Nanoparticles: From Science to Market

A personal quest and business approach

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Paul Borm

Short BIO

Academic carreer between 1980 and 2004,
Positions in Utrecht, Maastricht and Düsseldorf.
First encounter with nanotechnology 1999
Entrepreneur since 2004- still in research (clinical)
Prof at Düsseldorf University (Med Imaging)

Crossing borders

First company MagnaMedics (2004-2010)
Founder of second company Nano4Imaging (2011- now)
Founder of NanoHouse (2006), Nanopodium (2008) LIME (2016)
Nanotechnology content driver for all above
Making connections is inner motivation and inspiration.

Idea (2008): MRI for interventions

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Angiography

Visibility catheter/wire
tissue visibility
radiation exposure

MRI

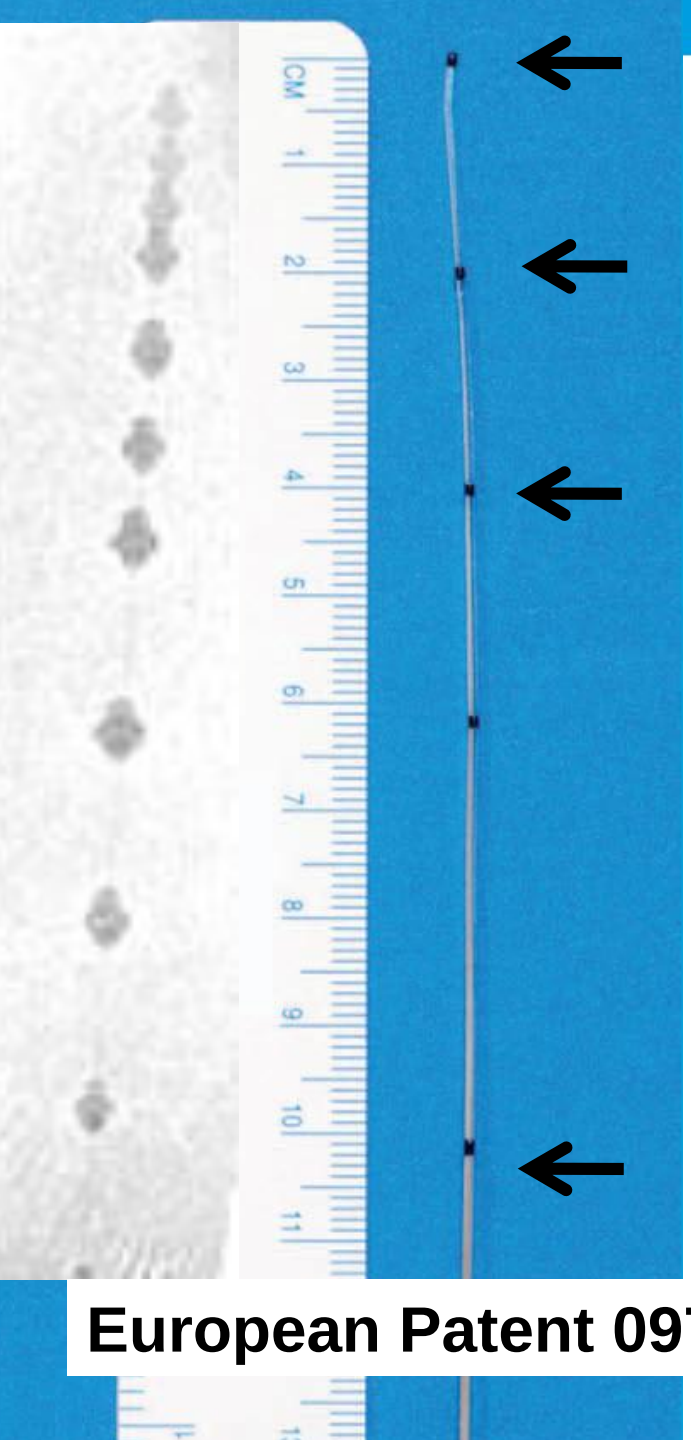
Visibility catheter/wire
tissue visibility
radiation exposure

All imaging methods use contrast agents For MRI these are gadolinium and SPIOs

- **Most SPIONS have been abandoned or production has been discontinued (Feridex IV, 2008; ResoVist, 2009; Sinerem, 2007; P905, 2012)-** *T_2-artefact*
- **Gadolinium-chelates are associated to renal complications and accumulate in the brain; (FDA restrictions in many clinical indications (e.g diabetes)-***T_1 positive contrast*

Pragmatic and effective approach

- **Incorporate MRI contrast agents into or onto Non-conductive devices**
- **This prevents release of contrast agent in blood**
- **Incorporated contrast agent used to create markers**
- **Markers make device visible and enable navigation**
- **No regulatory issues of contrast**



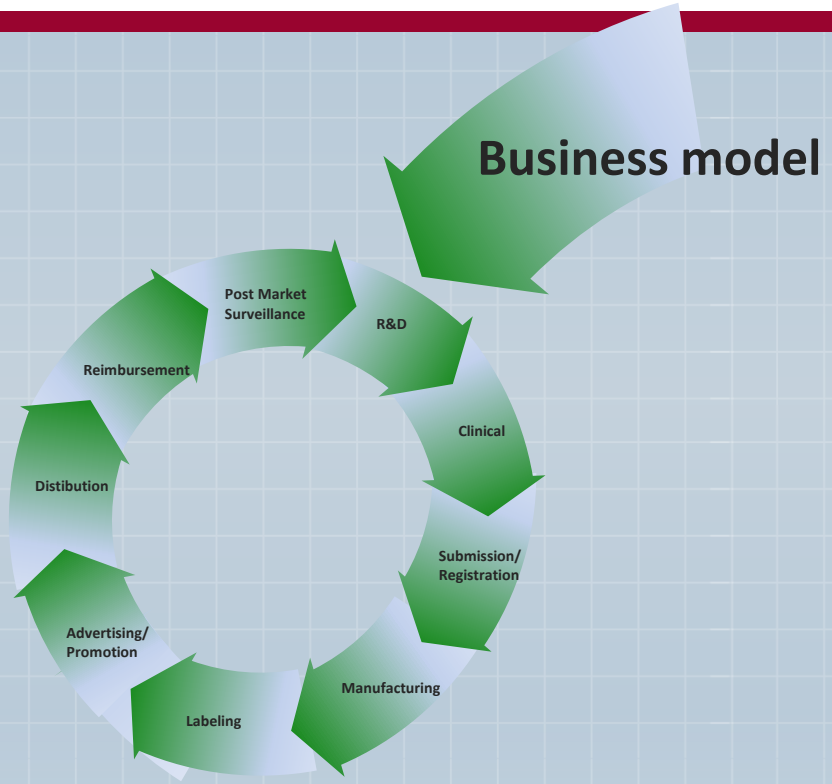
Markers (SPIONS) distort the magnetic field in MR (T2) and cause blackspots (artefacts)

Artefacts can be used to visualize and navigate instrument

Size of markers can be varied by concentration and width of line

European Patent 09705-788.9

Business model and product

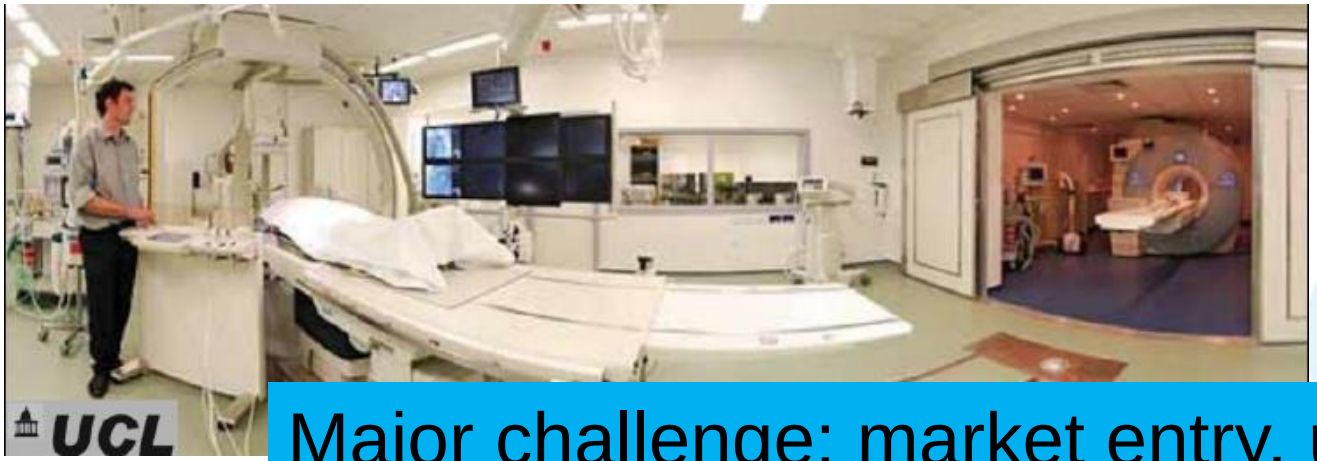


Product and business model

Expert in imaging

Nanoparticle customization

1. **B2B: coating to apply to other instruments for large instrument manufacturers. Low margin, dependency.**
2. **Own medical device (Class III)**
3. **OEM supplier: instrumental kits and accessories.**



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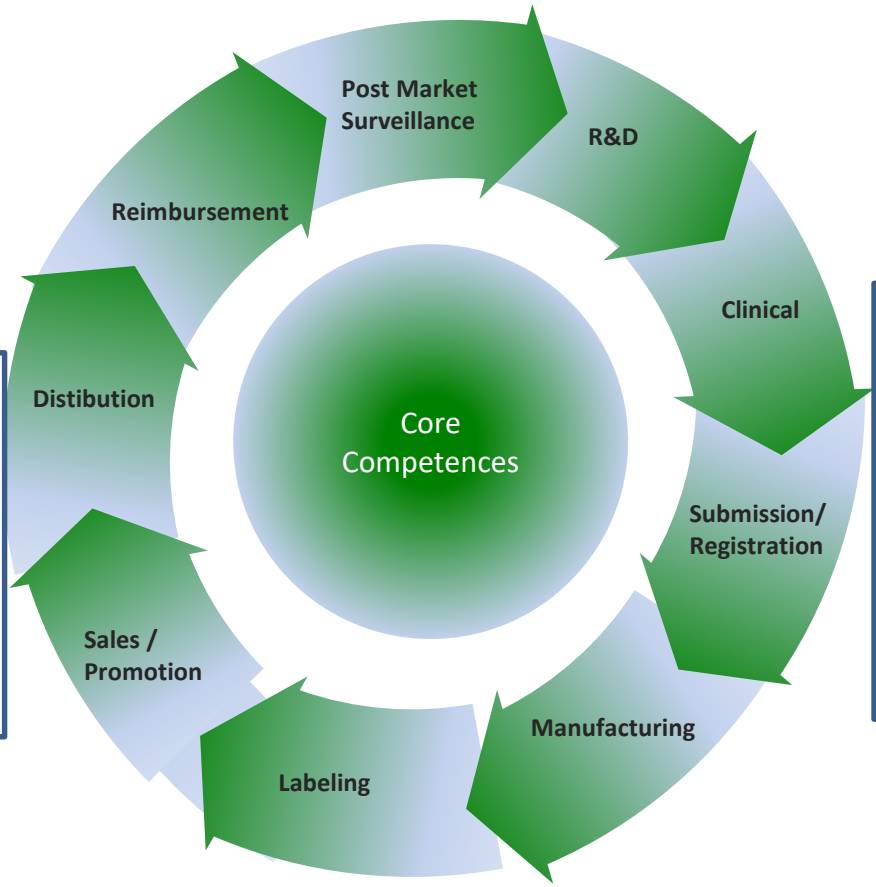
Major challenge: market entry, user and costs

Competence „Life Cycle“

- Controller
- Clinical Affairs Specialist

- **Distribution partners**
- **Sales support**



- Scientist
- Product Manager
- Product Developer

- **Regulatory Affairs hosting/QC and QA**
- **Operations Management**

Why outsourcing? Initial investment, tim to market, regulatory hosting (FDA)

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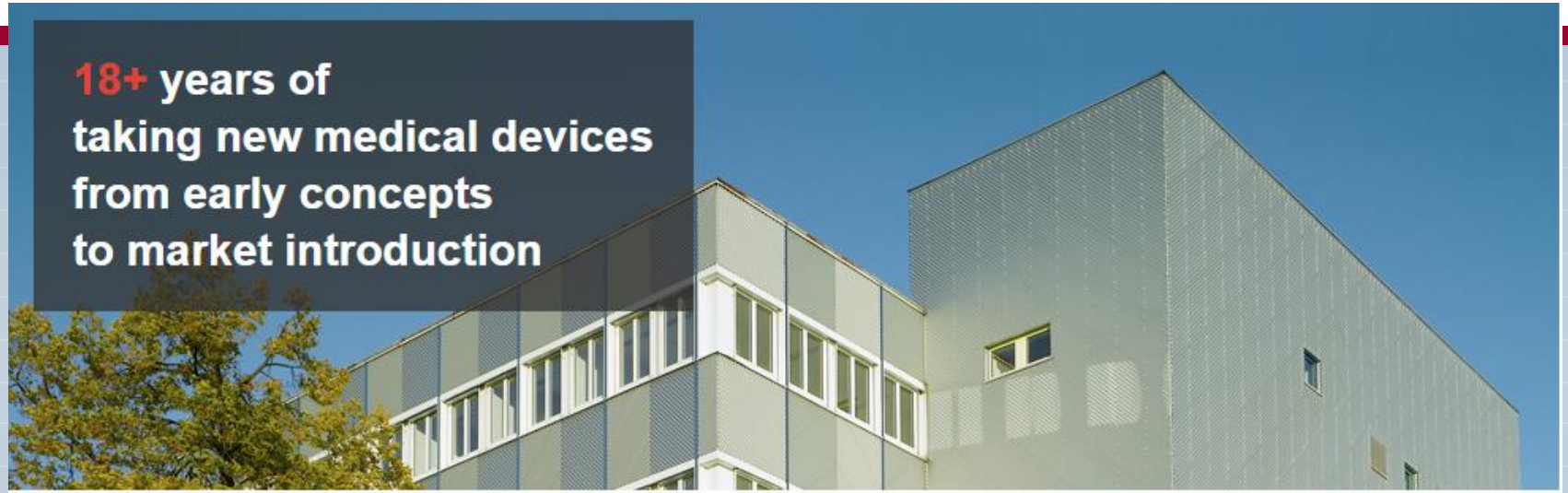
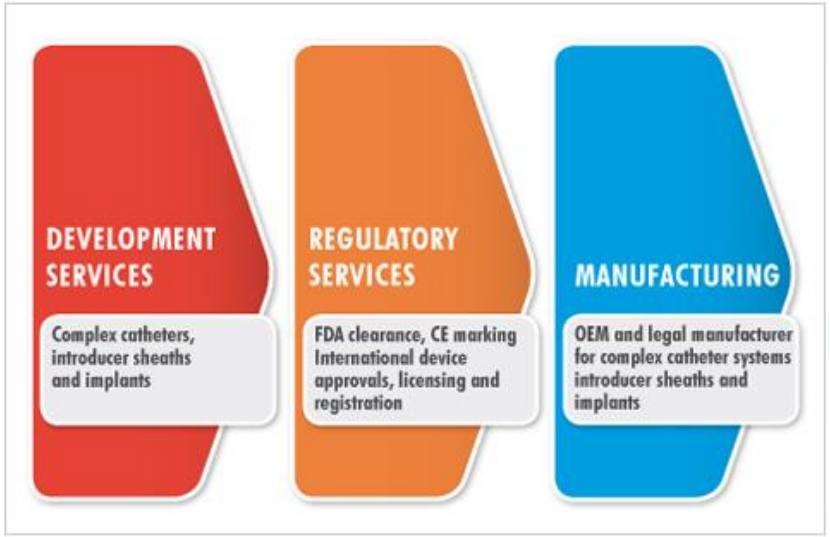


Comprehensive Services

We provide product development, regulatory and contract manufacturing services for minimally invasive medical devices for cardiology, cardiovascular, endoscopy, neurosurgery, gastrointestinal, respiratory, and other applications for a broad range of customers worldwide. We offer broad engineering experience, expert regulatory know-how, state of the art infrastructure, and a mature FDA inspected ISO 13485 certified quality management system to support market introduction of new medical devices in Europe, the United States and elsewhere.



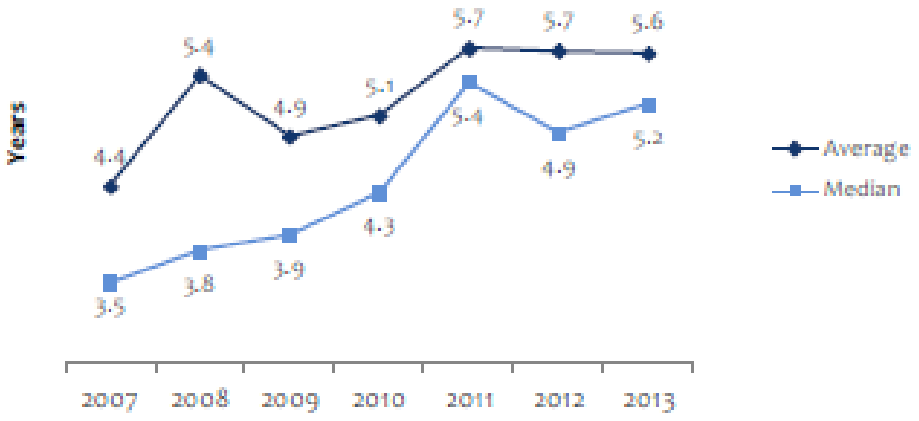
Perspectives

Exhibit 2

Time to First 510(k) Clearance*

(excl. outliers of <1 year and >16 years)

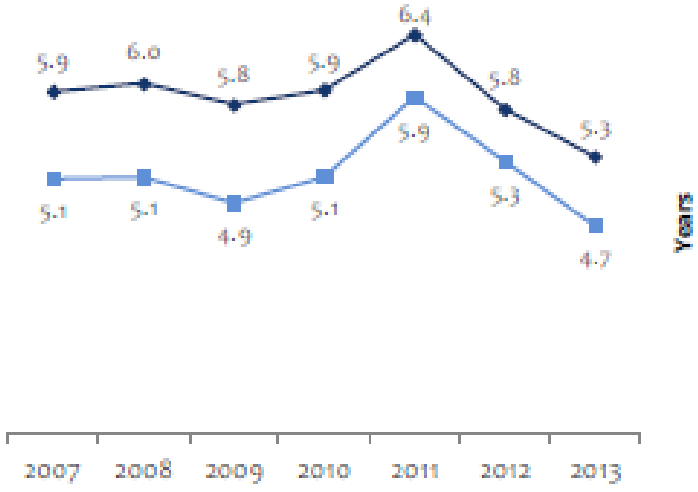
N=491, of which are 92% are Class II devices



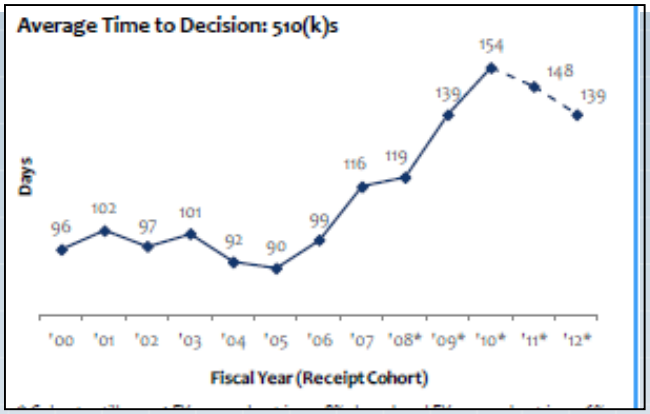
Time to First CE Mark* for '510(k)' Companies

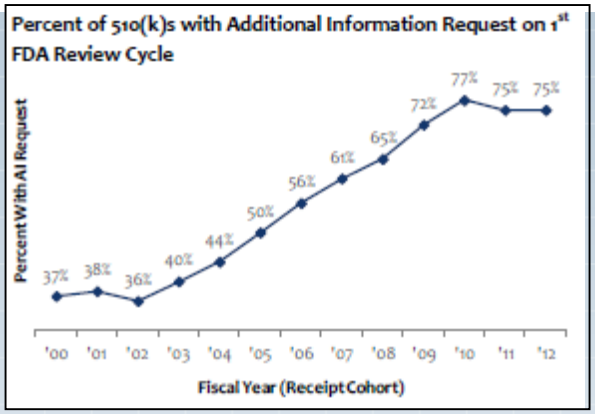
(excl. outliers of <1 year and >16 years)

N=288



Hirsch, 2013

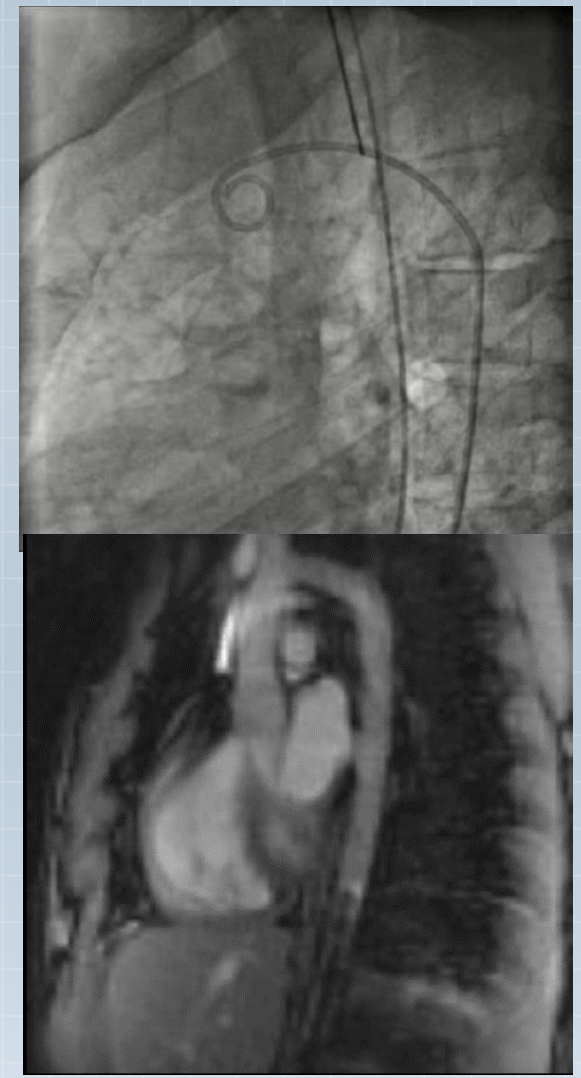




Safety intravascular procedures

- Damage to vessel wall
- Vessel wall rupture
- Tip detachment
- Device lost, stuck or broken
- Hemolysis
- Complications by contrast

Visibility and tactile response are major issues



Safety and toxicological issues

- Class III product!
- Primary concern: no damage to vessels,heart
- Secondary concern: Safe in MRI (heating)
- Quality control
- PMCF (annual)
- Clinical evaluation

FDA-510/CE- MDR

- Safe-by design!
- **Avoid internal exposure to NP**
- Compare worst case exposure to existing use (Contrast agent)
- Be transparent on use
- Follow test guidelines

ISO 10993 (1-11)

Arguments using nanoparticles incorporated in medical device: PRO

- No contrast agent in blood
- Markers make device visible and enable navigation of product in method visualizing vessel wall and organ
- No regulatory issues of iv contrast
- No risk for side effects (kidney, brain) of conventional MRI contrast agents (Gd)

Nanoparticles enable the use of MRI for interventions: PRO

SAFETY PATIENT & STAFF

- No exposure to radiation for patient and staff!
- Soft tissue visibility (vessel wall, heart, liver, brain)
- No or less iv contrast.

CLINICAL PROCEDURE

- Diagnostic power of MRI during intervention
- One-stop shop procedures

Arguments using nanoparticles in medical device: CON

?

- Particles may get into bloodstream upon rupture of guidewire or sleeve (bigger problem is the ruptured wire)
- In normal conditions no human exposure to NP

RIVM report 265001002 / 2005

Nanotechnology in medical applications: Possible risks for human health

W.H. de Jong, B. Roszek, R.E. Geertsma

Sponsor: Department of Pharmaceutical Affairs and Medical Technology, Ministry of Health, Welfare and Sports, The Netherlands

Downloadable from www.rivm.nl

rivm

Nanotechnology-based devices on the market

- Surgical tools
- Contrast agents for molecular imaging
- Bone replacement materials
- Pacemakers and hearing aids using spintronics (nano-electronics)
- DNA/protein microarrays and lab-on-a-chip for in vitro molecular diagnostics
- Wound dressings incorporating nanocrystalline silver particles

Meanwhile (15 years):

- Many EU framework programmes and strategies completed
- Few medical products on the market (clinical)
- Even less testing guidelines (OECD)

Current biocomp testing
ISO 10993 (1-11)- max 24 hrs use

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Testing medical device
Is driven by category,
Tissue contact and time

Tested materials:
- Extracts
- Leachates
- Full device (clotting)

Tests:
- Outdated
- Inadequate
- Irrelevant
- Animal numbers

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
Category (nature of body contact, see 5.2)	Contact	contact duration (see 5.3): A – limited (≤ 24 h); B – prolonged (> 24 h to 30 d); C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

Our biocomp testing

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ISO 10993- tests (FDA/CE) on device

Potential relevant effects of NP:

- ✓ Dose: worst-case product driven
- ✓ hemolysis (checked)
- ✓ complement activation (checked)
- ✓ Blood coagulation activation
- ✓ Kidney and liver clearance (contrast agent comparison)
- ✓ Accumulation in spleen (literature)
- ✓ Organ translocation (literature)

- ✓ Any suggestions?