks involved in medical procedures such as infections or severe bleeding. Enhancing battery lifetime is thus a critical issue to assure longer working time of the implanted medical device, and increase the replacement cycle. Using advanced nanotechnology, a research team in Korea has developed a self-powered cardiac pacemaker that is operated by a flexible single crystalline piezoelectric energy harvester ("nanogenerator") (Hwang *et al.*, 2014). Tested in an animal model, the nanogenerator stimulated the heart using electrical energy converted from body movements. The flexible energy harvester could lead to a robust method to enable longer operating time as well as miniaturization of batteries, because they could be readily recharged by cyclic deformation behaviours from biomechanical energy sources such as the heartbeat or diaphragm elevation. Another research team in the USA also developed a prototype device using polymer-based piezoelectric nanoribbons that can be used to harvest power from the beating heart or to harness the motion of other organs to recharge batteries for medical devices requiring power (Dagdeviren *et al.*, 2014).

The application of nanotechnology and nanomaterials can improve lithium-ion battery technology used for implantable medical devices such as cardiac rhythm management devices and neuromodulation devices. Today's implantable cardioverter defibrillators use lithium vanadium oxide batteries. Nanostructured vanadium oxides, such as

vanadium oxide nanotubes/nanowires/nanorods, silver vanadium oxide nanowires, are found to have higher capacity and are considered to be the most promising cathode materials. However, they still suffer from fast capacity fading during high-rate discharge/charge. The challenge is to improve the cycling stability of vanadium oxides at a high rate. A leading supplier and developer of implantable batteries for cardiac rhythm management devices is Greatbatch Medical Inc (USA).

Breath metabolomics, the study of the complex mixture of volatile organic compounds in exhaled breath, represents a new frontier in medical diagnostics. Standard volatile-compound detection methods using spectrometry and spectroscopy techniques have shown the potential for diagnosing illnesses via breath tests; this includes heart disease, cancer, and even more. Unfortunately, this approach requires expensive equipment and high levels of expertise to operate the necessary instruments, and the tests must be done quickly, all of which impede its adoption. Nanomaterial-based sensors are likely to become a clinical and laboratory diagnostic tool because they are significantly smaller, easier-to-use, and less expensive than spectrometry or spectroscopy. Studies have demonstrated that a breath print derived from a select group of volatile organic compounds, could accurately discriminate, for instance, between heart failure patients and control subjects (Samara *et al.*, 2013), patients with gastric cancer and other gastric disease (Xu *et al.*, 2013), or patients with multiple sclerosis and healthy subjects (Ionescu *et al.*, 2011). Breath analysis platforms using Bluetooth-enabled nanosensors are under development which are capable of transmitting breath print data to a smartphone for analysis and upload (Vantage mHealtcare Inc, USA). A breath print has the potential to offer patients a non-invasive and potentially inexpensive way of detecting diseases in a point-of-care setting.
Breath testing is a complex process involving numerous steps, each of which has several possible technological alternatives with advantages and drawbacks that might affect the performance of the nanomaterial-based sensors in a breath-testing system.

4.2 Dentistry

Current

Dentistry is one of the few fields of medical devices in which nanotechnology has long been used. Since the 1970s nanosized filler materials have been used in dental composites, although at that time they were called "microfilled composites" (Besinis *et al.*, 2015). Currently the range of dental products in which nanotechnology is used has widened (Table 4.2.1). According to an overview from FIDE, the European Dental Industry organisation, it is estimated that there are close to 3500 dental products containing nanomaterials in Europe. The main product groups reported are (>100 products estimated for the European market ordered from high to low) (Stock, 2014):

- Impression materials;
- Dental composites;
- Denture base resins;
- Veneering materials;
- Accessories for verification of occlusion;
- Bonding agents;

- Plastic materials for bite registration;
- Materials for crowns and bridges;
- Final luting cements;
- Cements;
- Artificial teeth.

The publicly available medical device databases from the FDA and Health Canada report 7 and 42 dental medical devices, respectively, that have "nano" in their name (FDA; Health Canada). The 46 unique products (3 duplicates) consist of 27 dental composites, 11 dental implants coated with NanoTite™, 4 bonding agents and 1 bone graft material. This corresponds with a recent literature review which states that fillers in dental composites and dental implants are the main application fields of nanomedical devices in dentistry (Besinis *et al.*, 2015). The same trend can be seen in European patents with regard to dental nanomedical devices. The European patent collection contains 21 patents on dental nanomedical devices, of which 11 are related to dental composites and four to dental implants (Espacenet). Interestingly, the FIDE overview shows that impression materials are the largest group of dental medical devices containing nanotechnology, while none of these products feature in the FDA, Health Canada and Espacenet databases. Although dental composites are abundant, dental implants (or artificial teeth) are much lower on the list.

Dental composites are restorative materials used to fill cavities or reconstruct parts of a tooth. They consist of three main components: organic matrix, inorganic matrix (filler) and a coupling agent. Most of the current conventional composites have a filler particle size in the range of 40-700 nm. New and advanced composites contain nanofillers with a particle size of 1-100 nm. The most important breakthrough is not the particle size, but the increased percentage of filler present within the composite (Besinis *et al.*, 2015). Nanofillers improve the mechanical properties of dental composites by increasing the microtensile bond strength, flexural strength, flexural modulus, fracture strength and material hardness (Besinis *et al.*, 2015). Nanoparticles have also been used to match the radiopacity of dental adhesives, and to reduce the working and setting times for dental resins (Besinis *et al.*, 2015). Furthermore, these so-called nanocomposites offer aesthetic advantages in terms of smoothness, polishibility, and modified translucency to improve colour matching with the patients' natural teeth (Besinis *et al.*, 2015)**.** However, there appears to be an optimum for the percentage of nanofiller, after which the mechanical properties do not improve further or even deteriorate (Atai *et al.*, 2009; Prentice *et al.*, 2006).

Table 4.2.1. Examples of nanomedical devices in dentistry (non-exhaustive)

Application	**Company**	**Product**
Bonding agent	3M Health Care	Adper™
Bonding agent	Pentron Clinical Technologies	NANO-BOND
Cement	GC	Fuji IX GP
Dental composite	Cosmodent	Renamel NANO
Dental composite	Dentsply	Ceram-X®
Dental composite	DMP	Nanoceram Bright
Dental composite	Ivoclar Vivadent	Tetric EvoCeram
Dental composite	Kerr	Premise™
Dental composite	S&C Polymer, Silicone- und Composite Spezialitäten GmbH	Zircore Flow Nano
Dental composite	Tokuyama Dental	Palfique® Estelite ®
Dental composite	Voco	GrandiO®
Dental composite	3M ESPE	Filtek™ Supreme XT
Dental composite	3M ESPE	Ketac™
Dental material	Dental Nanotechnology S.A.	NanoCare Gold
Dental material	Panasonic Healthcare Co. Ltd.	NANOZR milling blank
Implant surface coating	Astra Tech	OsseoSpeed™
Implant surface coating	Biomet 3i	NanoTite™
Implant surface coating	Brånemark Integration AB	BioHelix™
Implant surface coating	NanoMech	MultiCare™ NanoSpray
Implant surface coating	Straumann	SLActive®
Implant surface coating	Intra-Lock® International	Ossean®
Implant surface coating	Promimic	HA^{nano}
Impression material	Zhermack	Nanotech Elite H-D
Root canal sealer	Dentsply	AH plus™
Root canal sealer	BUSA® Dental Instrumentation	BC Sealer™
Veneering material	GC	G-Coat PLUS
Veneering material	GC	OPTIGLAZE

Sources: Besinis *et al*. (2015), FDA, Health Canada, Jain (2015), Khurshid *et al.*, (2015)

Dental implants ideally have a high success rate and longevity. The current failure rates of 5-10% are mainly due to poor osseointegration[1], infection, or rejection (Besinis *et al.*, 2015). The success of a dental implant is determined by the inflammatory response and the behaviour of the tissue at the tissue-implant interface. As a result, the implant surface chemistry and topography are of major importance (Besinis *et al.*, 2015). This is where nanotechnology can make a difference, as the body's cells and proteins interact with the implant on a nanometre scale. Often ceramic nanomaterials, such as hydroxy apatite, bioactive glass, and other calcium phosphate compounds, are used to create coatings on metallic implants (Besinis *et al.*, 2015). These coatings increase the biocompatibility of implants and encourage increased cell adherence.

[1] Osseointegration is the direct structural and functional connection between living bone and the surface of a load-bearing artificial implant (Wikipedia).

However, there have also been studies that show no significant benefits of modifying an implant surface with nanoparticles. It is currently unclear whether the improved characteristics of nanocoated dental implants are due to the coating's chemistry or due to the introduction of nanoscale surface roughness (Besinis *et al.*, 2015). In addition, it has been suggested that particle size and morphology (e.g. rod-shaped, prism) may play a role in bone-cell adhesion and bone formation (Mankani *et al.*, 2001; Shi *et al.*, 2009). This fits with current knowledge of nanoparticles, where size and morphology can have a large impact on functionality and particle properties.

In addition to these two major product groups of composites and dental implants, nanotechnology is also used in other dental product categories including, for example, bonding agents, dental materials, impression materials, root canal sealers and veneering materials (Table 4.2.1):

- Bonding agents are used to adhere dental composites and other materials to the natural substance of teeth. The use of nanotechnology ensures product homogeneity and better mixing in dental adhesive solutions (Arora and Kapoor, 2014).
- The dental material NanoCare® Gold contains gold and silver nanoparticles which have antibacterial properties and, as the manufacturer claims, should hereby prevent secondary caries formation on previously treated teeth (Bednarski *et al.*, 2013; Nanotec Endo).
- Impression materials are used to make a negative imprint of hard and soft tissues in the mouth, with the goal of forming a cast at a later stage. The commercially available Elite HD+ A-silicone contains nanofillers that provide high tear, distortion and heat resistance, and an instant set to reduce movement-induced errors (Arora and Kapoor, 2014).
- Root canal sealers, together with root canal fillers, seal the root canal after a root canal treatment. Sealing the root canal is important to prevent (re)infection with bacteria. Nanoparticles, composed of calcium silicate, calcium phosphate, calcium hydroxide or zirconia used in root canal sealers provide improved handling and physical properties. The nanosized particles provide a better fit to the irregular tooth and root canal surfaces. In addition, the formation of a hydroxyapatite nanostructure in the root canal provides antimicrobial properties due to its highly alkaline pH (Khurshid *et al.*, 2015).
- Veneering materials serve as a tooth coating to improve aesthetics or to protect the tooth's surface from damage. Nanotechnology is used to improve the aesthetic qualities, prevent discoloration, and increase the wear resistance of veneering materials.

Future perspectives

As nanotechnology in dental medical devices is already a common occurrence, what can be expected in the near future? Developments in material science will most likely have a strong impact on the dental industry, as materials and their fine-tuned properties play a major role in many dental products. This development will most likely result in increased performance of existing product types like dental composites

and implants. For example, single walled carbon nanotubes have recently been used in a laboratory setting as fillers in dental composites due to their improved mechanical properties, high strength and unique dimensional distribution (Besinis *et al.*, 2015). New materials are also being studied to improve osseointegration of dental implants, mainly in *in vitro* studies (Arsiwala *et al.*, 2014). There are currently 27 registered clinical trials on dental nanomedical devices, with 17 of them starting from 2010 onwards (Table 4.2.2). From the 10 clinical trials performed prior to 2010, the products NanoTite and Ostim® (see orthopaedics) are now available on the market. For the remaining clinical trials it was not possible to determine if they resulted in or will lead to a commercial product.

The clinical trials after 2010 do not show a particular trend in application area. However, most of them are investigating the possible superior properties of nanomaterials in existing dental applications, such as increased wear resistance of nano-hybrid denture teeth or improved tissue response to nanostructured dental implants. Several clinical trials are being conducted on existing products (Ketac Nano, Venus Pearl, NANOZR), as manufacturers try to broaden the number of conditions their products can be used for. Furthermore, the clinical trial from Indiana Nanotech LLC has resulted in the development of several Clinpro™ products, such as anti-cavity toothpaste and sealant, produced by 3M ESPE. These products contain fluoride and tri-calcium phosphate to promote dental mineral growth and thereby prevent or treat caries. Whether tri-calcium phosphate is present as a nanoparticle is not clear. Furthermore, it is uncertain whether Clinpro™ toothpaste should be considered a medical device or a medicinal product.

The oral microbiota[2] strongly determines oral health or disease. Oral microorganisms play a role in dental caries formation, periodontal disease, and dental implant or reconstructed tooth infections. Therefore, preventing biofilm[3] formation or removing pathogenic bacteria is important for dentists to ensure patient health. Dental nanomedical devices that contain antimicrobial properties are a field of interest and more products are likely to enter the market in the near future. From the first use of antimicrobial nanoparticles in wound dressings, it is a relatively small step to applying this concept in dental products (Ge *et al.*, 2014). The abovementioned commercially available product NanoCare® Gold already applies nanosilver and nanogold particles for this purpose. Furthermore, researchers have used nanosilver particles incorporated in dental composites to kill bacteria, which is an example of a drug/device combination product (Cheng *et al.*, 2015; Ge *et al.*, 2014).

[2] The oral microbiota is the ecological community of commensal, symbiotic and pathogenic microorganisms living in the oral cavity.
[3] A biofilm is a group of microorganisms living together on a surface, often embedded within a self-produced matrix. Microbes living in a biofilm are physiologically different compared to single-cells from the same species.

Table 4.2.2. Registered clinical trials on dentistry nanomedical devices (2010 onwards)

Product	Company or organisation	Application	Phase	Reference
Acrylic base plate of orthodontic removable retainer	Hamedan University of Medical Sciences	Antimicrobial effect of nanosilver particles for dental caries	NA	http://www.irct.ir/searchresult.php?id=9086&number=2
Ketac Nano	Tanta University	Filling cement for caries in primary teeth	NA	http://clinicaltrials.gov/show/NCT02093091
Venus Pearl	Heraeus Kulzer GmbH	Dental nanohybrid composite for dental restoration	NA	http://clinicaltrials.gov/show/NCT01925040
Dental composite	3M	Clinical performance of nanocomposite CAD/CAM milled dental restoration	NA	http://clinicaltrials.gov/show/NCT01464294
Ceramic coating	University of North Carolina	Reduced sliding resistance of orthodontic archwires	NA	http://clinicaltrials.gov/show/NCT02311491
Toothpaste	Indiana Nanotech, LLC	Anti-caries toothpaste	NA	http://clinicaltrials.gov/show/NCT01094210
Toothpaste	Federal University of São Paulo	Desensitizing toothpaste for cervical dentin hypersensitivity	NA	http://clinicaltrials.gov/show/NCT02018783
Denture teeth	University of California	Nano hybrid composite acrylic for denture teeth	NA	http://clinicaltrials.gov/show/NCT01188226
Dental implant	University Ghent	Nanostructured calcium-phosphate-coated implant abutment	NA	http://clinicaltrials.gov/show/NCT01620918
T3 implant system	Biomet 3i Inc	Dental implant	NA	http://clinicaltrials.gov/show/NCT02161874
NANOZR	Universitätsklinikum Tübingen, Panasonic Healthcare Co. Ltd.	NANOZR-based ceramic material in fixed partial dentures/crowns	NA	http://www.drks.de/DRKS00003348
Toothpaste	Coswell S.p.A.	Zinc-carbonate-hydroxyapatite nanocrystals for remineralisation of enamel surfaces and desensitising dentifrices	NA	http://www.anzctr.org.au/ACTRN12612000272897.aspx

Product	Company or organisation	Application	Phase	Reference
Antibacterial dental material	Hadassah Medical Organization	Antibacterial nanoparticles incorporated in root canal sealer material	2	http://clinicaltrials.gov/show/NCT01167985
Veneering material	Universidad Autonoma de San Luis Potosí	Nanosilver fluor varnish to promote remineralisation of temporary teeth	2	http://clinicaltrials.gov/show/NCT01975545
Orthodontic primer	Universidad Autonoma de San Luis Potosí	Nanosilver particles incorporated into Transbond™ XT orthodontic primer to prevent enamel demineralisation	3	http://clinicaltrials.gov/show/NCT02400957
Nanoseal	Hokkaido University Hospital, Nippon Shika Yakuhin Co., Ltd.	Remineralisation of root caries by application of nanoseal	3	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000015669&type=summary&language=E
Dental prosthesis (palatal obturator)	Hadassah Medical Organization	Antibacterial activity of quaternary ammonium polyethylenimine nanoparticle incorporated silicon	1	http://clinicaltrials.gov/show/NCT01007240

Abbreviation: NA – not available

In addition to nanosilver, other antibacterial nanoparticles are also under investigation, such as chitosan/rose-bengal, zinc oxide, chitosan/silver, and quaternary ammonium polyethylenimine (QPEI) (Besinis *et al.*, 2015). For example, researchers incorporated QPEI nanoparticles into commercially available sealers such as AH plus™, Epiphany™ and Guttaflow®, resulting in good antimicrobial and biocompatible properties (Khurshid *et al.*, 2015). A current clinical trial is investigating the use of QPEI nanoparticles in silicon palatal obturator prostheses (see table 4.2.2). Researchers are also investigating the use of nanotechnology to create antimicrobial implant surfaces (Bhavikatti *et al.*, 2014). Out of a total of 18 registered clinical trials on dental nanomedical devices performed from 2010 onwards, 3 clinical trials study the use of antimicrobial nanoparticles in a variety of applications, from orthodontic base plates and fluoride gels to dental materials for root canal treatment and dental prostheses (see table 4.2.2).
In the future, dentists might play a more prominent role in disease diagnosis. Dentists can keep an eye on both oral and systemic diseases through the screening of oral biomarkers via point-of-care diagnostics. These point-of-care tests can be used in risk determination, treatment planning and progression monitoring in a number of diseases. Many diagnostic tests are currently commercially available, and the development of new point-of-care diagnostics is expanding (Fuentes *et al.*, 2014).

4.3 Neurology

Neural interfaces that rely on electrical transduction consist of arrays of electrodes that are in close contact with neurobiological substrate (Pancrazio, 2008). These devices have proved useful in basic science research to elucidate how the nervous system encodes information, and they have a significant impact on reducing the burden of neurological disease and injury in individuals. Examples of clinically useful neural interfaces include the visual prosthesis, cochlear prosthesis, deep-brain stimulation, and neuro-motor prosthesis, each of which relies on implanted electrodes delivering electrical stimulation. Some of these devices are enabled by micro- and/or nanotechnologies.

Current

Visual prosthesis

No visual prostheses using nanometre-sized electrodes, i.e. diameter of electrode, are commercially available. Currently, two types of CE-marked visual prostheses are on the market, but these medical devices have micrometre-sized electrodes. Device developments show that electrode size has become smaller during the time span from conception of a prototype to marketed medical device. It is conceivable that future visual prostheses will have components ranging from a few microns to submicron scale. The first chronically implanted epiretinal prototype, the Argus I developed by Second Sight Medical Products Inc (USA), was a 16-electrode device (Humayun *et al.*, 2003). This visual prosthesis, or "bionic eye", restored rudimentary vision to those with severe vision loss. The next generation device, the Argus® II Retinal Prosthesis System, was a 60-electrode (200 µm in diameter) array and elicited visual perceptions by electrically stimulating surviving neurons in patients suffering from retinal degradation (retinitis pigmentosa) (Humayun *et al.*, 2012). Visual input is provided by a glass-mounted miniature camera and a video processor transforming images into electrical stimulation. The Argus® II was CE-marked in 2011. Artificial vision of the Argus ® II typically consists of dark and light spots or patterns, often shimmering, which the subject must learn to interpret as objects. This process takes time and patience, and it is analogous to learning a foreign language. Currently, an epiretinal prosthesis featuring 240 electrodes is being developed (Stronks and Dagnelie, 2014).

The Alpha IMS is a subretinal visual prosthesis manufactured by Retina Implant AG (Germany). The device consists of a microphotodiode-array ("microchip") with 1500 electrodes (50x50 µm each) implanted beneath the retina, specifically in the macular region. The microchip measures 3x3 mm with a thickness of 70 µm and is produced using 800 nm CMOS (constructing integrated circuits) technology. The electronic microchip design was provided by the Institute for Microelectronics (IMS), Stuttgart, Germany. Alpha IMS received CE mark approval in 2013. Patients with the Alpha IMS chip were able to recognize faces and read large letters and signs (Stingl *et al.*, 2015). Each pixel, i.e. an independent microphotodiode-amplifier-electrode element on the microchip, is used to analyse the brightness of incoming light. The Alpha IMS, unlike the Argus® II, utilises the subject's own eye to capture images and hence does not have an external video camera.

The functionality of a retinal implant is limited by many factors including physical (e.g., electrode interactions), physiological (e.g., retinal degeneration) and human factors (e.g., the subject's ability to comprehend prosthetic vision). At present, hardware engineering factors (e.g. electrode size and density) may be of lesser importance (Stronks and Dagnelie, 2014).

Future perspectives

Electrodes

The sizes of conventional electrodes range from tens of microns to millimetres. For deep brain stimulation, the surface area of each electrode contact is approximately 6 mm^2, a size that limits the specificity of stimulation and may contribute to the well-known side effects associated with deep brain stimulation for movement disorders, such as difficulty with speech. In the case of intracortical microelectrodes, the areas are typically much smaller, less than 2×10^{-3} mm^2. Reducing the size of conventional metal electrodes raises the impedance, compromising the ability to transfer an electrical charge between the electrode and the tissue.

For electrical stimulation, it is important to avoid reactions at the electrode-electrolyte interface that may result in nonreversible, toxic interactions with the surrounding tissue. Both charge density and charge per phase interact to determine the threshold for neural-tissue damage. On the other hand, to evoke a neural response, a certain magnitude of balanced charge must be delivered. Deposited films, such as iridium oxide and conductive polymers, can reduce electrode impedance and boost charge-injection capacity. A reduction in electrode impedance could also reduce the power requirements, improving the operational lifetime of device batteries. Although concerns exist regarding the stability of some of these materials, it is currently an active area of research and development.

Progress with carbon nanofibre-based and carbon nanotube-based electrodes has thus far been promising for improving the quality of the bioelectrical interface with the nervous system (Bareket-Keren and Hanein, 2012; Li and Andrews, 2007). Beyond precise electrical stimulation and monitoring electrical activity, these nanomaterial based electrodes offer the possibility of monitoring neurotransmitter levels, e.g. voltammetric detection of dopamine, which could be used in an implantable device as part of a feedback-control system (Andrews, 2007). There are several opportunities for research and development to gain a fuller understanding of these nanoscale interfaces and translate these findings from the bench to the clinic.

Visual prosthesis

Several types of visual prostheses are under development for the treatment of subjects with hereditary retinal degenerations.
The Artificial Silicon Retina (ASR) from Optobionics (USA) is a self-contained, self-powered subretinal prosthesis designed to convert light energy from images into electrical pulses (Chow *et al.*, 2010). The ASR is a microchip with approximately 5000 microelectrode-tipped microphotodiodes. Fabricated microphotodiode pixels, each measuring

20x20 µm, are electrically bonded with a 9x9 µm iridium oxide electrode. The separation between pixels is 5x5 µm. In the development of the ASR implant, a possible neurotrophic effect on visual function in retinitis pigmentosa subjects who underwent ASR implantation was discovered (Chow, 2013). This means, rather than a prosthetic effect, an even more important potentially therapeutic effect may be occurring.

In Europe, Pixium Vision SA (France) is developing the epiretinal implant IRIS® Vision Restoration System (clinical trial) and the subretinal implant PRIMA Vision Restoration System (preclinical phase) using microphotodiodes. Although these systems encompass 70 µm pixels, there is an indication that, due to low stimulation, thresholds pixel size could be reduced further, thereby enabling higher spatial resolution (Lorach and Goetz, 2015).
Bionic Vision Australia, a consortium of universities, research institutes and a hospital, is simultaneously developing three different bionic eye devices for subjects with retinitis pigmentosa. The Early prototype (24 electrodes) and the Wide-View device (98 electrodes) are inserted in the suprachoroidal space (Ayton *et al.*, 2014), whereas the High-Acuity device (256 electrodes) is an epiretinal visual prosthesis (Ahnood *et al.*, 2015). The High-Acuity device has an electrode array using nanocrystalline diamond. Diamond material is also used to seal the implant. The High-Acuity visual prosthesis can be modified for insertion in subjects with age-related macular degeneration.
Nano Retina Inc (Israel), a joint venture of Rainbow Medical Ltd (Israel) and Zyvex Labs LLC (USA), is developing the Bio-Retina. This device incorporates various nano-sized components in one implant. Zyvex Labs develops and exploits atomically precise manufacturing technology for micro/nanofabrication and 3D microassembly. The retinal implant is designed to work with the eye's natural functionality, including pupil dilation and eyeball movement. This functionality of the Bio-Retina distinguishes the system from other retinal prostheses.
Semiconductor nanocrystal systems are particularly attractive for neuronal stimulation applications due to their tunable optical and electronic properties, photostability, and chemical interfacing diversity. Recently, a novel approach for wire-free retinal photostimulation, based on the combination of semiconductor nanorods and carbon nanotubes has been presented (Bareket *et al.*, 2014). The nanorod geometry enables efficient light absorbance, followed by effective charge separation at the nanorod-carbon nanotube interface.

Besides the above mentioned retinal implantation sites (epiretinal, subretinal and suprachoroidal), the visual cortex is being explored as a stimulation site of the human visual system. The visual cortex is attractive for several reasons (Lewis *et al.*, 2015). Firstly, the large surface area of the visual cortex and the cortical magnification factor combine to render it more amenable to implanting large numbers of electrodes in cortical areas, potentially offering a higher-resolution visual experience than retinal implants. Secondly, stereotactic implantation of small occipital cortical electrode array is a relatively straightforward procedure compared to implanting electrode arrays onto or under the retina. Lastly, the utility of direct cortical stimulation extends to all causes of visual impairment in patients with late blindness due to retinal or optic nerve disease or injury. Cortical visual prosthesis research has

enormous potential for future treatment of visual impairment. However, one of the key obstacles to developing a cortical visual prosthesis is the deterioration of the interface between the electrode and the brain tissue. There are a variety of proposed mechanisms underlying the gradual loss of electrode functionality, which largely centre on the reactive tissue response to the insertion, continued presence of, and adverse effects of electrical stimulation with intracortical electrodes (Polikov *et al.*, 2005). Of the factors mediating the degree of tissue damage, irreversible electrochemical (Faradic) reactions occurring at the electrode-tissue interface are a well-known problem. The risk of irreversible electrochemical reactions can be lowered by using electrodes with high charge injection capacity, enabling neuronal stimulation while allowing electrode voltages to remain within safe levels. In an animal model, materials such as silicon electrodes containing embedded carbon nanotubes with high charge injection capacity have been studied (Musa *et al.*, 2012).

Cochlear prosthesis / hearing aid / bionic ear

Nanotechnology can be applied to antimicrobial coatings on cochlear implants, including hearing aids. Nanostructured coatings including diffusible silver ions that are released slowly from coatings to prevent infections in the ear have been developed. For cochlear implant electrodes, a special coating that releases neurotrophins, growth factors that preserve the auditory nerve in the inner ear at the same time as providing electric current, is being investigated. Carbon nanotubes can be used to deliver neurotrophins and electrical charge to neurons. Polypyrrole polymer coating with neurotrophins incorporated can be deposited on the surface of the nanotubes or around them. This greatly increased surface area facilitates the uptake and release of neurotrophins better than flat surfaces. Carbon nanotubes can be deposited onto substrates for patterned electrical stimulation of nerves and localised release of trophic factors. Stimulating electrodes are also composed of nanofibre wires and cables, which enable the implant to be bent into a curved shape. The nanofibre bundles are joined to an electrical conductor which are then directed to speech processor and induction coil devices in the cochlear implant.

Using 3D-printing, scientists have created a functional ear that can "hear" radio frequencies (Mannoor *et al.*, 2013). The technique is a convenient strategy to interweave electronics (using silver nanoparticles for the antenna) and a matrix of hydrogel and calf cells within the highly complex topology of a human ear. Further work and extensive testing is needed before the technology can be used on a patient. Electrical signals produced by the ear could be connected via electrodes to the acoustic nerve. The current system receives radio waves, but other materials could be incorporated, such as pressure-sensitive electronic sensors, to enable the ear to register acoustic sounds.

Upper-limb neuroprosthesis

Functional electrical stimulation can be used to successfully restore hand grasp in subjects with a spinal cord injury at the cervical level. An implantable grasp neuroprosthesis, developed at Case Western Reserve University (Cleveland, Ohio, USA), uses voluntary movement retained

by the subject to proportionally control the degree of hand opening and closing as well as grasp force. The device electrically activates paralyzed muscles by using electrodes that are either implanted within or sutured to the muscles in the hand and the forearm. The system requires a wearable external controller that communicates wirelessly with the hand-grasp neuroprosthesis to control the degree of the hand-grasp position and force, and to turn the device on and off. Specific transducers, manufactured by NVE Corporation (USA), use giant magnetoresistive sensing techniques to measure magnetic field strength. The sensors are made of sandwiches of thin films consisting of alternating nanometre thick layers of magnetic and nonmagnetic layers. Advantages of this sensing technique include increased sensitivity, temperature stability, and a larger signal level. A prototype of the controller was developed to measure wrist position (Wheeler and Peckham, 2009). Three giant magnetoresistive sensors are integrated into the controller that can be worn on the wrist. On the back of the hand, a disc-shaped rare earth magnet is fixed. The device is low-power, cosmetically acceptable, and reliable when measuring position along the flexion/extension of the wrist. The device can increase the functional skills of a person who has tetraplegia, and may significantly impact the quality of life.

Nanoelectromechanical systems

Nanoelectromechanical systems (NEMS) and microelectromechanical systems (MEMS) are created using a variety of refined miniaturized electrical and mechanical apparatuses such as actuators, beams, sensors, pumps, resonators, and motors. NEMS and MEMS enable the monitoring of mechanical physiological variables such as intracranial pressure, cerebrospinal fluid pulsatility, weight load, and strain (Mattei and Rehman, 2015). In addition to enabling the evaluation of these key mechanical properties, researchers have already developed microelectrode arrays and nanowires that are able to measure electrical field potentials. Nevertheless, in relation to the direct monitoring of brain variables using NEMS and MEMS, there are still some biocompatibility issues which need to be addressed. Secondary inflammatory response, potential long-term toxicity, and impaired signalling due to scar formation are only a few of these challenges. In order to overcome such difficulties, several strategies using the incorporation of (bio)polymers on such devices are under development (Vallejo-Giraldo *et al.*, 2014).

Nerve conduits/scaffolds for neural tissue repair

Synthetic nerve guide conduits require additional biochemical and physical factors to provide a more conductive microenvironment for (peripheral) nerve system regeneration, particularly over long lesion gaps. The proper choice of materials, structural architecture, lumen filler, incorporation of cell adhesion molecules and release of neurotrophic factors, and supportive cells are just a few important design factors to consider (Jiang *et al.*, 2010).

Electrospinning is a straightforward technique used to produce extracellular matrix-like (nano)fibrous structures. Electrospun nerve conduits/scaffolds hold considerable promise for neural tissue repair

(Lee and Arinzeh, 2011). A variety of polymers, including synthetic and natural polymers, have been applied by electrospinning. The composition and architecture of the electrospun conduits/scaffolds affect neural cell function. Configuring electrospun conduits into three-dimensional nanofibrous structures showed promise to promote neural tissue formation for full restoration of function using a spinal cord injury model in rats (Zamani *et al.*, 2014). Electrospun nerve conduits enhanced by carbon nanotubes have effectively promoted nerve regeneration using a peripheral nerve injury model in rats (Ahn *et al.*, 2015). Emphasis on scaffold design, given the greater level of complexity in forming functional three-dimensional neural tissue, will be needed in the future. The use of a combination of micro- and nanoscaled fibre morphologies to increase porosity and pore size is being explored.

There is still a gap between electrospun conduits/scaffolds for neural tissue repair and the clinical standard of care (Tian *et al.*, 2015). Response to injury or disease varies greatly between the central and peripheral nervous system due to the different structural properties and cellular components. For brain, spinal cord, and peripheral nerve repair, the challenge is not only on promoting neuronal survival, promoting regenerating axons across the injury site, and/or restoring connections with the target of innervations, but also to control the inflammatory response which results in further damage. Electrospun scaffolds in the future may also be combined with neuroprotective drugs or bioactive agents/growth factors to promote the formation of neural tissue. In addition, multiple materials, growth factors, and drugs may need to be combined and incorporated into the electrospun scaffold to obtain the appropriate response. Similarly, multiple cells types may need to be combined with the electrospun scaffold to obtain functional recovery. Nervous system injury remains a complex problem requiring innovative strategies for full functional repair.

4.4 Oncology

Current

Recent reviews on the use of nanotechnology in oncology show that there are currently 15 nanomedicinal products on the market and an increasing number of about 55-60 products under clinical investigation (Noorlander *et al.*, 2015; Wicki *et al.*, 2015). Nanomedical devices appear to be less common in oncology (Table 4.1.1). A search of Health Canada and FDA databases resulted in two nanomedical devices used for cancer therapy. One product is the FREND™ PSA Plus, a lab-on-a-chip cartridge to conduct quantitative immunoassays for measuring the levels of prostate specific antigen in patients with prostate cancer (see RIVM report on lab-on-a-chip technologies for more information on this technique, (Hermsen *et al.*, 2013)). The second product is Nanor™, which is a nanotechnology containing thermoplastic material used for immobilizing patients during radiation therapy. The nanomaterial used allows for a high strength and a thinner mask.

Table 4.4.1. Oncology nanomedical devices currently on the market (non-exhaustive)

Application	**Manufacturer**	**Product**
Diagnostics (*in vitro*)	NanoEnTek	FREND™ PSA Plus
Diagnostics (*in vivo*)	CellSearch	CELLSEARCH® system
Diagnostics (*in vivo*)	Gilupi	CellCollector™
Immobilization device	Orfit Industries	Nanor®
Thermal ablation	MagForce	NanoTherm®
Sentinel lymph node localisation	Endomagnetics	Sienna+®

Sources: FDA, Health Canada, Jain (2015)

A recent market report on nanobiotechnology provided three additional nanomedical devices used in oncology (Jain, 2015). Two of them, CellCollector® and the CELLSEARCH® system, are diagnostic tools for detecting and isolating circulating tumour cells (CTCs) from a patient's blood. CTCs leave the primary tumour and enter the bloodstream. Their presence serves as a biomarker for early diagnosis of primary tumours and metastases. CellCollector® consists of a probe for direct insertion into the bloodstream to capture CTCs *in vivo*. The probe has a functionalised surface covered with antibody containing polymer fibres that interact with CTC surface markers. The CELLSEARCH® system consists of a sample kit and a CE-marked *in vitro* diagnostic device (CELLTRACKS® AUTOPREP®). The system isolates CTCs from blood samples by using ferrofluid (iron) nanoparticles with antibodies that bind to surface markers on CTCs. Due to the nanoparticles, the CTCs can be magnetically separated from other cells in the blood.

The third product mentioned in the market report is NanoTherm®, a nanoparticle with a superparamagnetic iron oxide (SPIO) core and an aminosilane coating. NanoTherm® nanoparticles are injected into the tumour and generate heat when exposed to an alternating magnetic field. A temperature increase of a few degrees Celsius, called hyperthermia, sensitises tumour cells to chemo- or radiotherapy. A high temperature increase, referred to as thermal ablation, damages cell structures, resulting in cancer cell destruction (Gunaratnam *et al.*, 2015). A major issue of current systemic cancer therapies is the lack of selectivity between diseased and healthy tissue (Schleich *et al.*, 2015). Nanotechnology can play a role in improving the targeting of cancer therapy to minimise damage to healthy tissue. NanoTherm® attempts to damage only the tumour tissue by injecting the nanoparticles directly into the tumour and applying a local alternating magnetic field at the tumour site.

SPIO nanoparticles are also used for localising sentinel lymph nodes in, for example, breast cancer patients. Sienna+® is an SPIO nanoparticle tracer that is injected into the breast, after which it collects in the lymph nodes draining the breast. A magnetometer (or magnetic sensor device) is used to detect the tracer and guide the surgeon to breast-draining lymph nodes for biopsy. The benefits of using SPIOs include an 18-month shelf life, absence of special handling procedures otherwise required for conventional radioisotope tracer injections, and an apparent lack of toxicity (Foerster, 2014). Sienna+® received its CE mark in

December 2011. It is registered as a medical device because it functions via a physical mechanism (magnetism). Furthermore, it is not used for diagnosing disease, but only for localising certain tissue structures (i.e. lymph nodes) in patients who have already been diagnosed.
A search for European patents in Espacenet resulted in ten patents on medical devices related to oncology. These patents mainly concern the use of nanoparticles for hyperthermal therapies. One of these patents describes the use of biodegradable magnetic nanoparticles that should be applied to an operation area after surgical tumour resection. An alternating magnetic field heats the nanoparticles, resulting in destruction of any remaining tumour cells post-surgery. Actually, all but one of the patents related to inducing hyperthermia function according to electromagnetic heating of certain nanoparticles to weaken or kill tumour cells. One patent describes a nanoparticle that is heated using light. In addition to these hyperthermia patents, there is one patent on the use of nanoparticles for internal radiation therapy and one patent on the use of quantum dots for margin determination during cancer surgery.

Future perspectives

Interest in using nanotechnology to treat cancer is great, but this has not yet resulted in a large number of commercially available nanomedical devices. Nanomedicine oncology research focuses more on the development of drugs than on new medical devices. An increase in nanomedicinal products can be expected in the near future as a relatively large number of compounds are in clinical trials (Noorlander *et al.*, 2015). The same growth is not expected for nanomedical devices, although currently there are 11 registered clinical trials (Table 4.4.2). Nine of these trials are being conducted by universities. The two products under development by companies are AuroLase® and NBTXR3. Aurolase® therapy uses nanoshells, consisting of a silica core and a gold shell, to convert near infrared light into heat for the thermal ablation of solid tumours. The nanoshells are administered intravenously, and because of their small size they selectively accumulate in the tumour due to the enhanced permeability and retention (EPR)[4] effect. The EPR effect is seen in solid tumours, but not in healthy tissue. Because of the tumour specific targeting, the surrounding healthy tissue receives minimal damage during thermal ablation therapy. An additional advantage is that cancers cannot build resistance to this kind of therapy (Jain, 2015).

[4] The EPR effect is the property by which formulations of certain sizes tend to accumulate in tumor tissue much more than they do in normal tissues. The general explanation for the EPR effect is that tumors often have a leaky vasculature due to the formation of abnormal blood vessels, often combined with an ineffective lymphatic drainage (Duncan and Sat, 1998).

Table 4.4.2. Registered clinical trials on new oncology nanomedical devices

Product	Company or organisation	Application	Phase	Reference
AuroLase (silica core, gold shell nanoshells)	Nanospectra Biosciences Inc.	Thermal ablation therapy	NA	https://clinicaltrials.gov/show/NCT00848042
Carbon nanoparticles	Changzheng Hospital	Lymph node mapping in thyroid carcinoma	NA	http://www.chictr.org.cn/showproj.aspx?proj=4533
Carbon nanoparticles	West China Hospital of Sichuan University	Lymph node mapping in thyroid carcinoma	NA	http://www.chictr.org.cn/showproj.aspx?proj=4366
Carbon nanoparticles	Southwest Hospital, Third Military Medical University	Lymph node mapping in breast cancer	NA	http://www.chictr.org/en/proj/show.aspx?proj=5279
Carbon nanoparticles	Peking University	Lymph node dissection and harvesting in advanced gastric cancer	3	https://clinicaltrials.gov/show/NCT02123407
Carbon nanotube X-ray stationary digital breast tomosynthesis (hardware)	UNC Lineberger Comprehensive Cancer Center	Breast cancer diagnosis	NA	https://clinicaltrials.gov/show/NCT01773850
cRGDY-PEG-Cy5.5-C dots (silica nanoparticles)	Memorial Sloan Kettering Cancer Center	Image-guided intraoperative sentinel lymph node mapping	0	https://clinicaltrials.gov/show/NCT02106598
nanoFOD (nano-scintillator fibre-optic dosimeter)	Duke University	Real time dosimetry monitoring of internal radiotherapy treatment	NA	https://clinicaltrials.gov/show/NCT02040155
NBTXR3 (crystalline nanoparticles)	Nanobiotix	Nanoparticles to increase the dose and efficacy of radiotherapy	2/3	https://clinicaltrials.gov/show/NCT02379845
SPIO nanoparticles	University College London Hospitals	Thermal ablation therapy	0	https://clinicaltrials.gov/show/NCT02033447
SPIO nanoparticles	University of New Mexico	Detection of minimal residual disease in leukaemia	NA	https://clinicaltrials.gov/show/NCT01411904

Abbreviation: NA – not available

NBTXR3 (or NanoXray) nanoparticles are composed of an inorganic core of crystallized hafnium oxide, specifically designed to enhance the effects of radiotherapy. NBTXR3 is injected directly into the tumour.

When the nanoparticles are exposed to ionizing radiation, the hafnium oxide generates a large number of electrons that amplify the dose of energy inside the tumour, thereby increasing the efficacy of radiotherapy. As the NBTXR3 nanoparticles are only present in the tumour, healthy tissue still receives the normal, unamplified radiation dose. As a result, the benefits of radiotherapy are increased, while keeping the adverse effects on for healthy tissues the same. NBTXR3 is expected to receive CE marking by the end of 2016 (Nanobiotix, 2014).
Five of the clinical trials are about lymph node mapping, using either carbon or silica nanoparticles. Two of the carbon nanoparticle trials are on lymph node dissection in thyroid carcinoma patients. It is unclear if all the carbon nanoparticle clinical trials are about the same product. However, the particles have the same purpose, as they should colour lymph nodes black to guide the surgeon during dissection. Other techniques to assist surgeons during cancer resection are also under development, although not yet in clinical trials. For example, semiconductor quantum dots (QDs) can be used to determine exact tumour localisation and its margins, aiding the surgeon in precise resection (Singhal *et al.*, 2010). In addition, intraoperative imaging can be used to overcome problems with tissue penetration of traditional optical methods. Such agents include Cornell dots, QDs, and surface-enhanced Raman scattering nanoparticles (Petersen *et al.*, 2014). It has been debated whether these kinds of injectable nanoparticles used during active surgery should fall under medical device or medicinal product regulation.
In another clinical trial the use of SPIO nanoparticles for thermal ablation is being studied. It is unclear whether this clinical trial uses NanoTherm® nanoparticles or another kind of SPIO nanoparticle. SPIO nanoparticles for detecting minimal residual disease (MRD) in the bone marrow of leukaemia patients are also being investigated. MRD is the small number of leukemic cells that remain in the patient during or after treatment and is seen as a major cause for relapse of cancer. Measuring MRD is important for monitoring leukaemia in patients and for determining treatment efficacy. Again, it could be debated whether the detection of MRD is monitoring or (re-)diagnosis and whether these kinds of products should fall under medical device or medicinal product regulation.
Two clinical trials are researching the use of a non-injectable nanomedical device. The first uses carbon nanotubes as an X-ray source for the diagnosis of breast cancer. This provides increased spatial resolution and potentially faster imaging compared to current systems (Gidcumb *et al.*, 2014). The second is a sensor device for the real time monitoring of dosimetry in internal radiotherapy. Currently there is no convenient, inexpensive, real time method for confirming the delivered radiation dose, and for warning against a too low or too high dose.
According to a recent market report on nanobiotechnology, two nanomedical devices for the capture and isolation of CTCs are currently under pre-clinical development (Jain, 2015). The first nanomedical device uses gold nanoparticles conjugated with DNA aptamers combined with microfluidics for CTC isolation. Aptamers have binding capabilities comparable to antibodies, are engineered in test tubes, have a straightforward production process via chemical synthesis, and have a long shelf life. The aptamers are designed to interact with several receptors on the tumour cell. The second nanomedical device uses a

nano-Velcro technology on a microfluidic chip. It involves a nanopillar-covered silicon chip that interacts with nanostructures on the surface of CTCs to create a Velcro-like effect to capture the cells.
Detecting cancer at an early stage is an important factor associated with increased patient survival rates. Cancer-specific biomarkers can help to detect cancers early, so treatment can start directly. Furthermore, biomarkers can play a role in monitoring disease recurrence and determining treatment efficacy. As described in the Cardiology section (4.1), the diagnosis of cancer and other diseases by using a breath analyser to study breath metabolomics is under development. In addition, electrochemical biosensors are successfully being applied for detecting cancer biomarkers. Advances in nanotechnology have led to the development of new nanoscale materials and structures that can be used to improve these kinds of biosensors (Ravalli and Marrazza, 2015). Novel nanobiosensors have demonstrated improved sensitivity and specificity compared to traditional cancer testing approaches. These nanobiosensors are based on a range of different techniques, from using gold and magnetic nanoparticles to atomic force microscopy cantilevers. According to a recent review, nanobiosensors will begin to transition from research into clinically validated tests (Gdowski *et al.*, 2014). Nanotechnology allows miniaturization of the sensors, resulting in the measurement of multiple biomarkers simultaneously, reduced volumes of reagents and samples, and point-of-care diagnostics (see previous RIVM report for more information on lab-on-a-chip technologies (Hermsen *et al.*, 2013)). Early detection of cancer is necessary for early treatment, but new diagnostic products should be accurate in their predictions to prevent the unnecessary treatment of patients.

4.5 Orthopaedics

Current

Orthopaedics is the branch of medicine concerned with the prevention or correction of injuries or disorders of the skeletal system and associated muscles, joints, and ligaments. Orthopaedic medical devices include orthopaedic implants such as artificial knee and hip joints; orthopaedic prostheses like bone grafts, bone plates, fins and fusion devices; orthopaedic fixation devices such as screws, rods, pins and plates; and tissue engineering scaffolds for bone and cartilage. Nanotechnology is mostly used in bone graft materials and in orthopaedic implant surface coatings. In addition, several other products are commercially available, such as cartilage scaffolds and implant manufacturing materials (Table 4.5.1). In addition to the specialty of orthopaedics, dentistry also benefits from improvements in bone graft materials and implant coatings. There is a demand for bone substitutes that are biocompatible, bioactive and exhibit mechanical and surface properties comparable to those of natural bone (Jain, 2015). A number of nanotechnology-containing bone graft solutions have already gained regulatory approval. A search in the FDA database resulted in four orthopaedic nanomedical devices, all of which are bone graft materials. In large bone defects caused by, for example, trauma or surgery, the defect's size can be greater than the healing capacity of the bone. In such cases, the bone void is filled with a bone graft that serves as a matrix for regeneration. Over time, the graft is degraded and replaced by new bone. Autologous grafts from another bone are preferably used, however, this can be challenging for large

defects (Brydone *et al.*, 2010). Another option is to use a synthetic bone graft material. Manufacturers try to mimic the natural composition and microstructure of bone[5] by using hydroxyapatite (HA) nanocrystals, either alone or in combination with other common bone components such as collagen. Nanostructured materials can favour cell adhesion and stimulate new bone growth compared to conventional materials. Nanotechnology is also used to match bone graft degradation time to the rate of bone growth within the defect, resulting in better treatment outcomes (Bhavikatti *et al.*, 2014). In addition, nanoscale inorganic materials can contribute to mechanical strength (Yousefi *et al.*, 2014). Nanomaterials show a higher resistance to time-dependent strain, resulting in a longer time until stress-induced implant failure (Liu *et al.*, 2013). Furthermore, nanoscale HA particles incorporated in polymeric scaffolds have been shown to be better at guiding bone regeneration than microscale HA particles at the same concentration (Yousefi *et al.*, 2014).

Table 4.5.1. Examples of orthopaedic nanomedical devices (non-exhaustive)

Application	**Company**	**Product**
Bone graft material	Artoss	NanoBone®
Bone graft material	Heraeus Kulzer	OSTIM®
Bone graft material	Orthogen	NanoGen
Bone graft material	Orthovita Inc	Vitoss®
Bone graft material	3-D Matrix Inc	PuraMatrix®
Bone graft material	Pioneer Surgical Technology Inc.	nanOss® Bioactive
Bone graft material	Finceramica	SintLife
Bone graft material	Nanotherapeutics	nanoFUSE® DBM
Bone graft material	Finceramica	RegenOss
Bone graft material	ETEX Corporation	Beta-bsm
Bone graft material	ETEX Corporation	Gamma-bsm
Bone graft material	ETEX Corporation	EquivaBone
Bone graft material	ETEX Corporation	CarriGen
Bone graft material	Eucare	SyboGraf™
Cartilage scaffold	Finceramica	MaioRegen®
Implant surface coating	GfE Medixintechnik GmbH	TiMESH
Implant surface coating	Biomet	BoneMaster
Implant surface coating	Spire corporation	Ion Tite™
Implant surface coating	Promimic	HANANO™
Orthopaedic material	Zimmer	Trabecular Metal™

Source: FDA, Health Canada, complemented with internet searches for additional products.

[5] Bone consists mainly of cells and type I collagen stiffened by nanoscale inorganic calcium hydroxyapatite mineral crystals. Normal human bone has a mineral density of around 60% (Seeman and Delmas, 2006). Mature bone has an hydroxyapatite size of around 50 x 25 x 4 nm, resulting in a coarse nanometre surface roughness (Sullivan *et al.*, 2014).

HA is also used as a coating for orthopaedic and other medical implants to improve the interaction between the implant surface and the surrounding bone or soft tissue. This interaction is necessary for biocompatibility, cellular differentiation, and osseointegration. Aseptic implant loosening is the leading cause of total joint replacement failure. This can be the result of failed implant integration or loosening at a later stage (Abu-Amer *et al.*, 2007; Jacobs *et al.*, 2008). Many orthopaedic implants have a smooth surface. Smooth surfaces preferentially induce the growth of fibroblasts and the deposition of fibrous tissue instead of bone. A nanoscale three-dimensional surface topography mimics the natural cellular and extracellular environment normally encountered by the body's cells. Such a structure promotes cell differentiation and adsorption of extracellular adhesion molecules essential to osteoblast function. Furthermore, a nanoscale surface coating increases the implant's surface area by a factor thousand when compared to a microscale surface, thereby allowing for a larger contact area between the implant and the body (Sullivan *et al.*, 2014). BoneMaster®, IonTite™ and HANANO™ are examples of HA nanocoatings, while TiMESH is a titanium dioxide nanocoating.
In addition to bone graft materials and implant surface coatings, nanotechnology tissue scaffolds are starting to appear on the market. MaioRegen® is a scaffold composed of type I collagen and nanostructured hydroxyapatite and is used for the treatment of osteochondral defects[6] in the knee. The scaffold is a tri-layered biological implant consisting of a cartilage region (100% type I collagen), a transition region (nano-HA 40%, type I collagen 60%) and a bone region (nano-HA 70%, type I collagen 30%). This product has shown promising results in 2 to 5 year follow-up clinical case studies (Berruto *et al.*, 2014; Kon *et al.*, 2014). However, a recent prospective therapeutic study found incomplete cartilage repair and poor subchondral bone repair in patients treated with MaioRegen® (Christensen *et al.*, 2015). A current phase IV, single-blind multicentre clinical trial comparing MaioRegen® performance to standard surgical techniques for treating osteochondral defects should provide a clearer answer (Table 4.5.2).

Orthopaedic prostheses and fixation devices can also be made from a material containing nanotechnology properties. Trabecular Metal™, made by Zimmer, is a three-dimensional material made of the biocompatible metal Tantalum. It consists of an interconnected porous structure with a nanostructured surface topography. Trabecular Metal™ has been used for more than 15 years throughout Zimmer's product portfolio, including hip, knee, and shoulder implants; trauma applications; spine implants; bone void fillers and augments; AVN screws, and dental implants (Zimmer).
European patents on orthopaedic nanomedical devices show a distribution among different product groups. In total there are 23 patents directly aimed at orthopaedics. Eight of these are about orthopaedic implant coatings and surface modifications. The remaining patents are on bone graft materials (3), orthopaedic implants (1),

[6] Osteochondral defects are areas with cartilage damage combined with injury to the adjacent subchondral (subcartilage) bone.

orthopaedic materials (2), tissue engineering scaffolds (5), orthopaedic external fixation (1) and bone cements (3). In addition to these orthopaedic specific patents, there are also 18 patents on nanomedical device coatings in general, which could be applied to orthopaedic products.

Table 4.5.2. Registered clinical trials on orthopaedic nanomedical devices

Product	Company or organisation	Application	Phase	Reference
NanOss Bioactive	Pioneer Surgical Technology, Inc.	Bone grafting material used in spinal surgery	4	http://clinicaltrials.gov/show/NCT01829997
NanOss Bioactive	Pioneer Surgical Technology, Inc.	Bone grafting material used in spinal surgery	4	http://clinicaltrials.gov/show/NCT01968993
BoneMaster®	Biomet	Orthopaedic implant coating	NA	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1568
MaioRegen®	Finceramica	Cartilage scaffold for treatment of osteochondral defects	4	https://clinicaltrials.gov/show/NCT01282034

Abbreviation: NA – not available

Future perspectives

Significant orthopaedic nanomedical device innovations are not likely to appear on the market in the near future. Currently, only four clinical trials on orthopaedic nanomedical devices were identified, all for existing products (see Table 4.5.2). Nevertheless, there are developments in specific areas, most notably in new surface coatings and structures and in new bone graft materials. These developments are in a preclinical stage and therefore clinical application is still far off. A few potential applications with good *in vitro* data include nano-coated joint replacement implants, rapidly incorporating fillers for osteochondral defects, and anti-tumour nanoselenium-coated prostheses (Sullivan *et al.*, 2014).
There are several potential benefits of using nanotechnology in orthopaedics. Nanotechnology can be used to modulate implant materials for improved host acceptability, tissue integration, cellular function, bone growth, and better mechanical properties. Furthermore, it could play a role in reducing the foreign body immune reaction and in preventing implant infections (Arsiwala *et al.*, 2014; EFORT, 2014; Torrecillas *et al.*, 2009). New orthopaedic materials, surface coatings, and structures are being developed that aim to improve cell adhesion and osseointegration, or to act as antimicrobial agents. The goal is to use nanotechnology to reduce the rates of aseptic implant failure and periprosthetic infection (Nodzo *et al.*, 2015). However, researchers should take into account that surface topographies aimed at increasing cell adhesion might also promote bacterial adhesion (Hansom *et al.*, 2015).
Carbon nanotubes are currently receiving a lot of attention for both medical and non-medical applications. Carbon nanotubes can be designed to have the same stiffness as diamonds or to be a hundred times stronger than steel, while only a sixth of the weight (EFORT,

2014). Their strength, flexibility and limited weight make carbon nanotubes a candidate as scaffolds for bone regeneration. Carbon nanotubes can mimic the role of collagen in bone and induce the growth of HA crystals. Carbon nanotubes may lead to better artificial bones and new bone grafts (Jain, 2015).
An example of an antibacterial coating is the use of nanosilver particles incorporated onto the surface of titanium orthopaedic implants in the form of titanium nanotubes. This coating appears to have a strong bactericidal and anti-adhesive effect, which lasts up to 30 days (Sullivan *et al.*, 2014). Nanosilver particles can also have additional effects. A study in rabbits has shown that type I collagen scaffolds impregnated with nanosilver particles reduced the time needed for nerve regeneration (Sullivan *et al.*, 2014). Another approach to combat periprosthetic infections is the use of biodegradable nanofilm coatings for the delivery and controlled release of antibiotics (Sullivan *et al.*, 2014).
The clinical translation of many bone tissue-engineering scaffolds is still a long way off, despite the advances made over the past decades. Problems include insufficient vascularisation and mechanical strength, incomplete osseointegration of the bioresorbable scaffold, and osteomyelitis (bone related infection) (Arsiwala *et al.*, 2014). To improve vascularisation, researchers incorporate bone morphogenetic proteins and growth factors in the scaffolds. Although *in vitro* and *in vivo* studies have been promising, clinical translation remains unsuccessful (Arsiwala *et al.*, 2014).

4.6 Surgery

Surgery involves the treatment of injuries or disorders of the body by incision or manipulation, using surgical instruments. In other words, surgery entails opening of the body to get the surgeon's tools and/or hands to where repair and/or removal is needed. Surgery itself thus results in trauma to the body that requires recovery, and may lead to scarring or complications such as infection of the wound. Surgery has greatly advanced thanks to the development of minimally invasive surgery. For example, laparoscopy and thoracoscopy have reduced half-metre-long abdominal and chest incisions to a half centimetre; and endoscopic and percutaneous techniques have turned incisions into small puncture wounds. It thus makes sense to go even smaller; microsurgical or even nanosurgical tools can further minimise surgical invasion and allow for much greater precision and control. This will reduce complications as it minimises damage to surrounding, healthy tissues. As such, there will be less scarring, less pain and faster rehabilitation. In practice, however, nanosurgery is currently limited to *in vitro* techniques for cell and tissue manipulation and *in vivo* techniques in model organisms. In addition to the benefits of smaller surgical incisions, nanotechnology enables other advantages for surgery.

Current

Suture needles

Sandvik Materials Technology (Sweden) developed Sandvik Bioline 1RK91, a precipitation hardening stainless steel which uses nanotechnology techniques to combine very high strength with good ductility (Sandvik Materials Technology). Heat treatment of nanometre–sized particles in Sandvik Bioline 1RK91 has been reported to produce

lighter, thinner ophthalmic, plastic surgery and general suture needles with the potential for less tissue damage.

Nanocoated surgical blades

By adding nanocrystalline coatings onto specially prepared hard metal substrates, e.g. plasma polished diamond nanolayers, it is possible to manufacture surgical blades of extreme sharpness and low friction that are highly suited to optical- and neurosurgery. In addition, these blades exhibit low physical adhesion to materials or tissues and chemical/biological inertness. Manufacturer GFD Gesellschaft für Diamantprodukte mbH (Ulm, Germany) has developed and markets Diamaze PSD (Plasma Sharpened Diamond). This blade is plasma-polished, which decreases the thickness of the coating from 5-25 µm to 0.5 µm, and concurrently reduces surface roughness to approximately 20-40 nm. Surgical blades using this technology were reported to be on the market previously (Roszek *et al.*, 2005). Information on GFD's website, as well as on websites of companies selling products with their technology, currently does not clearly confirm whether this is still the case (Cadence; Cadence; GFD).

Sealing vessels with nanotechnology.

SurgRx, Inc. has developed ENSEAL® G2 Curved and Straight Tissue Sealers. These are sterile, single-patient-use surgical instruments for coagulating and transecting vessels up to and including 7 mm in diameter, as well as lymphatics. Launched commercially in 2004, these devices are able to seal vessels without the need for ties or adjunct manoeuvres, and they produce a minimal thermal spread to adjacent tissues (Ethicon; Project on Emerging Nanotechnologies). The nanoparticle technology of the EnSeal device aims to lower the temperature of the instrument to minimise heat transfer to adjacent tissue, and it enables different temperatures at different parts of the jaws. It turns off when collagen denatures at approximately 100 °C. The proprietary electrode consists of millions of nanometre-sized conductive particles embedded in a temperature-sensitive material. Each particle acts like a discrete thermostatic switch to regulate the amount of current that passes into the tissue area with which it is in contact. It can be used to seal arteries, veins, and transecting fatty tissue, small ligaments and connective tissue. A clinical trial is listed, however, it seems inactive (ClinicalTrials.gov, 2011).

Haemostasis

The ability to stop and control bleeding is critically important in all surgical procedures and in the practice of medicine in general. A haemostat is used in many surgical procedures to control bleeding. 3-D Matrix Medical Technology, Inc. (USA) has a CE mark for PuraStat® in the EU and is currently preparing investigational studies for FDA approval of PuraMatrix® as a surgical haemostat in the US. For this, self-assembling peptides that form 3-dimensional nanofibre scaffolds are used. PuraMatrix® gels on blood contact and stops the bleeding via mechanical blocking of the bleeding site for diffuse bleeds while allowing a full, transparent view of the target area. It can be injected through fine gauge needles and catheters which makes it useful in minimally

invasive surgery. Application of PuraMatrix® through small incisions to internal body tissues facilitates tissue regeneration, haemostasis, and drug delivery to the affected area while reducing the risks associated with open surgeries (3-D Matrix Medical Technology).

Future perspectives

Optical nanosurgery

Nanotechnological tools such as "optical tweezers" and "nanoscissors" can be used at the cellular level for cell manipulation and immobilisation. These devices use the forces arising from the momentum of, for example, laser light at specific tuned wavelengths to precisely reposition minute objects by steering the laser beam. This opens up the possibility for medical or surgical procedures at the cellular level, but it is currently at the *in vitro* stage (Berthelot *et al.*, 2014).

Catheters

Catheters are used to inject or drain fluids. Thrombus formation on the surface of these devices is a recurrent problem. Carbon nanotubes have been successfully added to catheters used in minimally invasive surgery to increase their strength and flexibility, thereby reducing their thrombogenic effect (De Volder *et al.*, 2013).

Tissue welding

An interesting potential future application is the use of nanoparticles for laser tissue welding. This is a stitch-free method for closing blood vessels and cartilage during surgery. Laser light is used to heat the tissue, sealing the rupture or wound. Researchers from Rice University (Houston, USA) have held a patent regarding this application since 2002. In 2013 they published an article where they used plasmonic nanocomposite gold nanorods wrapped in an elastic material to enhance the laser tissue welding and create stronger seals (Huang *et al.*, 2013). Their next step is to investigate this nanoparticle approach in living animals suffering from intestinal injuries.

This kind of technology may also lead to promising alternatives for microvascular anastomosis in neurosurgery. The deep location of some intracranial blood vessels adds to the problem of a very restricted space, which reduces the range of movements possible when suturing. Laser tissue soldering has been investigated for the performance of sutureless vascular anastomosis. The strength of the anastomosis seems to be directly related to the laser temperature. However, higher temperature increases the risk of tissue heat damage and cellular necrosis. In order to counterbalance the damage associated with the heating time, nanotechnology-based materials may lead to alternatives. For instance, polymer-coated chromophore-loaded silica nanoshell (diameter 250-270 nm) enabled controlled heat deposition, as the applied energy was selectively absorbed by these nanostructures during laser tissue soldering in rabbit aortic arteries (Schoni *et al.*, 2011). Ultimately, a strong fusion between the edges of the vessels was created without heat damage to the vessels regions further from the suturing line. Another clinically applicable anastomosis technique is the incorporation of gold nanoshells that are capable of absorbing light in the near-infrared

region. As such light frequencies are minimally absorbed by adjacent tissue, the use of gold nanoshells has been shown to successfully induce tissue welding while minimising secondary damage to surrounding structures (Gobin *et al.*, 2005).

Minimally invasive robotic surgery

In minimally invasive robotic surgery (MIRS), there is a need for sensorised surgical scissor blades. The lack of haptic (force and tactile) feedback to the user is currently an unresolved issue in modern MIRS systems. A gold-based nanodevice has been developed that has touch sensitivity on a par with the human finger. With it, surgeons can get a better feel for the firmness of the tissue (Maheshwari and Saraf, 2008).

Nanorobotic surgery

As described above, minimally invasive surgery has significantly improved the field of surgery. Further refinement in the more distant future may be enabled by the development of nanorobotic surgery. Nanorobots that can perform surgery at a cellular level are introduced into the body, externally guided and monitored by a surgeon. Nanorobots are made up of sensors and actuators derived from nanomaterials, such as synthetic zinc oxide, quartz and gold. Applying mechanical force to these nanomaterials produces electrical energy, turning some into sensors that track motion, movement and direction, and others into actuators that convert electrical energy into mechanical motion, to move parts like a nanorobot's gripper (Loscri and Vegni, 2015).

4.7 Textiles and wound care products

Current

The skin protects the body from pathogenic invasion and serves as a mechanical barrier between the internal organs and the outside world. In addition, it is crucial for body temperature regulation, fluid homeostasis and relaying sensory information (Augustine *et al.*, 2014). A wound is a defect or break in the skin caused by physical, chemical or thermal trauma, or by a medical condition or procedure resulting in a disruption of skin anatomy and function (Mayet *et al.*, 2014). Wounds are classed as either acute or chronic. Acute wounds heal within 8-12 weeks and are often caused by mechanical injuries or burns. Chronic wounds heal slower, and are mostly the result of diabetes, infections and poor primary treatment (Augustine *et al.*, 2014). A wound dressing accelerates the healing process, prevents infection and restores skin structure and function (Abrigo *et al.*, 2014). The optimal wound care product provides a moist wound environment, low adherence, a minimal number of dressing changes, cost efficacy, thermal insulation, absorption of excess fluids, infection prevention, adequate gaseous exchange, and covering of the wound site (Mayet *et al.*, 2014).

According to a review by Abrigo *et al.* (2014), currently available wound dressings can be divided into four main categories:

1. **Passive wound dressing** (e.g. gauzes, bandages, low adherent dressings, adhesive plaster); provide wound protection from mechanical trauma and bacteria, but are dry and adhere to the wound.

2. **Interactive wound dressing** (e.g. hydrogel, semipermeable films and foams); polymeric films or foams provide a barrier against bacteria, and are permeable to water vapour and oxygen.
3. **Advanced wound dressing** (e.g. hydrocolloid gels, alginate fibres, hydrofibres, hydrophilic granules); capable of maintaining a moist wound environment, thereby promoting the healing process.
4. **Bioactive wound dressing** (e.g. drug delivery dressing, biological dressings, skin substitutes and grafts); most advanced dressings composed of biological and/or living materials, sometimes combined with pharmaceutical compounds. This is an area of mostly research and development, as costs, wound type suitability, manufacturing techniques, and drug release rates all require further improvement.

All four types of wound dressings can be made from nanofibres. Electrospinning is most frequently used to create nanofibres, as it is a simple, cost-effective and versatile process (Abrigo *et al.*, 2014). The use of nanoscale fibres has several advantages. Nanofibres have a very large surface area to volume ratio. This high surface area, combined with a small pore size, is believed to promote haemostasis. In addition, they provide greater mechanical support, tensile strength, stiffness and flexibility than micro/macro-scale material fibres. As nanofibres are the same size and shape as natural extracellular matrix proteins, they promote wound healing processes such as cell adhesion, migration and proliferation (Augustine *et al.*, 2014; Jain, 2015; Mayet *et al.*, 2014). Furthermore, they allow drainage of wound fluids, are gas permeable and prevent wound contamination. Hydrophilic nanofibres have the added advantage of providing a moist wound environment (Rosic *et al.*, 2013). Nanofibre-based wound dressings are already commercially available (Table 4.7.1), but will remain the subject of research for many years. Current major problems are that nanofibre-based wound dressings are expensive and difficult to handle due to their delicacy, therefore they require a support fabric.

A search for medical textiles and wound care products in the Health Canada and FDA medical device databases resulted in 4 and 0[7] hits, respectively (see Table 4.7.1 for other products). Two of the products found were Nanogen Aktiv and Nanogen Aktigel manufactured by Genadyne Biotechnologies, Inc. Nanogen Aktiv is a membrane made from cellulose and is able to absorb fluid in order to keep a moist wound environment (Nanogen Aktiv). Nanogen Aktigel is a cellulose gel that is absorbed by the wound to form an extracellular matrix and stimulate cell migration. The wound has to be covered with a secondary bandage to prevent dehydration (Nanogen Aktigel).

[7] Acticoat™ is actually found in both the Health Canada and the FDA database, but did not show in our FDA 510(K) database search due to limited search options. For our search strategy and its limitations see methods.

Table 4.7.1. Examples of textiles and wound care products (non-exhaustive)

Application	**Company**	**Product**
Skin substitute	Axcelon Dermacare Inc	Nanoderm™
Skin substitute	Organogenesis Inc	Dermagraft®
Textiles	Egis Nanotech Pte Ltd	Nanomineral Fabric-T
Textiles	Hyosung	MIPAN® Magic Silver nano
Textiles	RAS Materials GmbH	AgPURE®
Textiles	RAS Materials GmbH	ECOS™ technology
Trauma dressing	Marine Polymer Technologies Inc	Mrdh®
Wound dressing	CGBio Co Ltd	CuraVAC® Silver
Wound dressing	Genadyne Biotechnologies Inc	Nanogen Aktiv
Wound dressing	HemCon Medical Technologies Inc	ChitoFlex™
Wound dressing	Marine Polymer Technologies Inc	Talymed®
Wound dressing	Medline Industries Inc	SilvaSorb®
Wound dressing	Novatec Healthcare Co Ltd	BluRibbon
Wound dressing	Smith & Nephew plc	Acticoat™
Wound dressing	Smith & Nephew plc	Biobrane™

Sources: Health Canada, Techtextil, Thomas *et al.*, (2015)

Skin substitutes or tissue scaffolds are 3D structures that mimic the natural extracellular matrix and thereby provide an adequate microenvironment for wound healing and cell growth (Gainza *et al.*, 2015). These products aid in wound closure and aim to replace the function of the skin, either temporarily or permanently. Due to their high cost, these products serve as an alternative therapy when standard wound care products are not sufficient, for example in deep and/or chronic wounds, and major burns. Skin substitutes can be taken from human or animal donors as skin grafts, or can be developed from both natural and synthetic polymers. Skin grafts from human or animal donors are decellularised, resulting in a bare extracellular matrix containing nanoscale protein components, such as collagen and elastin (Augustine *et al.*, 2014).

Nanoderm™ is an example of a manufactured synthetic polymer product. It is a nanofibre cellulose film that serves as a temporary skin substitute to accelerate wound closure, reduce pain, and protect against bacterial infections. Dermagraft® is a related example, although it is regulated as a (combination) advanced therapy medicinal product, since it contains living cells. It is used as a temporary skin substitute to treat diabetic foot ulcers. It consists of a polygalactic or polyglycolic acid mesh seeded with neonatal fibroblasts[8] to enhance wound healing (Augustine *et al.*, 2014). During the manufacturing process, the fibroblasts are given the time to produce extracellular matrix, resulting in a 3D nanostructure.

Bacterial infection is one of the major problems in wound care, and therefore, preventing or limiting bacterial colonization of a wound is important. Covering a wound with an impenetrable wound dressing is a start, but an actively antibacterial wound care product is even better.

[8] A fibroblast is a cell type that synthesises extracellular matrix proteins and plays a critical role in wound healing.

Acticoat™ is an antibacterial wound care product containing nanosilver particles, which has been on the market for over 10 years. The nanosilver particles (7-20 nm) provide antibacterial and antifungal activity, and are synergistic with common antibiotic drugs. Furthermore, they also work against antibiotic resistant bacteria such as multi resistant *Staphylococcus aureus.* In addition to their antimicrobial effect, nanosilver particles also appear to promote the wound healing process by reducing inflammation and promoting wound contraction (Tocco *et al.*, 2012). Nanosilver particles used in wound treatment exhibit low systemic toxicity, but can cause a blue-grey colouration of the skin (Tocco *et al.*, 2012). A search for European patents regarding nanotechnology, medical textiles and wound care products returned 13 patents, of which seven mentioned antimicrobial applications, underlining the importance of infection prevention in wound care.

According to a 2010 ObservatoryNANO report on medical textiles and nanotechnology, nanosilver particles are the principal nanomaterial used in the medical textile sector to create antibacterial textile products (Mantovani *et al.*, 2010). Furthermore, they state that applications of antibacterial textiles containing nanotechnology can be found in patient dresses, bed lines, reusable surgical gloves and masks, protective facemasks, and suits against biohazards (Mantovani *et al.*, 2010). An example of an antibacterial textile yarn containing nanotechnology that can be used for making hospital gowns is MIPAN® Magic Silver nano (see Table 4.7.1). In addition to a yarn, it is also possible to impregnate finished textiles with silver nanoparticles, as can be done with the AgPURE® technology (RAS Materials). RAS Materials also markets a different type of technology, called ECOS™. ECOS™ technology is based on silver nanowires with a 50 nm diameter that can be used to create highly transparent, conductive layers. This technology can be used to create smart medical textiles for biomonitoring and sensing. However, it is difficult to find examples of nanomedical device products where these abovementioned textile technologies are actually applied. The European 2014 manual on borderline and classification for medical devices states that clothes or products made using these technologies can only be considered a medical device if they themselves achieve a specific medical purpose and their principal mode of action is not achieved by pharmacologic, metabolic or immunologic means (EC, 2014). The combination of clothes with a medicinal substance, such as nanosilver particles, might therefore not be qualified as a medical device.

Future perspectives

A search for clinical trials resulted in nine trials conducted on textiles and wound care products containing nanotechnology (Table 4.7.2). The AWBAT-D clinical trial reported a negative result, as the product performed worse than Duoderm® standard treatment (Solanki *et al.*, 2012). In six of the clinical trials, the product contained silver nanoparticles. The aim is to either test their antibacterial effect or test the overall effect on wound healing. Two clinical trials on Agicoat®, a nanosilver containing wound dressing, are ongoing. Acticoat™ has been on the market for several years, but it is still being investigated in clinical trials to expand the number of its applications. One of these

studies is a phase IV clinical trial that aims to analyse the cost-effectiveness of Acticoat™ when compared to standard treatment. Nanofibre-based wound dressings are already on the market. However, this is also a hot research topic and new nanofibre wound care products are being developed. One clinical trial is currently investigating a poly(3-hydroxybutyrate-co-3-hydroxyvalerate) nanofibrous scaffold for healing burn, post-traumatic, and diabetic wounds. Another potential product is OmegaSkin™, a soybean protein nanofibre wound dressing.

Nanofibres are a popular material for creating wound care products as they combine many favourable properties, such as high oxygen permeability, variable pore size, high surface area to volume ratio, and morphological similarity to the extracellular matrix. Which materials are best for creating nanofibres is still an area of debate and intense research. In addition to nanofibres, normal fibres can also be improved by using nanotechnology, for example by incorporating carbon nanotubes to strengthen fabrics.

In the more distant future, nanofibre-based wound dressings may be combined with cells and bioactive molecules, such as growth factors and antibiotics, to further enhance the wound healing process. This would however result in the product shifting from medical device to medicinal product regulation. Several different nanofibre materials have been shown to promote fibroblast migration and proliferation (Augustine *et al.*, 2014). Combining antibiotics and nanofibres in one product still faces some obstacles, such as the lack of demonstrated large-scale production, the phenomenon of antibiotic burst release instead of slow and controlled release over time, and a current lack of *in vivo* application studies (Gao *et al.*, 2014). Similar problems are expected for other bioactive molecules. According to Abrigo *et al.* (2014), most research currently focuses on wound care products that are able to i) control the physiological mechanisms underlying wound healing; ii) monitor markers of healing and infection such as temperature, pH and microbial presence; iii) respond to infection via the controlled release of drugs.

Table 4.7.2. Registered clinical trials on textiles and wound care products

Product	Company or organisation	Application	Phase	Reference
Acticoat®	The Angior Family Foundation	Use of Acticoat antimicrobial nanosilver in healing leg ulcers	NA	http://www.anzctr.org.au/ACTRN12606000094572.aspx
Acticoat®	Hospital The Children's Hospital at Westmead	Use of Acticoat antimicrobial nanosilver dressing in healing burn wounds	NA	http://www.anzctr.org.au/ACTRN12611000590965.aspx
Acticoat®	Fundación Nacional para la Enseñanza y la Investigación de la Dermatología A.C.	Nanosilver wound dressing for new skin growth, reduced pain and itch in persons suffering from pemphigus and pemphigoid (auto-immune disease)	NA	http://clinicaltrials.gov/show/NCT02365675
Acticoat®	University of Sorocaba	Nanosilver wound dressing for wound healing, cost-effectiveness study	4	http://clinicaltrials.gov/show/NCT02108535
Agicoat®	Tehran University of Medical Sciences	Use of nanosilver Agicoat dressing for healing of skin graft donor site	1-2	http://www.irct.ir/searchresult.php?id=8177&number=2
Agicoat®	Emad pharmacy co.	Use of nanosilver Agicoat dressing for healing second degree burns	NA	http://www.irct.ir/searchresult.php?id=7913&number=2
AWBAT-D (negative)	Royal Adelaide Hospital	Biosynthetic skin substitute for healing skin graft donor sites	NA	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12610000399099
Nanofibre-based skin substitute	SASTRA University	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) nanofibre scaffold for wound healing	NA	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=7841
Wound dressing	Tehran University of Medical Sciences	Use of nanosilver particle wound dressing for treatment of pressure ulcers in patients with spinal cord injuries	2	http://www.irct.ir/searchresult.php?id=8286&number=1

Abbreviation: NA – not available

Nanotechnology can improve medical textiles in several ways, for example by improving the structure of fibres using nanocoatings, or by allowing the incorporation of sensor technologies within the textiles. The development of "smart" textiles that are able to react and adapt to environmental stimuli has been hailed as an important innovation for a number of years (Roszek *et al.*, 2005). However, it remains difficult to find specific "smart" textile commercial products that can be classified as a nanomedical device. None of the prototypes mentioned in the 2005 RIVM report on nanotechnology in medical applications has developed into a commercially available nanomedical device (Roszek *et al.*, 2005). However, nanotechnologies, such as RAS Materials ECOS™ technology, are available to integrate sensor technology in medical textiles to monitor, for example, a patient's vital signs. A New Zealand start-up company, Footfalls & Heartbeats, is trying to commercialise a sensor fabric that uses nanotechnology and textile structure to turn the fabric itself into a sensor, instead of requiring wires, straps or embedded electronics. With the current worldwide trends of wearables, big data, and increasing smartphone use, the further development of "smart" textile nanomedical devices is just a matter of time.

4.8 Overall analyses of clinical trials and patents

Clinical trials

The majority of clinical trials involving nanotechnology-based medical devices were registered in ClinicalTrials.gov (Table 4.8.1). Four clinical trials registered in ClinicalTrials.gov were not included in the ICTRP WHO database.

Table 4.8.1. Nanotechnology-based medical device clinical trials registered in databases

	Clinical trials	
Registry	*n*	*%*
ANZCTR	6	5.2
ChiCTR	5	4.3
ClinicalTrials.gov	74	64.3
CTRI	6	5.2
German Clinical Trials Register	3	2.6
IRCT	7	6.1
ISRCTN	8	7.0
JPRN	1	0.9
Netherlands Trial Register	5	4.3
Total	*115*	*100.0*

Abbreviations: ANZCTR – Australian New Zealand Clinical Trials Registry, ChiCTR – Chinese Clinical Trial Registry, CTRI – Clinical Trials Registry India, IRCT – Iranian Registry of Clinical Trials, ISRCTN – International Standard Randomised Controlled Trial Number, JPRN – Umin Clinical Trials Registry (Japan)

The number of registered clinical trials with medical devices involving nanotechnology has grown over recent years (Figure 4.8.1). The first clinical trial registered involved a randomised controlled trial comparing the effectiveness of a nanocrystalline silver wound dressing.

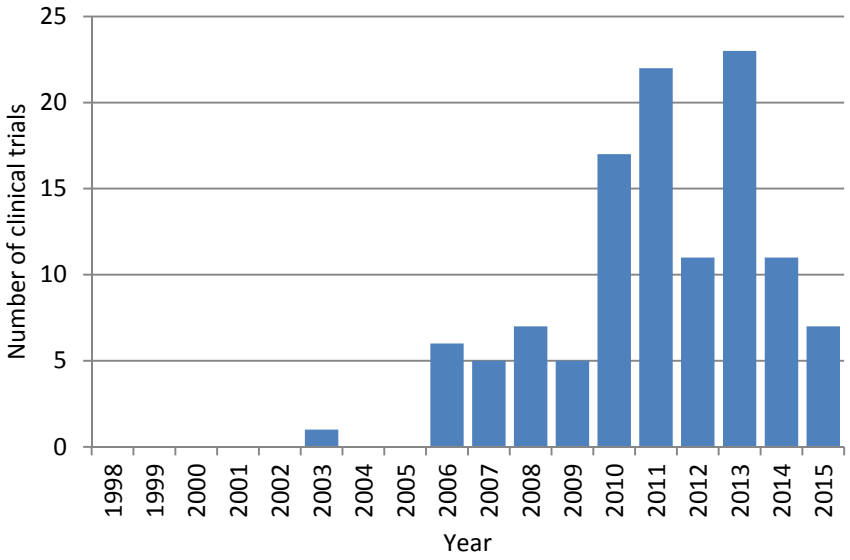

Figure 4.8.1. Number of clinical trials with medical devices involving nanotechnology. Note that the number of trials in 2015 was incomplete: only trials registered before April 2015 were included.

The majority of clinical trials with medical devices involving nanotechnology were in the field of dentistry (Table 4.8.2). Other applications were in the field of oncology, *in vitro* diagnostics, and wound care.

Table 4.8.2. Numbers of clinical trials per medical speciality

Medical speciality	**Clinical trials**	
	n	*%*
Anaesthesiology	1	0.9
Cardiology	6	5.2
Dentistry	34	29.6
In vitro diagnostics	20	17.4
Intensive care	1	0.9
Internal medicine	1	0.9
No specific medical specialty	1	0.9
Oncology, including multi-disciplinary	24	20.9
Ophthalmology	1	0.9
Orthopaedics	5	4.3
Radiology	3	2.6
Surgery, including vascular surgery	3	2.6
Wound care	13	11.3
Unknown	2	1.7
Total	*115*	*100.0*

Clinical trials were conducted worldwide, with the USA as leading country (Table 4.8.3). Eight trials were conducted in two or more countries. No country was assigned in nine registered clinical trials.

Table 4.8.3. Countries conducting clinical trials with medical devices involving nanotechnology

Country	Clinical trials	
	n	*%*[1]
Australia	5	4.8
Belgium	4	3.8
Brazil	4	3.8
Canada	2	1.9
China	5	4.8
Colombia	1	1.0
Egypt	1	1.0
France	5	4.8
Germany	8	7.7
Greece	1	1.0
Hungary	1	1.0
India	7	6.7
Iran	7	6.7
Israel	10	9.6
Italy	5	4.8
Japan	1	1.0
Mexico	3	2.9
Netherlands	8	7.7
Poland	3	2.9
Russia	2	1.9
Spain	4	3.8
Switzerland	1	1.0
Taiwan	2	1.9
UK	8	7.7
USA	24	23.1
Total	*122*	*117.3*

[1] Percentage of total number of clinical trials.

Patents

The number of patent applications concerning nanotechnology-based medical devices has increased progressively for more than a decade (Figure 4.8.2). The patent application filed in 1998 claimed the use of a diamond-like nanocomposite coating. As it takes 18 months before a patent application is published, there is always an 18 month gap before the most recent patents can be found. Patents granted in the beginning of 2015 were applied for in mid-2013.

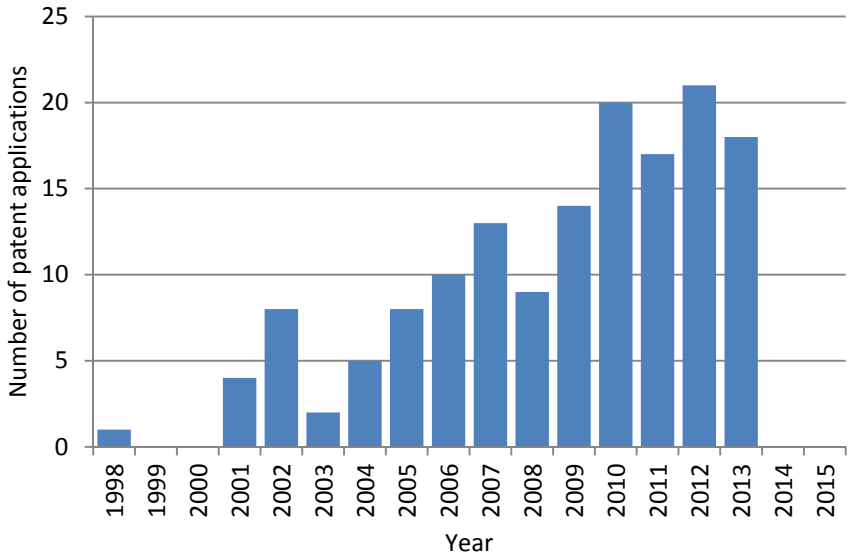

Figure 4.8.2. Number of patent applications concerning nanotechnology-based medical devices.

The majority of patents focused on surface modifications and coatings (Figure 4.8.3). Other most frequently (n≥10) filed patent applications focused on diagnostics and continuous monitoring, dentistry, cardiology, orthopaedics, textiles and wound care, and oncology. Compared to other categories of patent applications, patents focusing on neurology were filed more recently, i.e. year ≥2009.

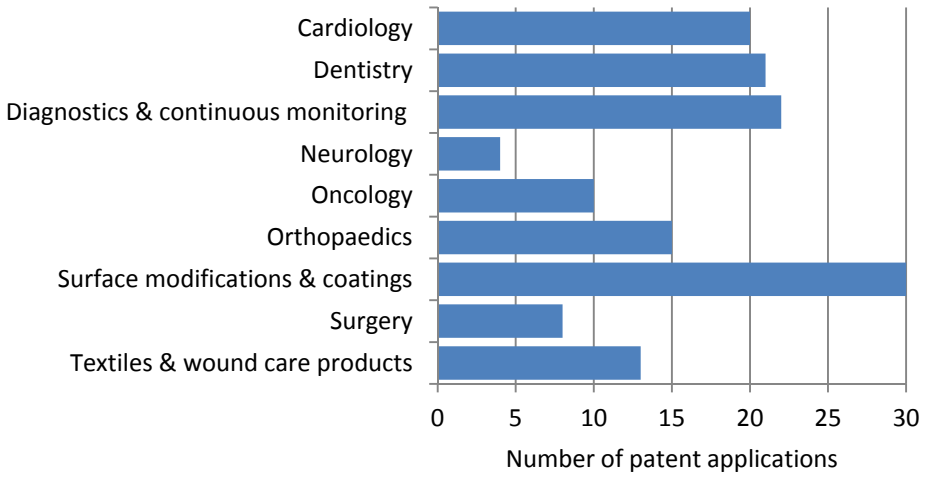

Figure 4.8.3. Number of patent applications per category nanotechnology-based medical devices.

5 Risk assessment considerations

Introduction
The risk assessment of medical devices containing nanomaterials is in principle no different to the risk assessment of medical devices in general. In agreement with the EU regulatory framework, the Medical Devices Directive 93/42/EEC (MDD) (EC, 1993), a medical device should comply with the essential requirements as indicated in Annex I of the MDD that contains the following general requirement:

The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

At the moment there is an evolving knowledge on the safety evaluation of nanomaterials in general and the use of nanomaterials in medical devices in particular. This knowledge has increased in the past 10-15 years, and a conclusion of one of the Opinions of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the DG Health and Consumers of the European Commission, was that nanomaterials can be considered similar to normal substances in that some may be toxic and some may not (SCENIHR, 2009). So, a classical risk assessment can be performed consisting of exposure estimation, hazard identification, hazard characterisation, and risk assessment. However, nanoparticles exhibit specific characteristics that differ from the characteristics of larger sized particles with the same chemical composition.

For the safety evaluation of nanomaterials used in various products, e.g. food/feed, cosmetics, and medical devices, guidance documents have been published by the European Food Safety Agency (EFSA, Parma, Italy), the Scientific Committee on Consumer Safety (SCCS, DG Health and Consumers, Brussels, Belgium) and SCENIHR (EFSA, 2011; SCCS, 2012; SCENIHR, 2015). In addition, a technical committee from the International Organization for Standardization, ISO/TC 194 "Biological and clinical evaluation of medical devices", is preparing a document on the safety evaluation of nanomaterials used in medical devices (ISO/TR 10993-22). The document will provide guidance on how to apply the ISO 10993 series of standards for biological evaluation of medical devices for those medical devices that contain, generate, or are composed of nanomaterials. It will contain large sections on the characterisation of the nanomaterial component, the sample preparation for biological testing, and on the actual testing. For the latter topic, it will indicate the extent to which the standard approach for testing can be used, and which pitfalls need to be avoided when nanomedical devices are tested.

The SCENIHR Guidance on the determination of potential health effects of nanomaterials used in medical devices (SCENIHR, 2015) describes

approaches to be used for the safety evaluation of medical devices containing or manufactured using nanomaterials. The guidance also refers to the generation of wear and tear particles of implants (i.e. hip implants) that may be in the size range of nanomaterials (Gill *et al.*, 2012). This chapter on risk assessment considerations is largely based on this SCENIHR document.

Exposure estimation

Nanomaterials can have a wide variety of uses in medical devices, including free nanomaterials (e.g. iron oxide for heat therapy to treat cancer, in a paste-like formulation in dental composite fillers, and nanosilver used in wound dressings), fixed nanomaterials as coatings on medical devices (e.g. nano-hydroxyapatite on bone implants), and embedded in a material matrix (e.g. carbon nanotubes in a catheter wall).

The safety evaluation of nanomedical devices can be performed using ISO 10993-1:2009, "Biological evaluation of medical devices- Part 1- Evaluation and testing within a risk management process" as a basis. This means an approach based on the type of medical device, type of contact, and contact time with the patient. ISO 10993-1:2009 recognises the following categories:

- Type of device: surface device, external communicating device and implant device,
- Location of contact: skin, mucosal membrane, breached or compromised surface, tissue/bone/dentin, or circulating blood,
- Contact time varying from limited contact (equal or less than 24 h), prolonged contact (>24 h to 30 days), and permanent contact (>30 days).

Depending on these three categories, several biological effects (e.g. cytotoxicity, genotoxicity, sensitisation, systemic toxicity) need to be considered for the biological safety evaluation of medical devices. The SCENIHR guidance also takes this approach, and it clearly distinguishes between non-invasive and invasive medical devices (SCENIHR, 2015). The use of medical devices may result in various exposure routes, including dermal exposure, inhalation exposure (intubation, dental procedures), mucosal exposure (via various mucosal tissues e.g. in the mouth), oral exposure, parenteral exposure (including by injection or via implants), and ocular exposure.

The nano-related risk of nanomedical devices is mainly associated with the possibility of the release of free nanoparticles from the device, and their potential toxic effects. However, toxic effects of fixed nanomaterials due to their chemical composition and/or enhanced reactivity should also be considered. For this purpose, a detailed characterisation and identification of the nanomaterials is essential. This may include, but not be limited to, determination of the following parameters: chemical composition/identity, particle size and size distribution (primary/secondary particles), physical form and morphology, particle and mass concentration, specific surface area, surface chemistry, surface charge, redox potential, solubility and partition properties, pH, viscosity, density and pore density, dustiness,

chemical reactivity and catalytic activity, and photocatalytic activity. For a number of these parameters, different techniques are available. For each individual nanomaterial, the proper technique needs to be selected and used. For example, for size determination, at least two different techniques are recommended, one of which should be electron microscopy (EFSA, 2011; SCCS, 2012; SCENIHR, 2015).

The release of nanomaterials from a medical device depends on how the nanomaterial is used within a medical device, either as the device itself (e.g. nanocomposites as dental fillers), as a fixed nanomaterial on the surface of a medical device (e.g. coatings) or embedded within a material matrix (e.g. carbon nanotubes to improve mechanical properties). Furthermore, if a medical device is biodegradable, any nanomaterials in or on the device will be released at some point during the degradation process. The type of medical device is also important. Table 3 of the SCENIHR Opinion estimates both external and internal exposure based on the type of device, type (location) of contact, and duration of contact (see Table 5.1 below, SCENIHR (2015)). The types of medical devices are subdivided in three categories: surface, external communicating, and implant devices (ISO 10993-1:2009).

- Surface devices are those devices that are, in their contact, limited to skin (e.g. bandages, electrodes), intact mucosal membranes (e.g. contact lenses, urinary catheters, intra-intestinal devices), and breached or compromised surfaces (e.g. wound dressings). Possible internal exposure for surface devices is generally limited or absent, unless there is a breached or compromised surface.
- Examples of external communicating devices are an administration set tubing for the administration of fluids (through the tubing) into the bloodstream, and medical devices contacting blood directly such as guide-wires or intravascular endoscopes. Other external communicating devices are those devices that contact tissue, bone or pulp/dentin systems (e.g. laparoscopes, draining systems, dental cements, dental filling materials, skin staples).
- Examples of implant devices are dental implants, hip implants, heart valves, orthopaedic screws and plates used for the fixation of bone fractures, and bone cements.

Table 5.1: An estimation of potential external and internal exposure as starting point for a risk evaluation for medical devices containing nanomaterials. [Table 3 from SCENIHR (2015), reproduced with the permission of the European Commission, DG Health and Food Safety, Luxembourg. Copyright remains with the European Union.]

			Type of application of nanomaterials External exposure/internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	Type of contact	Duration of contact		Weak (physisorb)	Strong (chemisorb)	In degradable materials*	In non-degradable materials
Surface device	Intact skin	≤ 24 h	H/N	M/N	M/N	L/N	N/N
		>24 h to 30 d	H/N	M/N	M/N	M/N	N/N
		>30 d	H/N	M/N	M/N	H/N	N/N
	Intact mucosal membrane	≤ 24 h	H/L	M/L	M/N	L/L	N/N
		>24 h to 30 d	H/M	M/M	M/L	M/M	N/N
		>30 d	H/M	M/M	M/L	H/M	N/N
	Breached or compromised surface	≤ 24 h	H/H	M/M	M/L	L/M	N/N
		24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		30 d	H/H	M/M	M/L	H/M	N/N
External communicating device	Blood path, indirect **	≤ 24 h	na	M/M	M/L	L/L	N/N
		>24 h to 30 d	na	M/M	M/L	M/M	N/N
		>30 d	na	M/M	M/L	H/M	N/N
	Tissue/bone/dentin	≤ 24 h	H/H	M/M	M/L	L/L	N/N
		>24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		>30 d	H/H	M/M	M/L	H/H	N/N
	Circulating blood***	≤ 24 h	na	H/H	H/H	L/L	N/N
		>24 h to 30 d	na	H/H	H/H	M/M	N/N
		>30 d	na	H/H	H/H	H/H	N/N
Implant device	Tissue/bone	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N
	Blood	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N

H=high, M=medium, L=low, N=negligible, na= not applicable

H/L means high potential contact and/or external exposure to the nanomaterial / low potential for internal systemic exposure of all organ systems

* the exposure will depend on the degradation time of the medical device

** contacting the blood path at one point. Examples of these types of devices are solution administration sets, transfer sets and blood administration sets (ISO 10993-4:2002)

Hazard identification

There are a number of pitfalls when testing the toxicity of nanomaterials. It should be realised that nanomaterials are present in a dosing or test medium as a nano-dispersion rather than in solution. So, any testing of nanomaterials should consider the possibility of agglomeration and aggregation of the nanomaterials, and the insolubility or partial solubility of the nanomaterial (EFSA, 2011; Kreyling *et al.*, 2010; SCCS, 2012; SCENIHR, 2015). Issues to be considered include: concentration of the nanomaterial (possibility of sedimentation), adherence of biomolecules to the nanomaterial, possible contamination by endotoxin, interaction between the nanomaterial and assay reagents (e.g. interference in light absorption), dissolution kinetics, and dose metrics. The last issue is important as it is not yet known what dose metric (mass, number of particles, or surface area) best describes a dose–response relationship between nanomaterials and a certain biological (toxic) effect (SCENIHR, 2015). The toxicity testing itself can be performed using the ISO 10993 series for the biological evaluation of medical devices, however, nanospecific aspects of the test agent (nanomaterial) need to be considered at all times. For certain endpoints, e.g. delayed type hypersensitivity (sensitisation), it is yet unknown how to evaluate this for nanomaterials. For most of the nanomaterials investigated, skin penetration was absent. So, the currently used local lymph node assay (LLNA) and the Buehler guinea pig test, which both use skin application on intact skin, cannot be considered appropriate as in these assays skin sensitisation requires skin penetration of the substance under investigation.

For genotoxicity, the commonly used *in vitro* bacterial reverse mutation assay (Ames test) may not be appropriate as there is doubt about the uptake of the nanomaterials by the bacteria, although recently, uptake of nanomaterials by bacteria was observed (Clift *et al.*, 2013). Unless uptake by the bacteria in the test can be demonstrated, a negative outcome might be a false negative result as nothing is known on the exposure of the bacterial DNA to the nanomaterial. Additionally, for the *in vivo* genotoxicity assays, exposure of the target organ investigated for DNA damage needs to be established by accompanying toxicokinetic studies. The combination of estimated exposure levels (low, medium, high) and the use of a medical device (non-invasive short term, non-invasive long term, invasive short term, invasive long term) provides a framework for assays to be performed according to SCENIHR (2015). In general, non-invasive medical devices including/incorporating nanomaterials, with the exception of local reactions, do not pose an additional risk compared to similar non-invasive medical devices not containing nanomaterials. For invasive medical devices, the potential release, accumulation, and persistence of the nanomaterials in the tissues is of utmost importance to further testing. In this context, the possible dissolution/degradation of the nanomaterials also needs to be considered.

Risk assessment

For the risk evaluation of medical devices with regard to nanomaterials, a phased approach is proposed based on the possibility of the release of free nanoparticles from the medical device.

Phase 1: exposure assessment, particle release. This may be the release of particles/nanomaterials used as a component of the device, but also the release of particles due to wear and tear of a medical device. It is important that the nanomaterials that are evaluated in the various safety assays for the risk assessment have the same physicochemical characteristics as the particles that are actually released from the medical device. So, a high quality physicochemical characterisation of both the released particles and the original particles used for the manufacturing of a medical device is very important.
In **Phase 2**: **exposure assessment,** the possibility for **distribution and persistence** needs to be evaluated. The knowledge on the (toxico)kinetics can be used for the choice of toxicity assays to be performed. In this respect, it is especially important to know whether it is an invasive or a non-invasive device, and whether there is a possibility for systemic exposure via release of nanoparticles into the blood circulation.
In **Phase 3: hazard assessment,** the toxicity is evaluated, looking both at local effects (e.g. irritation, cytotoxicity, genotoxicity) and systemic effects (e.g. genotoxicity, organ toxicity).
In the final **Phase 4: risk characterisation/risk assessment,** the estimated risk is compared to the risk from the use of comparable devices not incorporating nanomaterials. In addition to the estimated potential risk, ultimately the potential benefit for the patient should also be considered in the final benefit risk evaluation. The potential for release, leading to exposure to nanomaterials, is considered the most important feature that drives the extent of the risk assessment to be performed.

Table 5.2: Framework for risk assessment of nanomaterials used in medical devices. [Table 5 from SCENIHR (2015), reproduced with the permission of the European Commission, DG Health and Food Safety, Luxembourg. Copyright remains with the European Union.]

Release of nanoparticles	**Non invasive**		**Invasive Lung**		**Invasive Other**	
	Short exposure	Long exposure	Short exposure	Long exposure	Short exposure	Long exposure
Low/insignificant	N/VL*	L/F**	L	F	L	F
Medium	L/F	L/F	L/F	F	L/F	F
High	L/F	L/F	F	F	F	F

F=full assessment L=limited assessment VL =very limited or N= no further assessment
**=limited assessment if it can be shown that penetration/distribution is very limited.*

*** Full assessment when absorption is indicated in toxicokinetic studies*

6 Discussion and conclusions

Nanotechnologies represent one of the key enabling technologies (KETs), as defined by the European Commission (EC). As for many other types of products, nanotechnologies can also enable significant benefits for medical devices. Medical devices are a very diverse group of products and their applications can be either diagnostic or therapeutic, or even a combination of both. Some products are related to only one disease, disability or injury, while other products can be applied in the diagnosis and/or treatment of multiple conditions. Some products are primarily used by one medical discipline, while others can be used by a variety of medical specialists. This means that there are several different ways of categorising medical devices. In this report on nanotechnologies in medical devices, medical disciplines were chosen as the primary categories. Given the broad range of applications, this report cannot be comprehensive. However, it does provide an overview of the most important types of applications. No other sources were identified that provide a comparable overview of medical devices enabled by nanotechnologies.

The scope of this investigation included all medical devices enabled by nanotechnologies, except lab-on-a-chip applications for clinical diagnostics, as previously a report dedicated to that topic was published (Hermsen *et al.*, 2013). In addition, medical devices with (only) a computer chip as a nanotechnology enabled component were excluded. A size range of approximately 1 nm to 100 nm is used in various working definitions or descriptions regarding nanotechnology (EC, 2011; ISO/TS 80004-1:2010; OECD, 2011). There is, however, also general consensus that the upper limit of 100 nm is not based on scientific arguments and that size related phenomena can also occur at sizes above 100 nm (Rauscher *et al.*, 2015; SCENIHR, 2009). Therefore, this report is not restricted to the use of structures with an upper limit of 100 nm, but includes applications based on structures up to 1000 nm. This is in line with the approach followed by international regulatory bodies like the EMA, the FDA and Health Canada.

The diversity of product types and application areas implies that a combination of different sources is needed in order to obtain an overview of medical devices enabled by nanotechnologies. Taking into account limitations in budget, time and access to human resources, a combination of literature search and available databases for patents, products on the market or in clinical trials was selected. The main limitation in searching these sources is that medical devices containing nanotechnology do not necessarily have "nano" in their name. Furthermore, there are products that contain the term "nano" from a commercial viewpoint, which do not actually contain any nanotechnology. In addition, while a focus was placed on the European market, databases from the United States and Canada had to be used for products on the market, since there is no publicly available database of products on the market in Europe. Moreover, information on clinical trials taken from international sources and scientific literature most often do not distinguish geographical application areas. On the other

hand, European patents could be searched exclusively. A limitation in this source, however, was that the search did not pick up patents on manufacturing specific particles that could be used for any products including nanomedical devices. In general, while digging deeper into search results, it was often difficult to determine whether a product is actually enabled by nanotechnologies or not, and whether it is on the market or in some earlier phase.

Our results indicate that the application of nanotechnologies in medical devices is a growing area. When looking at general trends, the numbers of European patents have shown a gradual increase over the past 15 years. Given the fact that medical devices are generally subject to fast and incremental innovations which reduce the value of patents, this is a meaningful finding. Additionally, registered clinical trials have steadily increased over the past 10 years. Dentistry is a medical discipline where nanomedical devices have been used for a considerable amount of time and are already considered commonplace. The total number of nanomedical devices and the diversity of products is much higher in dentistry than in other disciplines. The reason for this difference is unclear. The short-term future of dental nanomedical devices will most likely consist of incremental improvements of existing products, as new nanomaterials become available. On the other hand, nanotechnology seems to be a long way from mainstream neurology. However, the potential of nanotechnology for that area is tremendous.

When looking at the results for the various medical disciplines, a number of general trends can be identified with regard to the application of nanotechnologies in medical devices and their benefits. One of the most important types of applications are nanocoatings and/or surface modifications at the nanoscale. This is also reflected by the number of patents related to this. In cardiology, stents, balloons and ventricular assist devices are increasingly being equipped with such features. Orthopaedic and dental implants are already benefiting from this, and neurological implants are expected to do so in the future. The most important benefit of nanocoatings over the various disciplines is an increased biocompatibility and thus integration with surrounding tissues. In addition, nanocoatings with antimicrobial properties are increasingly being used. Applications in wound care and medical textiles also take advantage of the antimicrobial properties of nanomaterials. Especially nano-silver is used for this purpose in a variety of applications used by many of the disciplines investigated.

Another clear trend is the use of nanomaterials to mimic naturally occurring structures. This phenomenon is applied in dentistry and in orthopaedics for both dental and bone filler materials. It yields optimal biological, physical, mechanical, and aesthetic characteristics (dental filers) and additionally it provides improved handling properties. Nanostructures can also mimic naturally occurring structures for soft tissues. Nanofibrous tissues can be prepared by using electrospinning production technologies which have applications in cardiology, orthopaedics, neurology and wound care.

A third trend of applications used in several medical disciplines is related to the electrical and magnetic properties of materials at the nanoscale.

These properties are being exploited in both cardiology and neurology: electrodes and sensors used in cardiac rhythm management, visual prostheses, hearing aids and brain stimulation are using increasingly smaller sized structures. It is believed that future nanosized applications can provide a significantly improved bioelectrical interface between the device and surrounding tissue which can both increase efficacy and reduce adverse side effects. Furthermore, nanotechnologies are expected to enable batteries with greatly increased lifetime for active implantable medical devices, thus reducing the need for surgical interventions to replace batteries, with the associated reduction in risks related to surgical interventions.

A number of nanotechnology applications are specific to oncology. Although most of the nanomedical research in oncology is related to medicinal products, a number of medical device applications have also been identified. In diagnostics, identification of biomarkers is important for the early detection of cancer. A relatively new area in this respect is breath metabolomics which also has applications in cardiology and other disciplines. Nanomaterial applications have also been developed for the identification of the boundaries of a tumour or metastases during surgical interventions. For therapeutic indications, products are on the market or under development that use increased temperature to either enhance the effect of other therapies like chemotherapy or radiation therapy (hyperthermia), or by killing tumour cells at high temperature (thermoablation).

New and emerging technologies bring new opportunities. At the same time, they can present new challenges to the risk assessment. At the moment, there is an evolving body of knowledge on safety evaluation of nanomaterials in general, and thus also for their use in medical devices. Nanomaterials exhibit specific characteristics that may or may not lead to toxic effects. As for all medical products, risk assessment of nanomedical products needs to be performed on a case-by-case basis. Guidance on how to do this is currently emerging. An ISO Technical Report is under development, providing guidance on how to apply the existing ISO 10993 series of standards for biological evaluation of medical devices to nanomedical devices. Furthermore, the SCENIHR has published a scientific opinion on guidance on the determination of potential health effects of nanomaterials used in medical devices (SCENIHR, 2015). This guidance refers to the same ISO standards. It describes approaches for the safety evaluation of medical devices containing or manufactured using nanomaterials, and also refers to wear and tear particles of implants that may be in the nanoscale size range. In order to help the user of the ISO standards, it provides estimates of potential exposure to nanomaterials from nanomedical devices, and it proposes a phased approach for risk evaluation. The potential for release, leading to a higher or lower exposure to nanomaterials, is considered the most important feature that drives the extent of the risk assessment to be performed. Using this approach, a limited or more extensive assessment with regard to the nano aspects is suggested. With the current state-of-the-art with regard to risk assessment of nanomedical devices, the combined guidance from the ISO and the SCENIHR documents provides a suitable basis for stakeholders to perform their risk assessments.

References

3-D Matrix Medical Technology. Puramatrix™. http://www.puramatrix.com/puramatrix.html. Accessed 16 November 2015.

Abrigo M, McArthur SL, and Kingshott P (2014). Electrospun nanofibers as dressings for chronic wound care: advances, challenges, and future prospects. *Macromol Biosci* 14:772-92.

Abu-Amer Y, Darwech I, and Clohisy JC (2007). Aseptic loosening of total joint replacements: mechanisms underlying osteolysis and potential therapies. *Arthritis Res Ther* 9 Suppl 1:S6.

Ahn H-S, Hwang J-Y, Kim MS, Lee J-Y, Kim J-W, Kim H-S, Shin US, Knowles JC, Kim H-W, and Hyun JK (2015). Carbon-nanotube-interfaced glass fiber scaffold for regeneration of transected sciatic nerve. *Acta Biomater* 13:324-34.

Ahnood A, Escudie MC, Cicione R, Abeyrathne CD, Ganesan K, Fox KE, Garrett DJ, Stacey A, Apollo NV, Lichter SG, Thomas CD, Tran N, Meffin H, and Prawer S (2015). Ultrananocrystalline diamond-CMOS device integration route for high acuity retinal prostheses. *Biomed Microdevices* 17:9952.

Allen B. The eleven most implantable medical devices in America. http://247wallst.com/healthcare-economy/2011/07/18/the-eleven-most-implanted-medical-devices-in-america/3/. Accessed 16 November 2015.

Andrews RJ (2007). Neuroprotection at the nanolevel--Part II: Nanodevices for neuromodulation--deep brain stimulation and spinal cord injury. *Ann N Y Acad Sci* 1122:185-96.

Arora R and Kapoor H (2014). Nanotechnology in dentistry - Hope or hype. *Oral Health Dent Manag* 13:928-33.

Arsiwala A, Desai P, and Patravale V (2014). Recent advances in micro/nanoscale biomedical implants. *J Control Release* 189:25-45.

Atai M, Solhi L, Nodehi A, Mirabedini SM, Kasraei S, Akbari K, and Babanzadeh S (2009). PMMA-grafted nanoclay as novel filler for dental adhesives. *Dent Mater* 25:339-47.

Augustine R, Kalarikkal N, and Thomas S (2014). Advancement of wound care from grafts to bioengineered smart skin substitutes. *Prog Biomater* 3:103-13.

Ayton LN, Blamey PJ, Guymer RH, Luu CD, Nayagam DA, Sinclair NC, Shivdasani MN, Yeoh J, McCombe MF, Briggs RJ, Opie NL, Villalobos J, Dimitrov PN, Varsamidis M, Petoe MA, McCarthy CD, Walker JG, Barnes N, Burkitt AN, Williams CE, Shepherd RK, and Allen PJ (2014). First-in-human trial of a novel suprachoroidal retinal prosthesis. *PLoS One* 9:e115239.

Bareket-Keren L and Hanein Y (2012). Carbon nanotube-based multi electrode arrays for neuronal interfacing: progress and prospects. *Front Neural Circuits* 6:122.

Bareket L, Waiskopf N, Rand D, Lubin G, David-Pur M, Ben-Dov J, Roy S, Eleftheriou C, Sernagor E, Cheshnovsky O, Banin U, and Hanein Y (2014). Semiconductor nanorod-carbon nanotube biomimetic films for wire-free photostimulation of blind retinas. *Nano Lett* 14:6685-92.

Bednarski M, Soska-Czop A, Zarzycka B, Ebert J, and Pawlicka H (2013). NanoCare Plus SilverGold® can eliminate *Enterococcus faecalis* from dentinal tubules. *Dent Med Probl* 50:418-23.

Berruto M, Delcogliano M, de Caro F, Carimati G, Uboldi F, Ferrua P, Ziveri G, and De Biase CF (2014). Treatment of large knee osteochondral lesions with a biomimetic scaffold: Results of a multicenter study of 49 patients at 2-year follow-up. *Am J Sports Med* 42:1607-17.

Berthelot J, Aćimović SS, Juan ML, Kreuzer MP, Renger J, and Quidant R (2014). Three-dimensional manipulation with scanning near-field optical nanotweezers. *Nat Nanotechnol* 9:295-9.

Besinis A, De Peralta T, Tredwin CJ, and Handy RD (2015). Review of nanomaterials in dentistry: interactions with the oral microenvironment, clinical applications, hazards, and benefits. *ACS Nano* 9:2255-89.

Bhavikatti SK, Bhardwaj S, and Prabhuji ML (2014). Current applications of nanotechnology in dentistry: a review. *Gen Dent* 62:72-7.

Bleeker EAJ, Evertz S, Geertsma RE, Peijenburg WJGM, Westra J, and Wijnhoven SWP (2015). Assessing health & environmental risks of nanoparticles: Current state of affairs in policy, science and areas of application. RIVM Report 2014-0157. National Institute for Public Health and the Environment: Bilthoven, the Netherlands. http://www.rivm.nl/dsresource?objectid=rivmp:276318&type=org&disposition=inline&ns_nc=1. Accessed 16 November 2015.

Bognitzki M, Czado W, Frese T, Schaper A, Hellwig M, Steinhart M, Greiner A, and Wendorff JH (2001). Nanostructured fibers via electrospinning. *Adv Mater* 13:70-2.

Bouten CV, Driessen-Mol A, and Baaijens FP (2012). In situ heart valve tissue engineering: simple devices, smart materials, complex knowledge. *Expert Rev Med Devices* 9:453-5.

Brydone AS, Meek D, and Maclaine S (2010). Bone grafting, orthopaedic biomaterials, and the clinical need for bone engineering. *Proc Inst Mech Eng H* 224:1329-43.

Cadence. Surgical blades & medical blades. http://cadenceinc.com/products/surgical-devices/surgical-blades-medical-blades/. Accessed 16 November 2015.

Cadence. Diamond. http://cadenceinc.com/technology-design-center/materials-coatings-information/Diamond/. Accessed 16 November 2015.

Cheng L, Zhang K, Weir MD, Melo MA, Zhou X, and Xu HH (2015). Nanotechnology strategies for antibacterial and remineralizing composites and adhesives to tackle dental caries. *Nanomedicine (Lond)* 10:627-41.

Chow AY, Bittner AK, and Pardue MT (2010). The artificial silicon retina in retinitis pigmentosa patients (an American Ophthalmological Association thesis). *Trans Am Ophthalmol Soc* 108:120-54.

Chow AY (2013). Retinal prostheses development in retinitis pigmentosa patients - Progress and comparison. *Asia-Pac J Ophthalmol* 2.

Christensen BB, Foldager CB, Jensen J, Jensen NC, and Lind M (2015). Poor osteochondral repair by a biomimetic collagen scaffold: 1- to 3-year clinical and radiological follow-up. *Knee Surg Sports Traumatol Arthrosc* [Epub ahead of print].

Clift MJD, Raemy DO, Endes C, Ali Z, Lehmann AD, Brandenberger C, Petri-Fink A, Wick P, Parak WJ, Gehr P, Schins RPF, and Rothen-

Rutishauser B (2013). Can the Ames test provide an insight into nano-object mutagenicity? Investigating the interaction between nano-objects and bacteria. *Nanotoxicology* 7:1373-85.
ClinicalTrials.gov. A service of the US National Institutes of Health. https://clinicaltrials.gov/. Accessed 16 November 2015.
ClinicalTrials.gov. EnSeal efficacy and bursting pressure in human vessels. https://clinicaltrials.gov/ct2/show/NCT01312246?term=NCT01312246&rank=1. Accessed 16 November 2015.
Costa JR, Jr., Abizaid A, Costa R, Feres F, Tanajura LF, Abizaid A, Maldonado G, Staico R, Siqueira D, Sousa AG, Bonan R, and Sousa JE (2009). 1-year results of the hydroxyapatite polymer-free sirolimus-eluting stent for the treatment of single de novo coronary lesions: the VESTASYNC I trial. *JACC Cardiovasc Interv* 2:422-7.
Costa JR, Jr., Oliveira BA, Abizaid A, Costa R, Perin M, Abizaid A, Chamié D, Tanajura LF, Sousa A, and Sousa JEMR (2014). Clinical, angiographic, and intravascular ultrasound results of the VestSaync II trial. *Catheter Cardiovasc Interv* 84:1073-9.
Dagdeviren C, Yang BD, Su Y, Tran PL, Joe P, Anderson E, Xia J, Doraiswamy V, Dehdashti B, Feng X, Lu B, Poston R, Khalpey Z, Ghaffari R, Huang Y, Slepian MJ, and Rogers JA (2014). Conformal piezoelectric energy harvesting and storage from motions of the heart, lung, and diaphragm. *Proc Natl Acad Sci U S A* 111:1927-32.
De Volder MFL, Tawfick SH, Baughman RH, and Hart AJ (2013). Carbon nanotubes: Present and future commercial applications. *Science* 339:535-9.
Du F, Zhao W, Zhang M, Mao H, Kong D, and Yang J (2011). The synergistic effect of aligned nanofibers and hyaluronic acid modification on endothelial cell behavior for vascular tissue engineering. *J Nanosci Nanotechnol* 11:6718-25.
Duncan R and Sat Y-N (1998). Tumour targeting by enhanced permeability and retention (EPR) effect. *Ann Oncol* 9:39.
EC. http://ec.europa.eu/growth/industry/key-enabling-technologies/index_en.htm. Accessed 16 November 2015.
EC (1993). Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. OJ L 169, 12.7.1993. Amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007. OJ L 247, 21.9.2007. European Parliament and the Council of the European Union: Brussels, Belgium. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF. Accessed 16 November 2015.
EC (2011). Commission recommendation of 18 October 2011 on the definition of nanomaterial (2011/696/EU). Official Journal of the European Union L275/38, 20.10.2011. European Commission: Brussels, Belgium. https://ec.europa.eu/research/industrial_technologies/pdf/policy/commission-recommendation-on-the-definition-of-nanomater-18102011_en.pdf. Accessed 16 November 2015.
EC (2012). Proposal for a Regulation of the European Parliament and of the Council on medical devicves, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, 26.9.2012, COM(2012) 542 final, 2012/0266 (COD). European Commission: Brussels, Belgium. http://ec.europa.eu/health/medical-

devices/files/revision_docs/proposal_2012_542_en.pdf. Accessed 16 November 2015.
EC (2014). Manual on borderline and classification in the Community regulatory framework for medical devices. Version 1.16. European Commission: Brussels, Belgium. http://ec.europa.eu/health/medical-devices/files/wg_minutes_member_lists/borderline_manual_ol_en.pdf. Accessed 16 November 2015.
EFORT. Nanotechnology has potential to revolutionise orthopaedics - experts call for research into safety. https://www.efort.org/nanotechnology-has-potential-to-revolutionise-orthopaedics-experts-call-for-research-into-safety/. Acessed 16 November 2015.
EFSA (2011). Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. *EFSA Journal* 9:2140.
EMA. Nanotechnology. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&. Accessed 16 November 2015.
Espacenet. Espacenet: free access to the database of over 90 million patients. http://worldwide.espacenet.com/. Accessed 16 November 2015.
Ethicon. ENSEAL(R) G2 Curved and Straight Tissue Sealers. http://www.ethicon.com/healthcare-professionals/products/advanced-energy/enseal/enseal-g2-tissue-sealers. Accessed 16 November 2015.
Farhatnia Y, Tan A, Motiwala A, Cousins BG, and Seifalian AM (2013). Evolution of covered stents in the contemporary era: clinical application, materials and manufacturing strategies using nanotechnology. *Biotechnol Adv* 31:524-42.
FDA. 510(k) Premarket Notification database. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed 16 November 2015.
FDA (2014). Guidance for industry - Considering whether an FDA-regulated product involves the application of nanotechnology. US Food and Drug Administration: Silver Springs, MD, USA. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM401695.pdf. Accessed 16 November 2015.
Feng ZQ, Lu HJ, Leach MK, Huang NP, Wang YC, Liu CJ, and Gu ZZ (2010). The influence of type-I collagen-coated PLLA aligned nanofibers on growth of blood outgrowth endothelial cells. *Biomed Mater* 5:065011.
Foerster V (2014). SentiMag® and Sienna+® for sentinal lymph node localisation in breast cancer. Health Policy Advisory Committee on Technology (HealthPACT): State of Queensland, Australia.
Fuentes L, Yakob M, and Wong DT (2014). Emerging horizons of salivary diagnostics for periodontal disease. *Br Dent J* 217:567-73.
Fulton JL, Deverman GS, Yonker CR, Grate JW, De Young J, and McClain JB (2003). Thin fluoropolymer films and nanoparticle coatings from the rapid expansion of supercritical carbon dioxide solutions with electrostatic collection. *Polymer* 44:3627-32.

Gainza G, Villullas S, Pedraz JL, Hernandez RM, and Igartua M (2015). Advances in drug delivery systems (DDSs) to release growth factors for wound healing and skin regeneration. *Nanomedicine (Lond)*.

Gao Y, Truong YB, Zhu Y, and Louis Kyratzis I (2014). Electrospun antibacterial nanofibers: production, activity and in vivo applications. *J Appl Polym Sci* 131.

Gdowski A, Ranjan AP, Mukerjee A, and Vishwanatha JK (2014). Nanobiosensors: role in cancer detection and diagnosis. *Adv Exp Med Biol* 807:33-58.

Ge L, Li Q, Wang M, Ouyang J, Li X, and Xing MM (2014). Nanosilver particles in medical applications: synthesis, performance, and toxicity. *Int J Nanomedicine* 9:2399-407.

GFD. http://en.blades.diamaze-gfd.com/51.html. Accessed 16 November 2015.

Ghanbari H, de Mel A, and Seifalian AM (2011). Cardiovascular application of polyhedral oligomeric silsesquioxane nanomaterials: a glimpse into prospective horizons. *Int J Nanomedicine* 6:775-86.

Gidcumb E, Gao B, Shan J, Inscoe C, Lu J, and Zhou O (2014). Carbon nanotube electron field emitters for X-ray imaging of human breast cancer. *Nanotechnology* 25:245704.

Gill HS, Grammatopoulos G, Adshead S, Tsialogiannis E, and Tsiridis E (2012). Molecular and immune toxicity of CoCr nanoparticles in MoM hip arthroplasty. *Trends Mol Med* 18:145-55.

Gobin AM, O'Neal DP, Watkins DM, Halas NJ, Drezek RA, and West JL (2005). Near infrared laser-tissue welding using nanoshells as an exogenous absorber. *Lasers Surg Med* 37:123-9.

Gunaratnam E, James K, and Vasdev N (2015). The increasing application of nanotechnology and nanomedicine in urological oncology. *JSM Nanotechnol Nanomed* 3.

Hansom D, Ramage G, Burgess K, Gadengaard N, Millar N, and Clarke J (2015). The effects of nanopattern surface technology on orthopaedic joint replacement infection. *Bone Joint J* 97-B.

Health Canada. Medical Devices Active Licence Listing. http://webprod5.hc-sc.gc.ca/mdll-limh/index-eng.jsp. Accessed 16 November 2015.

Health Canada. Policy Statement on Health's Canada Working Definition for Nanomaterial. http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php. Accessec 16 November 2015.

Hermsen SAB, Roszek B, van Drongelen AW, and Geertsma RE (2013). Lab-on-a-chip devices for clinical diagnostics - Measuring into a new dimension. RIVM Report 080116001. National Institute for Public Health and the Environment: Bilthoven, the Netherlands. http://www.rivm.nl/dsresource?objectid=rivmp:241587&type=org&disposition=inline&ns_nc=1. Accessed 16 November 2015.

Huang HC, Walker CR, Nanda A, and Rege K (2013). Laser welding of ruptured intestinal tissue using plasmonic polypeptide nanocomposite solders. *ACS Nano* 7:2988-98.

Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, Mech B, Cimmarusti V, Van Boemel G, Dagnelie G, and de Juan Jr E (2003). Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. *Vision Res* 43:2573-81.

Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Sahel J-A, Stanga PE, Cideciyan AV, Duncan JL, Eliott D, Filley E, Ho AC, Santos A, Safran AB, Arditi A, Del Priore LV, and Greenberg RJ (2012). Interim results

from the international trial of Second Sight's Visual Prosthesis. *Ophthalmology* 119:779-88.
Hwang GT, Park H, Lee JH, Oh S, Park KI, Byun M, Park H, Ahn G, Jeong CK, No K, Kwon H, Lee SG, Joung B, and Lee KJ (2014). Self-powered cardiac pacemaker enabled by flexible single crystalline PMN-PT piezoelectric energy harvester. *Adv Mater* 26:4880-7.
ICTRP WHO. International Clinical Trials Registry Platform of the World Health Organization. http://www.who.int/en/. Accessed 16 November 2015.
Ionescu R, Broza Y, Shaltieli H, Sadeh D, Zilberman Y, Feng X, Glass-Marmor L, Lejbkowicz I, Mullen K, Miller A, and Haick H (2011). Detection of multiple sclerosis from exhaled breath using bilayers of polycyclic aromatic hydrocarbons and single-wall carbon nanotubes. *ACS Chem Neurosci* 2:687-93.
ISO 10993-1:2009 Biological evaluation of medical devices - Part 1: Evaluation and testing with the risk management process.
ISO/TR 10993-22 Biological evaluation of medical devices - Part 22: Guidance on nanomaterials (in preparation).
ISO/TS 80004-1:2010 Nanotechnologies - Vocabulary - Part 1: Core terms.
ISRCTN. ISRCTN registry. http://www.isrctn.com/. Accessed 16 November 2015.
Jacobs JJ, Campbell PA, Y TK, and Implant Wear Symposium Biologic Work G (2008). How has the biologic reaction to wear particles changed with newer bearing surfaces? *J Am Acad Orthop Surg* 16 Suppl 1:S49-55.
Jain KK (2015). Nanobiotechnology: Applications, markets and companies. Jain PharmaBiotech: Basel, Switzerland.
Jiang X, Lim SH, Mao H-Q, and Chew SY (2010). Current applications and future perspectives of artificial nerve conduits. *Exp Neurol* 223:86-101.
Kharlamov AN, Tyurnina AE, Veselova VS, Kovtun OP, Shur VY, and Gabinsky JL (2015). Silica-gold nanoparticles for atheroprotective management of plaques: results of the NANOM-FIM trial. *Nanoscale* 7:8003-15.
Khurshid Z, Zafar M, Qasim S, Shahab S, Naseem M, and AbuReqaiba A (2015). Advances in nanotechnology for restorative dentistry. *Materials* 8:717-31.
Kidane AG, Burriesci G, Edirisinghe M, Ghanbari H, Bonhoeffer P, and Seifalian AM (2009). A novel nanocomposite polymer for development of synthetic heart valve leaflets. *Acta Biomater* 5:2409-17.
Kon E, Filardo G, Di Martino A, Busacca M, Moio A, Perdisa F, and Marcacci M (2014). Clinical results and MRI evolution of a nano-composite multilayered biomaterial for osteochondral regeneration at 5 years. *Am J Sports Med* 42:158-65.
Kreyling WG, Semmler-Behnke M, and Chaudhry Q (2010). A complementary definition of nanomaterial. *Nano Today* 5:165-8.
Lapotko D (2009). Therapy with gold nanoparticles and lasers: what really kills the cells? *Nanomedicine (Lond)* 4:253-6.
Lee YS and Arinzeh TL (2011). Electrospun nanofibrous materials for neural tissue engineering. *Polymers* 3:413-26.

Lewis PM, Ackland HM, Lowery AJ, and Rosenfeld JV (2015). Restoration of vision in blind individuals using bionic devices: A review with a focus on cortical visual prostheses. *Brain Research* 1595:51-73.
Li J and Andrews RJ (2007). Trimodal nanoelectrode array for precise deep brain stimulation: prospects of a new technology based on carbon nanofiber arrays. *Acta Neurochir Suppl* 97:537-45.
Liu Y, Lim J, and Teoh SH (2013). Review: development of clinically relevant scaffolds for vascularised bone tissue engineering. *Biotechnol Adv* 31:688-705.
Loh JP and Waksman R (2012). Paclitaxel drug-coated balloons: a review of current status and emerging applications in native coronary artery de novo lesions. *JACC Cardiovasc Interv* 5:1001-12.
Lorach H and Goetz G (2015). Photovoltaic restoration of sight with high visual acuity. *Nat Med* 21:476-82.
Loscri V and Vegni AM (2015). An acoustic communication technique of nanorobot swarms for nanomedicine applications. *IEEE Trans Nanobioscience* 14:598-607.
Maheshwari V and Saraf R (2008). Tactile devices to sense touch on a par with a human finger. *Angew Chem Int Ed* 47:7808-26.
Mankani MH, Kuznetsov SA, Fowler B, Kingman A, and Robey PG (2001). In vivo bone formation by human bone marrow stromal cells: effect of carrier particle size and shape. *Biotechnol Bioeng* 72:96-107.
Mannoor MS, Jiang Z, James T, Kong YL, Malatesta KA, Soboyejo WO, Verma N, Gracias DH, and McAlpine MC (2013). 3D printed bionic ears. *Nano Lett* 13:2634-9.
Mantovani E, Zappelli P, Conde J, Sitja R, and Periales F (2010). Report on Nanotechnology & Textiles - Medical Textiles, Sport/Outdoor Textiles. AIRI/Nanotec IT and Bax & Willems Consulting Venturing.
Mattei TA and Rehman AA (2015). "Extremely minimally invasive": recent advances in nanotechnology research and future applications in neurosurgery. *Neurosurg Rev* 38:27-37.
Mayet N, Choonara YE, Kumar P, Tomar LK, Tyagi C, Du Toit LC, and Pillay V (2014). A comprehensive review of advanced biopolymeric wound healing systems. *J Pharm Sci* 103:2211-30.
Mellert F, Konietzko P, Schneider C, Gersing E, Kreuz J, Balta O, Preusse CJ, and Welz A (2008). Evaluation of fractal-coated temporary pacing leads in the early postoperative course. *Pacing Clin Electrophysiol* 31:198-206.
Moffa M, Sciancalepore AG, Passione LG, and Pisignano D (2014). Combined nano- and micro-scale topographic cues for engineered vascular constructs by electrospinning and imprinted micro-patterns. *Small* 10:2439-50.
Mohammadi H (2011). Nanocomposite biomaterial mimicking aortic heart valve leaflet mechanical behaviour. *Proc Inst Mech Eng H* 225:718-22.
Mol A, Smits AI, Bouten CV, and Baaijens FP (2009). Tissue engineering of heart valves: advances and current challenges. *Expert Rev Med Devices* 6:259-75.
Musa S, Rand DR, Cott DJ, Loo J, Bartic C, Eberle W, Nuttin B, and Borghs G (2012). Bottom-up SiO 2 embedded carbon nanotube electrodes with superior performance for integration in implantable neural microsystems. *ACS Nano* 6:4615-28.

Nakano K, Egashira K, Masuda S, Funakoshi K, Zhao G, Kimura S, Matoba T, Sueishi K, Endo Y, Kawashima Y, Hara K, Tsujimoto H, Tominaga R, and Sunagawa K (2009). Formulation of nanoparticle-eluting stents by a cationic electrodeposition coating technology: efficient nano-drug delivery via bioabsorbable polymeric nanoparticle-eluting stents in porcine coronary arteries. *JACC Cardiovasc Interv* 2:277-83.

Nano4Imaging. http://www.nano4imaging.com/. Accessed 16 November 2015.

Nanobiotix. Nanobiotix 2014 Review, 2015 Anticipated Milestones and Financial Calendar. http://www.nanobiotix.com/news/release/nanobiotix-2014-review-2015-anticipated-milestones-and-financial-calendar/. Accessed 16 November 2015.

Nanogen Aktigel. Nanogen Aktigel gebruiksaanwijzingen. http://www.biologiq.nl/UserFiles/NANOGEN%20AKTIGEL%20GEBRUIKSAANWIJZINGEN.pdf. Accessed 16 November 2015.

Nanogen Aktiv. Nanogen Aktiv Advanced wound care from nature. http://www.biologiq.nl/UserFiles/Nanogen%20Aktiv%20folder%20E%2004%202014.pdf. Accessed 16 November 2015.

Nanotec Endo. NanoCare Gold. http://www.nanotecendo.com/nanocare-gold/. Accessed 16 November 2015.

NET WG (2007). Report on nanotechnology to the Medical Device Expert Group - Findings and recommendations, 12 July 2007. European Commission: Brussels, Belgium. http://ec.europa.eu/health/medical-devices/files/net/entr-2007-net-wg-report-nano-final_en.pdf. Accessed 16 November 2015.

Nodzo SR, Hohman DW, and Chakravarthy K (2015). Nanotechnology: Why should we care? *Am J Orthop* 44:E87-E8.

Noorlander CW, Kooi MW, Oomen AG, Park MV, Vandebriel RJ, and Geertsma RE (2015). Horizon scan of nanomedicinal products. *Nanomedicine (Lond)* 1-10.

NVE Corporation (2001). NVE Corporation receives sensor order from St. Jude Medical. http://www.nve.com/2001prs/april112001.htm. Accessed 16 November 2015.

OECD (2011). Regulated nanomaterials: 2006-2009. ENV/JM/MONO(2011)52. Environment, Health and Safety Publications Series on the Safety of Manufactured Nanomaterials No. 30. Organisation for Economic Co-operation and Development: Paris, France. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2011)52&doclanguage=en. Accessed 15 November 2015.

Pancrazio JJ (2008). Neural interfaces at the nanoscale. *Nanomedicine (Lond)* 3:823-30.

Petersen DK, Naylor TM, and Ver Halen JP (2014). Current and future applications of nanotechnology in plastic and reconstructive surgery. *Plast Aesthet Res* 1:43-50.

Polikov VS, Tresco PA, and Reichert WM (2005). Response of brain tissue to chronically implanted neural electrodes. *J Neurosci Methods* 148:1-18.

Polyak B, Fishbein I, Chorny M, Alferiev I, Williams D, Yellen B, Friedman G, and Levy RJ (2008). High field gradient targeting of

magnetic nanoparticle-loaded endothelial cells to the surfaces of steel stents. *Proc Natl Acad Sci U S A* 105:698-703.

Prentice LH, Tyas MJ, and Burrow MF (2006). The effect of ytterbium fluoride and barium sulphate nanoparticles on the reactivity and strength of a glass-ionomer cement. *Dent Mater* 22:746-51.

Project on Emerging Nanotechnologies. EnSeal Laparoscopic Vessel Fusion System. http://www.nanotechproject.org/inventories/medicine/apps/medical_tools/enseal_laparoscopic_vessel_fusion_system/. Accessed 16 November 2015.

RAS Materials. AgPure™. http://rasmaterials.com/docs/TI_AgPURE.pdf. Accessed 16 November 2015.

Rauscher H, Roebben G, Boix Sanfeliu A, Emons H, Gibson N, Koeber R, Linsinger T, Rasmussen K, Riego Sintes J, Sokull-Klüttgen B, and Stamm H (2015). Towards a review of the EC Recommendation for a definition of the term "nanomaterial". Part 3. Scientific-technical evaluation of options to clarify the definition and to facilitate its implementation. JRC95675, EUR 27240 EN. European Commission. http://publications.jrc.ec.europa.eu/repository/bitstream/JRC95675/towards%20review%20ec%20rec%20def%20nanomaterial%20-%20part%203_report_online%20id.pdf. Accessed 15 November 2015.

Ravalli A and Marrazza G (2015). Gold and magnetic nanoparticles-based electrochemical biosensors for cancer biomarker determination. *J Nanosci Nanotechnol* 15:3307-19.

Rosic R, Kocbek P, Pelipenko J, Kristl J, and Baumgartner S (2013). Nanofibers and their biomedical use. *Acta Pharm* 63:295-304.

Roszek B, de Jong WH, and Geertsma RE (2005). Nanotechnology in medical applications, State-of-the-art in materials and devices. RIVM Report 265001001. National Institute for Public Health and the Environment: Bilthoven, the Netherlands. http://www.rivm.nl/dsresource?objectid=rivmp:12100&type=org&disposition=inline&ns_nc=1. Accessed 16 November 2015.

Safak E, Schmitz D, Konorza T, Wende C, De Ros JO, and Schirdewan A (2013). Clinical efficacy and safety of an implantable cardioverter-defibrillator lead with a floating atrial sensing dipole. *Pacing Clin Electrophysiol* 36:952-62.

Samara MA, Tang WH, Cikach F, Jr., Gul Z, Tranchito L, Paschke KM, Viterna J, Wu Y, Laskowski D, and Dweik RA (2013). Single exhaled breath metabolomic analysis identifies unique breathprint in patients with acute decompensated heart failure. *J Am Coll Cardiol* 61:1463-4.

Sandvik Materials Technology. Sandvik Bioline 1RK91 medical wire. http://smt.sandvik.com/en/products/wire/high-performance-materials/sandvik-bioline-1rk91/. Accessed 16 November 2015.

SCCS (2012). Guidance on the safety assessment of nanomaterials in cosmetics, 26-27 June 2012. European Commission: Brussels, Belgium. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_005.pdf. Accessed 16 November 2015.

SCENIHR (2009). Risk assessment of products of nanotechnologies, 19 January 2009. European Commission: Brussels, Belgium. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf. Accessed 16 November 2015.

SCENIHR (2015). Guidance on the determination of potenital health effects of nanomaterials used in medical devices, 6 January 2015. European Commission: Brussels, Belgium. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_045.pdf. Accessed 16 November 2015.

Schleich N, Danhier F, and Preat V (2015). Iron oxide-loaded nanotheranostics: major obstacles to in vivo studies and clinical translation. *J Control Release* 198:35-54.

Schoni DS, Bogni S, Bregy A, Wirth A, Raabe A, Vajtai I, Pieles U, Reinert M, and Frenz M (2011). Nanoshell assisted laser soldering of vascular tissue. *Lasers Surg Med* 43:975-83.

Seeman E and Delmas PD (2006). Bone quality - The material and structural basis of bone strength and fragility. *N Engl J Med* 354:2250-61.

Shi Z, Huang X, Cai Y, Tang R, and Yang D (2009). Size effect of hydroxyapatite nanoparticles on proliferation and apoptosis of osteoblast-like cells. *Acta Biomater* 5:338-45.

Singhal S, Nie S, and Wang MD (2010). Nanotechnology applications in surgical oncology. *Annu Rev Med* 61:359-73.

Solanki NS, Mackie IP, and Greenwood JE (2012). A randomised prospective study of split skin graft donor site dressings: AWBAT-D vs. Duoderm(R). *Burns* 38:889-98.

Stingl K, Bartz-Schmidt KU, Besch D, Chee CK, Cottriall CL, Gekeler F, Groppe M, Jackson TL, MacLaren RE, Koitschev A, Kusnyerik A, Neffendorf J, Nemeth J, Naeem MA, Peters T, Ramsden JD, Sachs H, Simpson A, Singh MS, Wilhelm B, Wong D, and Zrenner E (2015). Subretinal Visual Implant Alpha IMS - Clinical trial interim report. *Vision Res* 111:149-60.

Stock G (2014). Overview for EC New & Emerging Technologies WG. FIDE European Dental Industry.

Stronks HC and Dagnelie G (2014). The functional performance of the Argus II retinal prosthesis. *Expert Rev Med Devices* 11:23-30.

Sullivan MP, McHale KJ, Parvizi J, and Mehta S (2014). Nanotechnology: current concepts in orthopaedic surgery and future directions. *Bone Joint J* 96-B:569-73.

Suwannasom P, Benit E, Gach O, von Birgelen C, Hofma SH, Bo X, Zhang Y-J, Nakatani S, Ishibashi Y, Onuma Y, García-García HM, Gao R-L, and Serruys PW (2015). Short-term effects of Nano+™ polymer-free sirolimus-eluting stents on native coronary vessels: an optical coherence tomography imaging study. *AsiaIntervention* 1:57-70.

Takimura CK, Galon MZ, Gutierrez PS, Sojitra P, Vyas A, Doshi M, and Lemos PA (2015). A new polymer-free drug-eluting stent with nanocarriers eluting sirolimus from stent-plus-balloon compared with bare-metal stent and with biolimus A9 eluting stent in porcine coronary arteries. *Cardiovasc Diagn Ther* 5:113-21.

Tan A, Farhatnia Y, de Mel A, Rajadas J, Alavijeh MS, and Seifalian AM (2013). Inception to actualization: Next generation coronary stent coatings incorporating nanotechnology. *J Biotechnol* 164:151-70.

Techtexil. http://techtextil.messefrankfurt.com/frankfurt/en/aussteller/willkommen.html. Accessed 16 November 2015.

Thomas S, Grohens Y, and Ninan N (2015). *Nanotechnology Applications for Tissue Engineering*. Elsevier: Waltham, MA, USA.

Tian L, Prabhakaran MP, and Ramakrishna S (2015). Strategies for regeneration of components of nervous system: scaffolds, cells and biomolecules. *Regen Biomater* 2:31-45.
Tocco I, Zavan B, Bassetto F, and Vindigni V (2012). Nanotechnology-Based Therapies for Skin Wound Regeneration. *J Nanomater* 2012:11.
Torrecillas R, Moya JS, Diaz LA, Bartolome JF, Fernandez A, and Lopez-Esteban S (2009). Nanotechnology in joint replacement. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 1:540-52.
Vallejo-Giraldo C, Kelly A, and Biggs MJP (2014). Biofunctionalisation of electrically conducting polymers. *Drug Discovery Today* 19:88-94.
Vellayappan MV, Balaji A, Subramanian AP, John AA, Jaganathan SK, Murugesan S, Supriyanto E, and Yusof M (2015). Multifaceted prospects of nanocomposites for cardiovascular grafts and stents. *Int J Nanomedicine* 10:2785-803.
Wheeler CA and Peckham PH (2009). Wireless wearable controller for upper-limb neuroprosthesis. *J Rehab Res Dev* 46:243-56.
Wicki A, Witzigmann D, Balasubramanian V, and Huwyler J (2015). Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. *J Control Release* 200:138-57.
Wikipedia. Osseointegration. http://en.wikipedia.org/wiki/Osseointegration. Accessed 16 November 2015.
WIPO. http://www.wipo.int/classifications/ipc/en/. Accessed 16 November 2015.
Xu ZQ, Broza YY, Ionsecu R, Tisch U, Ding L, Liu H, Song Q, Pan YY, Xiong FX, Gu KS, Sun GP, Chen ZD, Leja M, and Haick H (2013). A nanomaterial-based breath test for distinguishing gastric cancer from benign gastric conditions. *Br J Cancer* 108:941-50.
Yousefi A-M, Oudadesse H, Akbarzadeh R, Wers E, and Lucas-Girot A (2014). Physical and biological characteristics of nanohydroxyapatite and bioactive glasses used for bone tissue engineering. *Nanotechnol Rev* 3:527-52.
Yu M, Xu B, Kandzari DE, Wu Y, Yan H, Chen J, Qian J, Qiao S, Yang Y, and Gao RL (2014). First report of a novel polymer-free dual-drug eluting stent in de novo coronary artery disease: results of the first in human BICARE trial. *Catheter Cardiovasc Interv* 83:405-11.
Zamani F, Amani-Tehran M, Latifi M, Shokrgozar MA, and Zaminy A (2014). Promotion of spinal cord axon regeneration by 3D nanofibrous core-sheath scaffolds. *J Biomed Mater Res A* 102:506-13.
Zimmer. Trabecular Metal™ Technology. http://www.zimmer.com/medical-professionals/our-science/common/trabecular-metal-technology.html. Accessed 16 November 2015.

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