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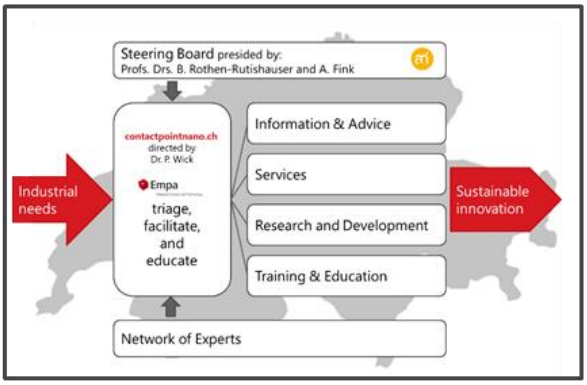

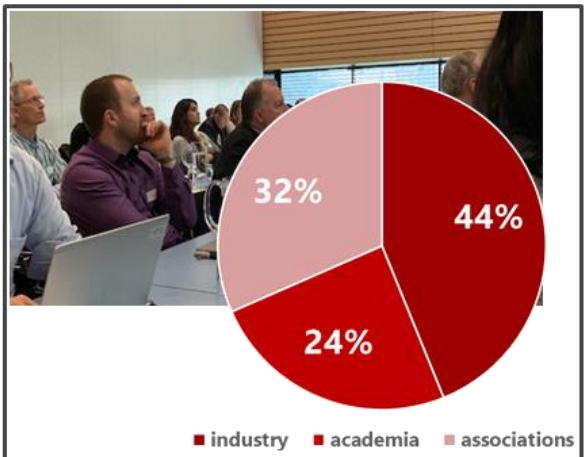

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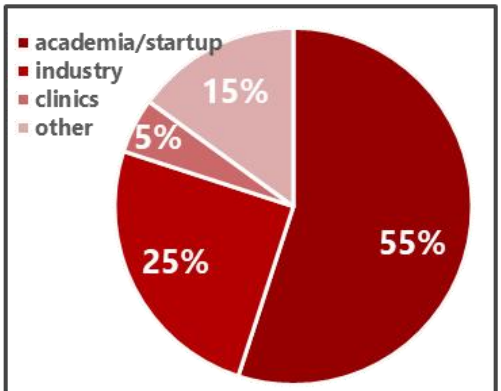

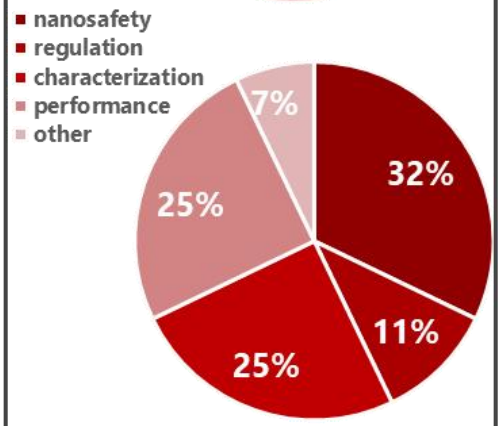

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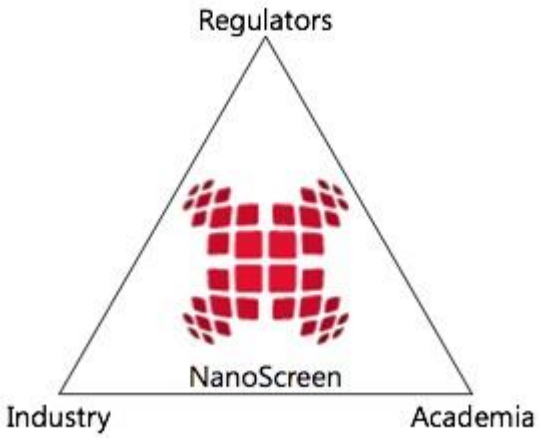
NanoScreen- CCMX Materials Challenge



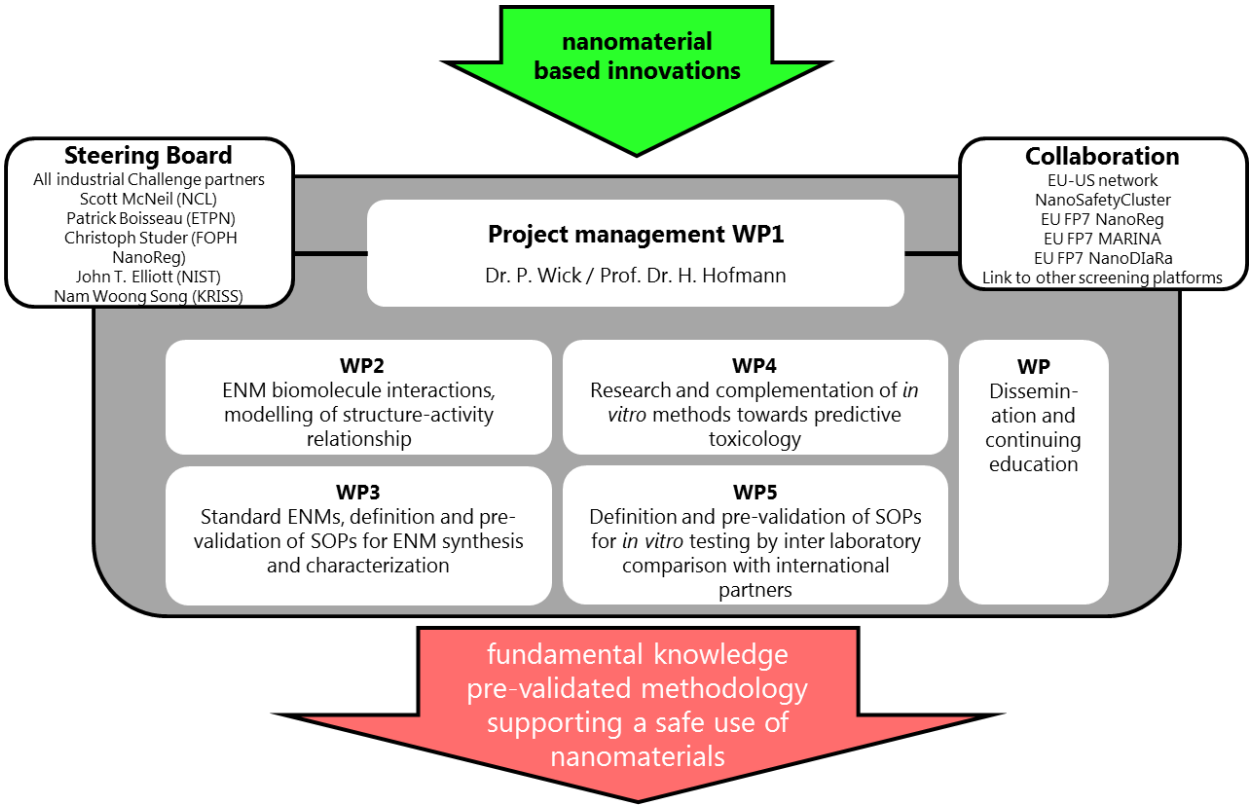
Engineered nanomaterials (ENMs) are a class of nanoscale substances that are purpose-designed with very specific and novel properties. All new technologies are hampered by insecurity concerning their safe implementation. Therefore, industries and regulatory bodies are very dependent on the fundamental understanding of 'nano-bio interactions' and the development of reliable and cost-efficient testing strategies to avoid social - as well as economic drawbacks.

There is a general lack of

1. understanding how ENM properties influence the adsorption of biomolecules and their effect on cellular reactions,
2. standardized methods assessing material characteristics as well as biological reactions.

Consequently, a comprehensive assessment of potential side effects of ENMs cannot be made.

On October 1st 2014 the CCMX Materials Challene "NanoScreen" (www.ccmx.ch) was launched. This project is headed by Dr. P. Wick (Empa) and Prof Dr. H. Hofmann (EPFL) and brings together partners form Industry Cetics Healthcare Technologies, Midatech and the Swiss Federal Office of Public Health.



Scope: This Material Challenge brings together expert knowledge in ENM design, production, characterization, *in vitro* testing and measurement science. This unique combination of expertise allows correlation of the physical and chemical properties of solid inorganic ENMs with their potential side effects towards predictive power. Furthermore, NanoScreen is directly linked with attempts and institutions in the USA (e.g. NIST and Nanotechnology Characterization Lab) Asia e.g. Korean Research Institute of Standards and Science (KRISS) as well as in Europe (European Technology Platform Nanomedicine); all working along the same lines. NanoScreen creates a unique connection point for the Swiss industry, Regulatory bodies and researcher strengthening the collaborative activity in this interdisciplinary field. Moreover, it will increase public confidence in nanotechnology which is an important pre-condition for commercial success. NanoScreen will allow considerable harmonization of the methodology and thus reduce costs notably as well as cut down the time to bring novel high technology products from the Swiss industry on the market.

GoNanoBioMat

The aging population represents an enormous financial burden for society, unless ways can be found to maintain independence and quality-of-life (QoL) as long as possible for each individual. To achieve this, novel concepts and technologies for new solutions and products are needed. For example, the use of polymeric nanobiomaterials in medicine might be a solution for answering to this need.

Currently, the number of health applications on the market remains small due to the unclear situation of the future regulatory assessment of efficacy and safety. In this context, the Go-BioNanoMat project aims to enable SMEs (small and medium size enterprises) and their suppliers, and Research Institutes to work on the development and production of polymeric nanobiomaterials for drug delivery implementing Safer-by-Design (SbD) approach. The major expected outcomes of this project are:

1. A verified knowledge base (built on peer-reviewed scientific publications on polymeric nanobiomaterials, their environmental and human health risks and the regulatory aspects.),
2. and guidelines to implement SbD approach for polymeric nanobiomaterial drug delivery systems
3. as well as in depth investigation of three selected materials like Chitosan, Polylactic (PLA) acid and Polyhydroxyalkanoates (PHA) regarding drug delivery applications.

The GoNanoBioMat consortium combines expertise in the area of nanobiomaterial science and technology, life science, pharmaceutical science, as well as nanosafety and life cycle thinking. A strong regulatory background and knowledge base building, dissemination and training belong as well to the core competences of this consortium.

ProSafe - Tom van Teunenbroek

Infrastructure and water management, Directorate General Environment International

The uncertainty regarding the effects and risks of nanomaterials on human health and the environment, and how they should be tested and assessed in the context of current regulations, is clearly holding back the full exploitation of the innovative potential of nanomaterials. To reduce this uncertainty, the European Union funded NANoREG and ProSafe projects (jointly referred to as N1P) have made a critical evaluation of methods to test and assess

these risks in the context of the current registration, evaluation, authorisation and restriction of chemicals (REACH) regulation. Where essential methods were lacking, new ones have been developed. For several existing methods, adjustments have been proposed. Possible improvements to the REACH regulation have also been identified in these projects. The results of N1P have been translated into recommendations for (European) policy makers and regulators. Part of them have a "no regret" character, meaning that the proposed actions can be considered as necessary, feasible, effective and cost efficient. The recommended measures proposed for data quality and data management will create a more solid information basis for risk assessment of nanomaterials. When implemented, the recommendations regarding REACH will improve the application of REACH in both a legal and scientific sense. In practical terms however, the application of REACH will remain complex, time-consuming and costly. Besides that, adapting and specifying the information requirements and test methods in REACH for nanomaterials that are now on the market, will not solve the regulatory hurdles for next generation (nano) materials. To better align the dynamic character of developing new materials and the static character of regulations, it is recommended to explore possibilities of a more future proof approach for securing the safety of new (nano) materials.

NANoREG OBJECTIVES:

To deliver the answers needed by regulators and legislators on environmental health and safety by linking them to scientific evaluation of data and test methods.

Based on questions and requirements supplied by regulators and legislators, the project will:

• Provide answers and solutions from existing data, complemented with new knowledge • Provide a toolbox of relevant instruments for risk assessment, characterisation, toxicity testing and exposure measurements of manufactured nanomaterials (MNMs) • Develop, for the long term, new testing strategies adapted to innovation requirements • Establish close collaboration among authorities, industry and science leading to efficient and practically applicable risk management approaches for MNMs and products containing MNMs

KEY COLLABORATORS

For a full list of project partners, please visit:

http://nanoreg.eu/index.php/project/ project-partners

FUNDING: EU Seventh Framework Programme (FP7) (20%) + National contributions (80%)

Reliable nano-safety. What we know, what we should learn – an overview from a distance – Peter Gehr

Em.Prof. University of Bern

Without any doubt, the topics of nano-science and the associated fields of nano-medicine, nano-biology and nano-toxicology, as well as nano-techniques, are growing rapidly. In all these fields, the interaction of nanoparticles with biological systems has become a rapidly growing dynamic field of research. Understanding these interactions will help understand the risk and the impact of nanomaterials on health. Nanoparticles, when interacting with biological systems, may have unexpected biological effects and they may create adverse effects.

We understand quite well how nanoparticles can enter our organism through the lung; however, we poorly understand how nanoparticles, coming from the lung, enter secondary organs to which they are transported via blood circulation. The interaction with tissue and cells in these organs may influence vital processes or cause serious health problems.

What do we know, what should we learn, what should we be concerned about? Consider this an overview from a distance.

Particles Synthesis and characterization in alignment with NANoREG 1+2 - Heinrich Hofmann

EPFL Institute of Materials

The characterization of nanoparticles is still a scientific and technical challenge. Not only is particle sizing under discussion, but other important physical and chemical properties are not as easy to determine as with molecules or macroscopic materials. For thermodynamic reasons, typical properties such as density, solubility, distribution coefficient in different solvents etc. are not or only insufficiently defined for nanoparticles. One reason for this is that the particles are not in thermodynamic equilibrium and change over time, and therefore the existing standards are not applicable. In this lecture, the standards worked on in Nanoreg

for the determination of physico-chemical properties of nanoparticles are critically examined and new or modified SOP's are presented.

Determining what really counts: Modeling and measuring nanoparticle number concentrations - Matthias Roesslein,

Empa, Particles-Biology Interaction Laboratory

Particle number concentration (PNC) measurements are critical for research and regulatory decision making related to the potential applications and implications of nanotechnology. However, the degree to which different analytical methods yield similar PNCs has not yet been studied. In this presentation a study of monodisperse gold nanoparticles (AuNPs) with varying sizes and surface coatings, which were evaluated using five techniques: scanning electron microscopy (SEM), dynamic light scattering (DLS), differential mobility analysis (DMA), nanoparticle tracking analysis (NTA), and single particle inductively coupled plasma-mass spectrometry (spICP-MS), will be presented. The two techniques that only measured the NP core size (spICP-MS and SEM), as opposed to the larger hydrodynamic diameter, yielded PNCs with the closest agreement (within 20 % of each other), while PNCs among all techniques sometimes varied by a factor of 3.

Deriving the PNC using the full size distribution has several advantages over using only the mean size based on these results and statistical modeling given the substantial impact of the tails of the distribution toward smaller particles. The size distributions measured by the different techniques were also used to model the AuNP concentration that would reach the cells in an in vitro toxicity experiment. Surprisingly, there was a strong impact of the analytical technique on the modeled cellular AuNP concentration for some of the AuNPs.

Understanding nanosafety – the importance of assay performance *in vitro* - Cordula Hirsch

Empa, Particles-Biology Interaction Laboratory

Compared to the numerous nanotechnological inventions made during the last decades only a small number of nano-enabled products finally made their way to the market. There are several reasons why these innovative approaches got stuck in translation; one key factor being uncertainties in the safety assessment of these new materials. Numerous examples exist where nanomaterials have deceived scientists by generating false positive or false negative results in in vitro studies. The following parameters are important to prevent such false results and assure reliable in vitro safety assessment. (1) Material characterization. (2) Interference reactions with the different assay components. (3) Dosimetry. (4) Benchmarking and general assay performance. These issues add additional complexity to the well-known challenges of in vitro – in vivo comparability and finally animal-to-human predictability.

On the other hand, especially during early developmental stages of new, smart (nano)materials the safety of a multitude of technically suitable candidates has to be assessed. Potential adverse biological effects need to be "designed out" to select for the most promising material; not only in terms of technical efficacy but also in terms of safety. Therefore, fast in vitro tools/methods are needed. However, there is more to it than speed. Reliable, robust and reproducible (the alternative 3Rs) results are key to success.
My presentation will focus on research highlights gathered during five years of NanoScreen and tackling exactly the nano-related in vitro challenges detailed above. I will present illustrative examples of how we get to know our "simple" in vitro systems and why this is so important. How we elucidate sources of variability and which challenges we faced when trying to correlate material properties and biological effects.

Future of nano safety assessment on an advanced in vitro intestinal mode – Claudia Hempt

Empa, Particles-Biology Interaction Laboratory

Nanotechnology provides many benefits to the food industry due to their versatile properties. Engineered nanomaterials (ENM) deliver for example new tastes, antimicrobial properties or improve the nutritional value of food (novel food). However, the impact of ENMs on the gut epithelium and their translocation through the intestinal barrier is still poorly investigated and understood. Mechanistic insights required for the safe design and use of ENMs in food applications can be obtained from advanced human in vitro models of the intestinal barrier that contain mucus and different cell types of the intestine (e.g. enterocytes, goblet cells and M cells). The mucus layer as a physical barrier is particularly important to achieve predictive results, however, it interferes with many conventional assays.

Here, we aimed to establish an in vitro platform comprised of an advanced human in vitro intestinal co-culture model and a set of mucus-compatible assays for the toxicity assessment of food-relevant nanomaterials. We successfully implemented co-cultures of enterocytes (Caco-2), goblet cells (HT-29-MTX) and M cells (differentiated from Caco-2 cells in presence of Raji B-lymphocytes) with a continuous mucus layer. Different cell seeding numbers were exploited to achieve an in vivo relevant continuous mucus layer and the formation of a tight barrier. Moreover we have identified assays that are suitable to investigate ENM impact on cell viability, production of reactive oxygen species, cytokine release, mucus coverage, barrier integrity, microvilli function and relevant physiological endpoints (e.g. iron, glucose or lipid transport) in the mucus-containing intestinal co-cultures.

In future studies, we will use this platform to investigate the interaction of nanostructured food grade synthetic amorphous silica (SAS, E551) with the mucosal lining and distinct cell types of the intestinal barrier. A panel of four different SAS products, which differ in size, surface area and production route will be assessed to identify potential structure-activity relationships.

Implementing a Safe-by-Design (SbD) approach for nano-based drug delivery systems - Mélanie Schmutz

Empa

Safe-by-Design (SbD) is a general approach or concept used to identify the risks and uncertainties involved in human health and environmental safety during the early stages of product development, thereby supporting efficient processes towards creating safe products, safe production methods and safe handling. The general approach of SbD within the field of nanomaterials began with the EU's NANoREG project (www. nanoreg.eu) and was propagated by its H2020 ProSafe initiative (www.h2020- prosafe.eu) and H2020's NanoReg2 project.

Within the GoNanoBioMat framework, the SbD approach focuses on addressing human health and environmental safety throughout the development phase of nanocarriers. The regulatory frameworks applied in Switzerland and the European Union are considered. The SbD approach here is an iterative, interdisciplinary process including the following aspects:

I. Safe Nanobiomaterials: designing low-hazard nanocarriers for specific applications by assessing human health and environmental risks early on in the development process

II. Safe Production: manufacturing and control of nanocarriers to ensure their safety and quality

III. Safe Storage and Transport: ensuring the safety and quality of nanocarriers

Regulation in nanomedicine - Robert Geertsma

RIVM – National Institute for Public Health and the Environment

In general, regulatory requirements as well as regulatory/scientific guidance on nanotechnologies and nanomaterials applied in medicinal products as well as medical devices are emerging. A new regulatory framework for medical devices was recently published in Europe. The new regulation contains several provisions for nanomaterials, including a definition, specific attention for safety of nanomaterials and classification rules leading to different routes for conformity assessment. For the implementation of these provisions, more

guidance is needed. Work is currently ongoing in European Commission Working Group for New & Emerging Technologies to develop guidance. The regulatory framework for medicinal products in Europe does not contain specific regulatory requirements for nanomedicinal products (NMPs). However, as in other regions around the world, it is acknowledged that guidance is needed how to apply the regulatory requirements to NMPs in order to accommodate their specific characteristics. The Nanomedicines Working Group (NWG) of the International Pharmaceutical Regulators Programme (IPRP) works on the exchange of non-confidential information on nanomedicines and nanomaterial in drug products and borderline and combination products between international regulators. This includes cooperation and coordination with regard to guidance on evaluation of such products. Also standard development organisations like ISO, CEN and ASTM are working on standards that can help implementation of emerging regulatory requirements for nanomedicinal products and medical devices. Furthermore, work done in European projects such as REFINE (Regulatory Science Framework for Nano(bio)material-based Medicinal Products and Medical Devices) will provide important contributions for this purpose.

Design of nanobiomaterials for drug delivery - what is needed? - Gerrit Borchard

University of Geneva, School of Pharmaceutical Sciences Geneva-Lausanne

Nanomedicines offer the opportunity to address disease targets in novel ways. Nanosize drug systems need to interact with biological systems such as the immune system, cell membranes and the intracellular environment. These interactions are determined mostly by parameters such as size, size distribution and surface properties such as charge (zeta potential). Understanding the way and extent to which such properties influence the PK/PD profile and toxicity of nanomedicines will lead to the design of nanobiomaterials and improved nanomedicines in terms of their efficacy and safety. Some of these aspects will be discussed.

Bacterially produced PHA: From packaging material to nano applications in medicine – Manfred Zinn

University of Applied Sciences and Arts Western Switzerland (HES-SO Valais), Institute of Life Technologies, Sion, Switzerland

Polyhydroxyalkanoates (PHAs) are natural biopolyesters that are biosynthesized by many bacteria under specific growth conditions. In the mid 1980-ies, the cosmetic company Wella commercialized shampoo bottles that were produced from a copolymeric PHA, poly(3-hydroxybutyrate-co-3- hydroxyvalerate) demonstrating its suitability for biodegradable packaging applications.

Some 20 years ago, PHAs entered the medical field because of their biodegradability excellent biocompatibility. In 2007, another type of PHA, poly(4-hydroxybutyrate) was the first PHA that was approved by FDA for suture applications. To date, PHAs are also entering the nanoscale in medical research as a drug carrier polymer of active pharmaceutical ingredients.

During the presentation, particular material properties of PHAs are introduced and also different methods of PHA nanoparticle production explained.

Use of molecular modeling as a reliable tool in material and device design - Tommaso Casalini

University of Applied Sciences and Arts of Southern Switzerland (SUPSI), Department of Innovative Technologies, Institute for Mechanical Engineering and Materials Technology

The injection of nanomaterials into an organism leads to a complex network of interactions between the surface of the device and body fluids components (protein, carbohydrates, fatty acids, et cetera), whose rationalization is still challenging. These interactions play a fundamental role in determining not only the fate of the nanomaterials but also the attainment of side effects.

Computational techniques at molecular level emerged as the natural complement to experimental activity by virtue of the accessible time and length scales, the atomistic description

of the system and its dynamic behavior and the inclusion of environmental effects. Methods like molecular dynamics simulations can provide some insights about the early events that characterize nano-bio interface, providing some insights that are challenging or impossible to obtain experimentally. This talk aims at exploring and discussing the opportunities and the limitations as well as some perspectives of molecular modeling techniques to characterize material bio-interactions.

Prediction of the pharmacological profiles and toxicological endpoints of some chito-oligomers – Adriana Isvoran

Department of Biology-Chemistry and Advanced Environmental Research Laboratories, West University of Timisoara, Romania

Chitosan is a natural polymer used in different biomedical applications, including drug delivery systems, tissue engineering and wound healing. Low-molecular degradation products of chitosan, the chito-oligomers, are resulting under the influence of enzymes. The aim of our study was to assess the pharmacological profiles and toxicological endpoints of small chito-oligomers with distinct molecular weights, deacetylation degrees, and acetylation patterns by using a computational approach. Investigated chito-oligomers reflect promising pharmacological profiles and limited toxicological effects on humans, regardless of molecular weight, deacetylation degree, and acetylation pattern.

Human health risks of polymeric nanobiomaterials: immunotox perspective – Olga Borges

Faculdade de Farmácia & Centro de Neurociências e Biologia Celular (CNC) - Universidade de Coimbra

With the exception of nanoparticles (NPs) with vaccine adjuvant role, the effect of the NPs on the immune system has been only moderately studied and reported in the scientific literature. Additionally, contradictory results have been observed among the reports published. This fact can be explained by the lack of appropriate characterization of the polymeric nanobiomaterials or the use non LPS-free polymers or by factors related with the analytical methods, like the lack of appropriate controls and particle interferences on analytical methods. The objective of this seminar is to present some case-studies that will illustrate these concerns, mainly related with the evaluation of the immunotoxicology of nanomaterials and to offer the necessary background to support the safe-by-design of drug nanocarriers, not only intended for clinical applications, but also for other applications where the risk of human exposure to NPs is a real scenario.

Environmental risks of polymeric nanobiomaterials – Marina Hauser

Empa

Nanobiomaterials (NBMs) used in medical applications are likely to find their way into the environment either after use or in case of accidents. Therefore, we aimed to evaluate the ecotoxicity and environmental risk of five polymeric NBMs (chitosan, polyacrylonitrile (PAN), poly(lactic-co-glycolic acid) (PLGA), Polyhydroxyalkanoates (PHA), and Poly(lactic acid) (PLA)) and one inorganic NBM (Hydroxylapatite (HAP)).

For an environmental risk assessment, first the predicted environmental concentration (PEC) needs to be evaluated through exposure modelling. This has been done for several engineered nanomaterials but no data are available so far for NBM.

The data availability is sufficient to perform for some NBM a hazard assessment by deriving the predicted no effect concentration (PNEC) of the material in specific environmental compartments. The investigated NBM show a very wide range of observed toxicities to environmental organisms. The most toxic NBM in freshwater is chitosan with a mean PNEC of 8 µg/l. For soil, the most sensitive NBM is HAP with a mean PNEC of 0.3 mg/kg. We can compare these values with the PNECs of other nanomaterials or common pollutants. In freshwater even the most toxic of the selected NBMs, chitosan, is less toxic than for example the engineered nanomaterials nano-ZnO or nano-Ag, common antibiotics or several heavy metals.

The risk that the NBMs may pose for a specific compartment is calculated by dividing the PEC by the PNEC value. Complete risk assessments for NBMs are not yet possible at the moment as only limited environmental hazard data and no exposure data is available.

Guidelines to implement a Safe-by-Design approach for medicinal polymeric nanobiomaterials – Claudia Som

Empa

Small and medium enterprises (SMEs) are considered important actors in driving the innovation in nanomedicine including polymeric nanobiomaterials (NBMs) for drug delivery. Even though scientific literature has shown the potential of polymeric NBMs for drug delivery to increase drug efficacy and safety, this technology has not yet achieved its maximum potential. In order to promote the development of this technology, the state of knowledge and insights of what makes the nanoscale in medicine special should be made available to SMEs.

The guidelines' goals are to (1) support informed decision-making in the field of polymeric NBMs for use in drug delivery during the early phases of innovation, (2) to improve and facilitate communication (develop a common language) between the different stakeholders contributing to the value chain and between industry and regulatory authorities, (3) to prevent misguided investments, and (4) to enable SMEs to deliver safe products in an internationally competitive market.

These guidelines do not only address SMEs developing nanocarriers, but also SMEs having some link to the topic and that may play a role in the value chain.

The guidelines are based on a knowledge base built up from peer-reviewed scientific publications and compile the current state of science, including trends, gaps and uncertainties. The knowledge base consists of three knowledge base reports:

- Polymeric nanobiomaterials for drug delivery
- Human health risks of polymeric nanobiomaterials
- Environmental risks of polymeric nanobiomaterials

The guidelines also include case studies of three selected materials: chitosan, polylactic acid (PLA) and polyhydroxyalkanoates (PHAs) exemplifying some aspects of the SbD approach. Although the focus is on polymeric NBMs, the principles laid out in the guidelines could be extrapolated to a certain extent to others, e.g. inorganic NBMs, such as metal and metal oxide NBMs.

Lessons Learned in Regulation of Nanomaterials - Marcus Morstein

Hightech Zentrum Aargau AG

The presentation will address our experiences made during the search for potential industrial users of safe-by-design for nanodrugs and the work performed in work packages 1 and 2. We will furthermore address our lessons learned concerning the regulatory framework for chemicals, drugs and medical devices. The talk will conclude by a brief example on how we make nanomaterial-related know-how available via the community platform nano.swiss.

Nanotechnology and the EMPA collaboration in the GoNanoBioMat project: a perspective from the Pharma Industry partner - Stefan Mühlebach

University of Basel, Department of Pharmaceutical Sciences

Vifor is a small, Switzerland-based global Pharma company with leading competence in the nano-pharmaceutical field. Using nanotechnology in drug research and development, innovative synthetic complex drugs, nanomedicines, could be introduced in the market covering so far unmet medical needs. Nanomedicines with their properties target specific cells and organs in the body adding to better safety and efficacy profiles of drugs. Vifor's nano-colloidal iron carbohydrate drugs, used in millions of patients worldwide are golden standards for efficient and safe i.v. treatments of iron deficiency, a most prominent worldwide disease. Nevertheless and despite the treatment progress, many questions and challenges around these drugs arose from drug design, manufacturing, characterization and quality control, drug packaging, stability, and final ready-to-use administration to the patients. Also challenges by competitors and follow-ons, called nanosimilars, and their deviating profile were seen but difficult to evaluate in a not yet defined regulatory landscape of complex drugs aiming aiming to demonstrate efficacy and safety but also comparability of similars to the reference product. The requested scientific and product-related answers ask for multidisciplinary collaboration also with outside experts. As nano-pharmaceutical science is rapidly evolving, skilled and experienced experts are lacking and collaboration also in a private public partnership is attractive and supported by important international funding like Horizon 2020 in the EU. The GoNanoBioMat project intended implementing guidelines for a safety-by-design approach also attractive for Vifor in its research and practical application for targeted medicinal polymeric nanocarriers. A collaboration from the different institutions including knowledgeable academic sites like EMPA is attractive to scientifically and practically better understand nanomedicines and their design for the benefit of patients and the environment. The project was also aligned with the major mission of the NBCD consortium in the Netherland, another private-public partnership Vifor has engaged successfully since its creation.

Nanostructure and physico-chemical properties of synthetic amorphous silica (SAS) - Claus-Peter Drexel

Evonik Resource Efficiency GmbH

The presentation gives an overview on the properties of synthetic amorphous silica (SAS) in particular regarding the particle size and nanostructure.
Silicon dioxide exists in amorphous and crystalline modifications. SAS are types of amorphous silicon dioxide, which are manufactured by different production processes. SAS consists of aggregates and agglomerates and can be regarded as a nanostructured material. No isolated primary particles exist in SAS (except colloidal silica). The size of aggregates typically ranges from around one hundred to several hundreds of nm, agglomerate sizes typically range from the µm to the mm scale. For precipitated SAS the agglomerate size can be designed by the process and measured by laser diffraction. Intense ultrasonic treatment can destroy the agglomerates, however it is not possible to disintegrate the aggregates.

Challenges in medical device development for SMEs - Roger Christinger

Acrostak (Schweiz) AG

Medical device development, design controls and regulatory submission turn more and challenging for small and medium enterprises. Swiss medical device ordinance (MedDO) and EU regulation 2017/745 dramatically increased requirements on medical device testing, evaluation and certification. Especially when it comes to nanomaterials or substances derived from biological origin, the device risk classification and therefore the risk, biological and clinical evaluation become more challenging.

Robert Geertsma

Regulation in nanomedicine

In general, regulatory requirements as well as regulatory/scientific guidance on nanotechnologies and nanomaterials applied in medicinal products as well as medical devices are emerging. A new regulatory framework for medical devices was recently published in Europe. The new regulation contains several provisions for nanomaterials, including a definition, specific attention for safety of nanomaterials and classification rules leading to different routes for conformity assessment. For the implementation of these provisions, more guidance is needed. Work is currently ongoing in European Commission Working Group for New & Emerging Technologies to develop guidance. The regulatory framework for medicinal products in Europe does not contain specific regulatory requirements for nanomedicinal products (NMPs). However, as in other regions around the world, it is acknowledged that guidance is needed how to apply the regulatory requirements to NMPs in order to accommodate their specific characteristics. The Nanomedicines Working Group (NWG) of the International Pharmaceutical Regulators Programme (IPRP) works on the exchange of non-confidential information on nanomedicines and nanomaterial in drug products and borderline and combination products between international regulators. This includes cooperation and coordination with regard to guidance on evaluation of such products. Also standard development organisations like ISO, CEN and ASTM are working on standards that can help implementation of emerging regulatory requirements for nanomedicinal products and medical devices. Furthermore, work done in European projects such as REFINE (Regulatory Science Framework for Nano(bio)material-based Medicinal Products and Medical Devices) will provide important contributions for this purpose.

Bio	Robert Geertsma has worked at the Dutch National Institute for Public Health and the Environment (RIVM) for more than twenty-five years. As a senior scientist and project leader he is responsible for the provision of scientific advice to regulators on quality and safety of medical technology and nanomedicine. He works on multiple research projects on opportunities as well as risks of nanotechnologies and nanomaterials in medical applications, performing both desk research and experimental research. He participated in FP7-projects ObservatoryNano and NanoMedRoundTable, and is currently one of the partners in the H2020 project REFINE (Regulatory Science Framework for Nano(bio)material-based Medicinal Products and Medical Devices). He is also one of the experts of the Risks of Nanotechnology Knowledge and Information Centre (KIR nano), a Dutch government-supported observation organisation based at RIVM. His areas of expertise include risk management, biological safety, nanotechnology and emerging medical technologies. He participates actively in international ISO/CEN Standards Committees on these subjects and he is chairman of the joint CEN/CENELEC/TC3 responsible for horizontal standards on topics like quality and risk management systems. He was a member of the SCENIHR WG that wrote the Scientific Opinion “Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices”. He is co-chairing the ISO/TC194/WG17 on Biological Evaluation of Medical Devices – Nanomaterials, and he is a member of the Nanomedicines WG of the International Pharmaceutical Regulators Programme. Furthermore, he frequently represents the Dutch competent authority in European Commission’s working groups such as the New & Emerging Technologies WG, of which he was appointed co-Chair in 2009. He is a member of the European Society for Nanomedicine and the European Technology Platform Nanomedicine. **Recent publications** - Giannakou C, Aimonen K, Bloois L van, Catalán J, Geertsma RE, Gremmer E, Jong WH de, Keizers PHJ, Schwillens PLWJ, Vandebriel RJ, Park MVDZ. Sensitive method for endotoxin determination in nanomedicinal product samples. *Nanomedicine 2019; 14:1231-1246.*

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