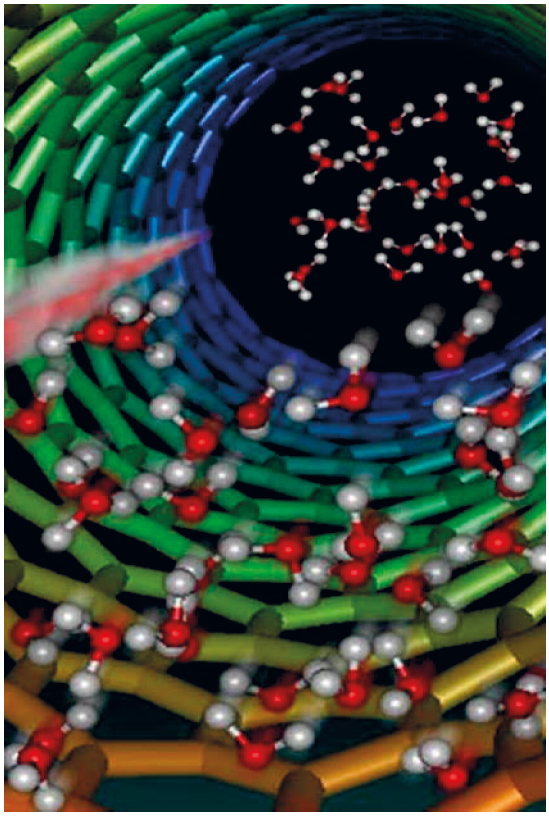
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport



RIVM-KIR-Nano National Platform Nanomedicine Report on the 5th Annual Meeting

Date: 27 November 2015
Place: RIVM, Bilthoven, The Netherlands

Introduction

RIVM - KIR-Nano (Risks of Nanotechnology Knowledge and Information Centre) organised the fifth meeting of the Dutch National Platform Nanomedicine on 27 November 2015. The Platform was organised at the request of the Dutch Interdepartmental Working Group on Risks of Nanotechnologies.

Main purpose of the Platform

The main purpose of the RIVM – KIR-Nano National Platform Nanomedicine is to exchange knowledge and vision related to scientific developments (benefit and risk), ethical-legal-social and regulatory-governance aspects between all relevant stakeholders in the Netherlands. The scope of the Platform covers all medical applications of nanotechnologies, including medicinal products, medical devices and combination products.

Participants

See separate enclosure for a list of the participants.

Opening

The participants were welcomed by Robert Geertsma (project leader RIVM – KIR-Nano National Platform Nanomedicine). He expressed his enthusiasm on the diversity of backgrounds of the group of stakeholders that was present. Furthermore, he explained that the meeting was held in English, because more and more people from abroad are working in the Netherlands and some of them have recently joined the Platform. In principle, the National Platform is intended for all Dutch stakeholders - also when they are living/working abroad - and for stakeholders from abroad, who are living/working in the Netherlands.

Review of workshop 28 November 2014 and Network EU National Platform Nanomedicine

Robert Geertsma briefly looked back at the 2014 meeting, where lively discussion and debate took place on topics including a review of the conference "NanoCity 2014", organized by the national nanotechnology programme NanoNextNL, a session on interaction of nanomedicinal products with the immune system, a session on regulation, standards and governance of nanomedical products and a "Tour de Table" with various small presentations.

NanoNextNL and beyond

Gerdine Stout (Technology STW, Program Officer NanoNextNL) briefly looked back at the conference "NanoCity 2015", as organized by NanoNextNL after the 2014 edition had proven a successful concept. Also in 2015, the participants enjoyed high quality science in a attractive and vibrant atmosphere. NanoCity 2016 was announced for 21 June 2016. In addition, Gerdine presented activities of NanoNextNL to prepare for the situation after the current programme stops in 2016, i.e. "beyond NanoNextNL". Five topics/themes had been selected that address a scientific and societal challenge, where nano/microtechnologies are crucial to make a difference, and where the Dutch community can make such a difference.

Two of these themes are directly linked to nanomedicine: Organs-on-chips, promoted by ambassadors Albert van den Berg and Vinod Subramaniam; and Synthetic Biology, promoted by ambassadors Menno Prins and Jan van Hest. Organs-on-chips have potential innovative applications in personalized medicine, drug testing for efficacy and safety and reduction of animal experiments. With the help of synthetic biology, new molecular systems can be developed that can adapt to biological systems and that will help us to stay healthy.

Session 1 – Nanotechnologies in medical devices

Robert Geertsma (RIVM) presented the results of a horizon scan of RIVM on the use of nanomaterials in medical devices. (NOTE: now available as RIVM report at: http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2015/december/Nanotechnologies_in_medical_devices).
A wide range of very diverse products and technologies was identified for the use of nanomaterials/nanotechnology in medical devices. Nanotechnology in medical devices is a growing area and there is a steady increase in patents, clinical trials and products on the market. The highest number of medcial devices using nanotechnology can be fiound in dentistry, but it is anticipated that most if not all medical disciplines will benefit from nanotechnological developments. In addition to dentistry, other disciplines already benefiting from nanotechnology products are: cardiology, interventional radiology, oncology, orthopedics, and surgery. Also in the electronic area medical devices will benefit in view of the decrease in size for electronics (e.g. batteries). One of the benefits for medical devices is to increase the biocompatibility (e.g. better tissue integration) of implants that can be obtained by using nanocoatings on the devices. In addition, also coatings with antibacterial properties are already marketed. For example, the antibacterial activity of nanosilver is used in wound dressings and various medical textiles. Products already on the market are: bone replacement materials, implant surface coatings, cartilage scaffolds, metal implants, textiles with antimicrobial activity and wound care products. In general, changes in healthcare can be expected with regard to disease diagnosis and therapy, novel tools for disease prevention, local point of care testing including fast screening of health status, and a more dedicated individual medical treatment (personalised medicine).

Wim de Jong (SCENIHR, ISO,RIVM) presented the SCENIHR Guidance on the determination of potential health effects of nanomaterials used in medical devices that was published early 2015 (available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_045.pdf).
The SCENIHR Guidance addresses various aspects on the safety evaluation of medical devices containing or using nanotechnology. The basic principles of ISO 10993-1 Biological Evaluation of Medical Devices. Part 1. Evaluation and testing within a risk management process are applicable. This means that for the risk assessment the basic principles of type of device, type of contact and duration of contact are driving the assays that need to be considered for the safety evaluation. However, also the complexity of the nanomaterials should be considered as a multitude of variations exists (e.g. size, shape, surface characteristics, dissolution and many more). Specific attention is given to the characterization of the nanomaterials when they are applied in medical devices. This is especially important also for the identification of the nanomaterials. In addition the

guidance discusses possible pitfalls in the toxicity testing of nanomaterials. The Guidance highlights the need for special considerations in relation to the safety evaluation of nanomaterials, in view of the possible distinct properties, interactions, and/or effects that may differ from conventional forms of the same materials. The highest risk was concluded to be associated with the presence and/or release of free nanoparticles from a medical device in view of possibilities for migration of the nanoparticles in the body. A risk assessment approach is presented following the classical risk assessment paradigm of exposure assessment, hazard identification, hazard characterization, and risk characterization.

Session 2 – Safe Innovation Approach for nanomedicinal products

Hedwig Braakhuis (RIVM) presented the Safe Innovation Approach (SIA), developed by RIVM colleagues in several projects (NanoReg, NanoNextNL, iSCAN-risk) and in interaction with stakeholders. The aim of SIA is to go beyond the traditional situation of safety testing by applying regulatory requirements when products are already close to the market. Product development can be informed about safety aspects much earlier, while regulatory risk assessment can be timely adapted in response to novel functions and materials and related uncertainties. The first is about 'Safe-by-Design' (SbD), the second about 'Regulatory Preparedness' (RP). SIA links both objectives in a stepwise manner, conceptualized in the stage-gate model: for each stage in product development different questions have to be addressed, each requiring particular modes of interaction between product development and risk assessment. For nanomaterials this has been operationalized in a screening strategy, a testing strategy and tools for testing. The screening strategy consists of six risk potentials (solubility, stability (of coating), accumulation, genotoxicity, immunotoxicity, ecotoxicity), which can be checked in a decision tree. So far, SIA has been developed as a generic model for nanomaterials. For specific application areas, like nanomedicine, SIA could be tailored, for example by incorporating clinical trial procedures, defining the gate-keepers between stages and information protection.

Bart Metselaar (Enceladus) reported from his experiences in interacting with regulatory authorities on scientific and regulatory advice for the liposomal corticosteroid products of Enceladus. Bart discussed four moments of interaction: in 2009 with the EMA innovation task force (ITF) about general advice on the liposomal delivery platform (discussion with large group of experts); in 2013 with the FDA: a pre-IND procedure (written correspondence); in 2014 with a EMA scientific advice working party (discussion with smaller group of experts) and in 2015 with the German BfArM (written feedback on testing protocol). The interaction with the EMA-ITF was rather formal, with half of the questions referred to Scientific Advice (SA). The written correspondence in the FDA pre-IND procedure also had its drawbacks (e.g. not possible to respond to remarks about appropriate model), but the FDA provided very clear guidance on clinical development and market application strategy, including much attention for quality issues. The EMA SA also provided clear guidance on clinical development strategy, less on quality and toxicology. The interaction with a smaller group of experts was successful, although this appeared to be quite depending on the composition of the expert group. The advantage of interacting with the German BfArM is that the competent authority is also the registration

authority and BfArM delivers scrutiny in quality checking and clinical development strategy. Nonclinical data received less attention. Overall, the interaction with these authorities has been helpful, but a lot of work and with complementary strengths and weaknesses of the different authorities. Bart's impression is that it is useful to contact authorities in an early stage when the aim is to inform them. For specific guidance in the early stages, having experienced business consultants might be more helpful. At somewhat later stages, interaction with the authorities becomes more important for the manufacturer.

In the discussion, the often formal (and hence less cooperative) attitude of authorities was attributed to the limitations to discuss proprietary information. Another reason to contact authorities is to check which animal tests are necessary. Guidance of the authorities is less on safety aspects at non-clinical level, because interaction is mostly related to the clinical trial phase. At this moment there is no specific nano-related safety testing. Here, SIA could be of help for incorporating a screening strategy (although tailored for nanomedicine; e.g. how to go about risk potentials for the combination of drug and carrier and test guidance (e.g. on reproducibility, stability, changes in design after toxicology testing etc.).

Tour de table: hot topics, news, discussion items by all participants

During the tour de table, six topics were presented.

- *International cooperation opportunities – NMP-DeLA roadmap nano - follow up (Ineke Malsch, Malsch Technovaluation)*

a. NMP-DeLA roadmap nano ended. Fact sheets were made. Translation. European key priorities but also tropical diseases. Scattered nanomedicines. A single platform for nanomedicines in South America. Nanodrug delivery platforms. UN sustainable development. See also http://www.nmpdela.eu/
b. Nano2all dialogue started October 1, 2015.

- *Nanosimilars (Rob VandeBriel, RIVM)*

Driven by the ongoing discussion on how "similarity" of generic forms of nanomedicines (nanosimilars) could/should be demonstrated, RIVM and the Dutch Medicines Evaluation Board had a joint meeting on this topic (March 2015). For liposomes, iron oxide and surface coatings EMA has formulated ideas on the data required to register nanosimilars in reflection papers (RP). It was questioned whether a set of general requirements should be drawn up for nanosimilars. Ten nanomedicines were identified for which additional guidance might become useful in the near future. They comprise 5 nano dispersions, 2 protein NP and 3 different polymer conjugates. Their differences suggest that general requirements are not be suitable. Still, for each category a RP may be useful.

- *Lipophilic prodrugs (to improve uptake and bypass activation) (Frits Peters,VU)*
  - new modulation strategies of anticancer drugs
  - chemical compound => prodrug => targeted therapy
  - pharmaceutically inactive => metabolized to active
  - improved ADME, bioactivity and selectivity
  - gut epithelium, cell membrane, and blood-brain barrier

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- bypass transporter, kinase, efflux pump

The ProTide approach increases cell accumulation of gemcitabine. A second example of the ProTide approach is FUDR.
Elacytarabine (CP-4055): intracellular activation, carrier independent, retained in intracellular compartment, prolonged release, retained longer, differential effect on signalling.

- *Nano drug delivery in reversing MDR in cancer cells (Mayur Yergeri, VU)*

Mayur presented an overview of nanodrug delivery systems.

- *Future Projects in development of point of care tests (Arend Kolk, UvA)*

Research on biomarkers for *M. tuberculosis*: lipids, proteins

- *Companies distributing nanoparticles in dry form as standard reference materials worldwide …is it somehow regulated? (Ingrid van Nugteren)*

She mentioned three activities:1. low-angle scattering; 2. Powders and 3.Saxion.
Powder: "ARBO" awareness - bringing guidance to the people.

- *Nanomedicinal products in pharmaceutical and clinical practice (Susanne Tesink, KNMP)*

Elderly people often have difficulties swallowing. Therefore, the formulation in which drugs are taken is modified at home: they are crushed before being swallowed. This may, however, affect their efficacy or may even be dangerous. This reduced efficacy holds for instance for drugs with regulated release (delayed, deferred, targeted), such as nanomedicinal products. Next, if they are given intravenously their safety is not always known.

- *Biocompatibility requirements (Cornelis Kluft)*

See http://gbsleiden.com. Tests for many compounds, drugs.
Testing order:

1. fluid, plasma (protein binding)

⇓ activation

2. blood cells (TLR, inflammation, platelets)

⇓ invasion

3. tissue cells (consequences, clotting, inflammation, tissue growth)

Selecting optimal tests:

clotting	-coagulation
activation	-kallikrein, complement, platelets, white cells

Factor XII	→ Factor XI	-clotting
	→prekallikrein	-inflammation

- *European Technology Platform Nanomedicine update (Robert Geertsma)*

Last October, Robert went to the European Technology Platform Nanomedicine (ETPN) meeting, where a number of interesting initiatives were discussed.
The European Nanomedicine Characterization Laboratory (EU-NCL) is a part of the "Translational Hub", set up by ETPN with the help of H2020 funding. Manufacturers can submit candidate nanomedicinal products for testing by EU-NCL. The first call to submit candidate products was expected soon.
The main objective of ENATRANS (Enabling Nanomedicine Translation) is to network and support SMEs in translation of nanomedicine in Europe by giving access to advice from experienced business people.
A strategic Research & Innovation agenda exists for unmet clinical needs in strategic technical and applied areas. ESTHER is a new initiative that is under development: Emerging Strategic Technologies for HEalth caRe.

- *International Pharmaceutical Regulators Forum (IPRF) – Nanomedicines Working Group (Robert Geertsma)*

Robert has become member of this working group. See https://www.i-p-r-f.org/en for more information.

Conclusion

During the meeting, presentations provided interesting updates on various nanomedicine topics, followed by lively discussions between participants at the meeting. A record number of contributions was presented during the Tour de Table. This is exactly what the Platform is meant for: sharing updates on nanomedicine activities with the possibility for interaction providing different perspectives from the various stakeholders.

Closing

Robert Geertsma thanked the participants for their contributions and invited everyone to continue networking enjoying informal drinks.