REFINE 2ND KNOWLEDGE EXCHANGE CONFERENCE

November, 2-3 2020

Introduction

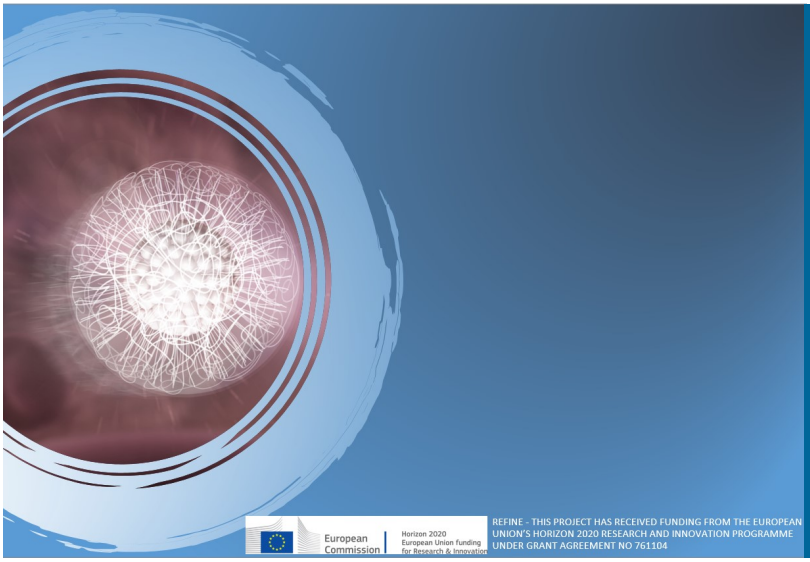
REFINE project aims at setting up a Regulatory Science Framework (RSF) for the risk-benefit assessment of NBM-based medicinal products and medical devices.

In this context, the second Knowledge Exchange Conference (KEC) focused on building solutions for knowledge sharing on regulatory challenges in Nanotechnology and sharing the experience and knowledge on regulatory challenges and solutions of different sectors and communities, which have been using nano-enabled or nano-formulated products.

Objectives of the 2nd KEC

The second KEC has the mission to confirm the interest of the creation of a dedicated space and time for the various sectors and communities using nano-enabled or nano-formulated products to share experience, expertise and knowledge on the different regulatory requirements and needs from their perspective and more globally. This second KEC has been organized around the following objectives:

- Confront the WP1 White paper identified challenges and gap analysis to the other communities and sectors.
- Share and discuss common challenges with the other communities.
- Discuss the support role of a Decision Support System (DSS) in the development and regulatory challenges of nanobiomaterials.
- Foresee the potential role of similarity assessment, grouping and read-across for the assessment of nanoforms, nanosimilars and biosimilars.



Content

- Regulatory challenges across different sectors
- Decision support tools addressing the challenges related to the use of nano(bio)materials under different regulatory frameworks
- Assessment of the similarities of nanotechnology products
- Conclusion

Regulatory challenges across different sectors

Session objectives

Regulatory challenges for nanotechnology-based products in different sectors including health, food, cosmetics and industrial chemicals, were identified in the REFINE White Paper and during the Gov4nano transregulatory risk assessors summit. The regulatory questions are related to different aspects of the regulatory assessment and include e.g. critical parameters to determine equivalence/ similarity of different nanotechnology products, availability of test methods, harmonisation of regulatory practice, terminology and definition. The goal of the session was to identify those challenges that are common for many sectors. The interaction with participants should help to identify most critical regulatory questions, translate them into research questions, and prioritize the research activities that could be initiated in a common cross-sectorial effort.

Session description

The session started with a presentation of Dr B. Halamoda-Kenzaoui (EC JRC), who provided an overview on most pressing needs and regulatory challenges for nanotechnology-enabled medicinal products and medical devices. Several of these challenges are being addressed in the REFINE project by development of relevant methods and a decision support system. Others, such as harmonisation of regulatory practice and terminology require engagement of a larger community of stakeholders. Dr A. Sips (RIVM) provided a broader perspective on challenges across different regulatory frameworks, highlighting open questions and research needs, that were identified at the transdisciplinary regulatory risk assessors summit in Gov4nano. Many of them were similar to challenges identified in the medical sector. More specific information requirements extracted from regulatory guidance documents for nanotechnology-based products across different sectors were presented by Dr P. Sayre (RIVM, Gov4Nano). He highlighted the areas of common interest related to physi-cochemical characterisation, in vitro methods and PBPK modelling for which relevant validated methods are needed. Such common areas could be a starting point for the initiation of transsectorial collaboration helping to increase the efficiency in developing regulatory frameworks for nanomaterials and nanotechnology-based products.

Speaker and Rapporteur

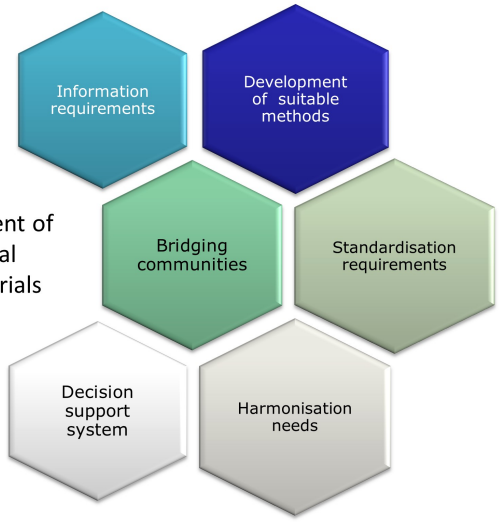
Blanka Halamoda –Kenzaoui

Adrienne Sips

Phil Sayre

Aim:

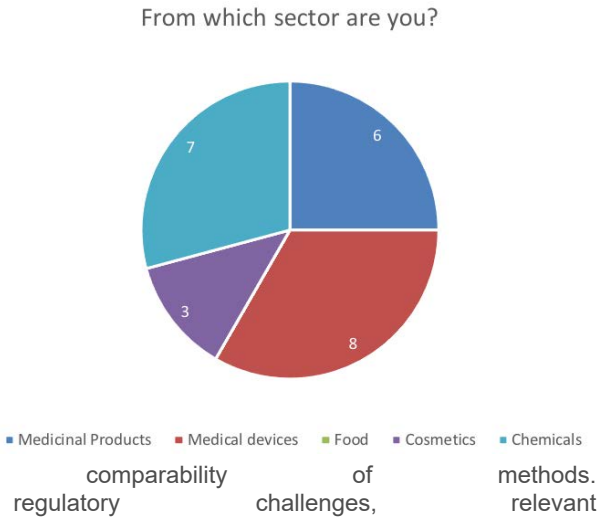
Improve the risk-benefit assessment of medicinal products and medical devices based on nano(bio)materials



REFINE project: Regulatory science framework for Nano(bio)material-based medicinal products and devices

Interaction with audience

The interaction with participants through dedicated interaction tools (slido) allowed to obtain more quantitative feedback on the identified regulatory challenges for nanotechnology-based products. Availability of suitable test methods, and identification of quality attributes that have an impact on biological effects were recognised as most important challenges by at least half of the participants. Furthermore, harmonisation of the regulatory practice (across different sectors and in different geographical regions) and selection of the regulatory path were considered challenging by 42% of the participants, whereas 20% of the participants agreed that all identified topics were representing challenges in their respective sectors. Additional challenges were related to e.g. availability of easily accessible databases and comparability of methods. In order to overcome regulatory challenges, relevant research activities and scientific projects should be initiated. In addition, standardisation activities and regulatory initiatives such as e.g. providing more detailed guidelines were indicated as possible solutions by session participants.



Available presentations

Regulatory challenges for nanotechnology-enabled products in medical sector (B Halamoda-Kenzaoui)
Research questions and regulatory challenges across regulatory perspectives (A Sips)

Conclusions

Session 1 provided an overview on different regulatory frameworks and information requirements for nanotechnology-based products across different industrial sectors including chemicals, cosmetics, biocides, food, medicinal products and medical devices. Several areas of common interest were identified and regulatory challenges across different sectors were highlighted. The outcomes of the transdisciplinary regulatory risk assessors summit in Gov4nano matched the outcomes of the REFINE White Paper, indicating that transdisciplinary collaboration on the identified topics would increase the efficiency in developing regulatory frameworks for nanomaterials and nanotechnology-based products.
The interaction with the audience allowed to identify the most relevant regulatory challenges such as availability of suitable test methods and identification of physicochemical properties that have an impact on biological effects. In addition, availability of easily accessible databases and comparability of methods were highlighted by the workshop participants.

Speaker and Rapporteur

Lisa Pizzol

Alex Zabeo

Robert Geertsma

Decision support tools addressing the challenges related to the use of nano(bio) materials under different regulatory frameworks

Session objectives

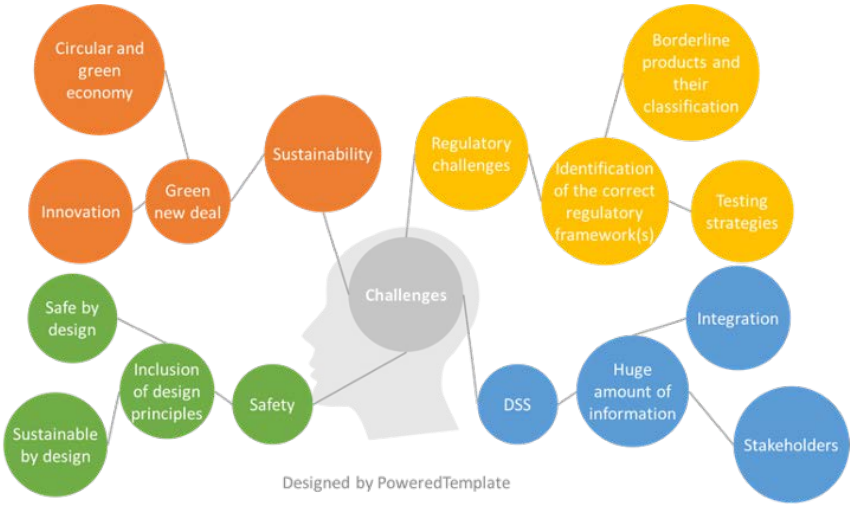
The objective of this section was to discuss the variety of aspects that need to be considered and assessed when designing sustainable products enabled by nano(bio)materials in line with the relevant regulatory frameworks and the Green Deal objectives. These aspects include the assessment and management of human health and environmental risks and comparing those with the socioeconomic benefits of the technologies. Considering the huge amount of information that needs to be properly assessed and integrated, different decision support systems have been developed, all aiming to support developers and decision makers in selecting optimal solutions/ alternatives. One specific objective was to give participants the possibility to acquire a brief overview of the existing DSSs for nano(bio)materials currently being developed in a number of European projects (e.g., REFINE, SAFE-n-MEDTECH, GRACIOUS, BIORIMA, NanoInformaTIX) and obtain first-hand information on their intended objectives and characteristics. To engage the audience and to make the session interactive SLI.DO polls have been organised and participants have been asked to provide information about their interest in and familiarity with DSSs in their daily work and their perception/ experience with this kind of tools.

Session description

The session started with the presentation of Dr. Lisa Pizzol (GreenDecision srl) who introduced the challenges in developing new nano(bio)materials used in different sectors (e.g. medical, cosmetics, biocides, consumer products). Some examples of such challenges are the identification of the correct regulatory framework and its information needs, the selection of optimal testing strategies to generate the required data for this, and in addition to fulfil the increasing requirements for sustainability introduced by new Green Deal policies. The specific challenges related to borderline products and their classification has been the focus of the presentation by Dr. Robert Geertsma (RIVM). In theory it should be clear whether a product is regulated as a medicinal product or as a medical device based on their definitions: if the (primary) mechanism of action is pharmacological, immunological or metabolic, or if it is a substance administered for the purpose of making a diagnosis it is a medicinal product, and otherwise it is a medical device. In practice it turns out this is not so easy to determine, as illustrated with some examples of different products based on iron oxide. For medical devices, an additional challenge consists of applying the classification rule 19, which determines the conformity assessment procedure to be applied for medical devices incorporating or consisting of nanomaterial, depending on their potential for internal exposure to the nanomaterial(s). Again, the rule turns out to present questions of interpretation when applied in practice.

The multiplicity of aspects to be considered and assessed when designing sustainable nano(bio)-enabled products and the related large amounts of information that need to be processed has created the need for software-based Decision Support Systems (DSS). Dr. Alex Zabeo (GreenDecision srl) introduced the topic of DSS and presented six such tools developed for nano(bio)materials used in consumer products and in the medical sectors:

- The FP7 SUN DSS which is a web application able to assess and compare several production scenarios in terms of human health and environmental risks and socioeconomic benefits.
- The H2020 GRACIOUS blueprint to enable practical implementation of grouping and read-across approaches in software-based risk assessment and decision making tools.
- The REFINE DSS which is a web application implementing the intelligent testing strategies (ITSs) developed in the frame of the project. The DSS is intended to inform pre-clinical safety testing for the market approval of medicinal products and medical devices.
- BIORIMA DSS which is a web application implementing the Integrated Risk Management (IRM) framework developed in the frame of the project. The DSS will assess occupational and environmental risks along the lifecycles of nano/biomaterials used in Medical Products and Devices.
- SAFE-N-MEDTECH DSS which is a web application aimed at evaluating if Medical Devices have good chances to reach the market. The probability of success of these products is being assessed according to several criteria such as safety, efficacy, costs, regulatory requirements and ethical implications.
- NanoinformaTIX platform, a virtual infrastructure to enable user-friendly access to high-quality datasets and in silico modelling tools for the safety assessment and risk management of nano/biomaterials used in consumer products.



Challenges related to the production of nano(bio)materials in different sectors

Presentations

Challenges to be addressed for the development of sustainable nano(bio) materials-enabled products to be used in different sectors (L.Pizzol)

Specific challenges related to the determination of the applicable regulatory frame-work(s) (borderline products and their classification) (R. Geertsma)

Overview of available decision support tools for nano(bio)materials used across different sectors (A. Zabeo)

Conclusions

This session discussed the complexity of information and assessments needed to develop safe and sustainable nano(bio)materials and how DSSs can support developers, regulators and decision makers in making informed and transparent decisions. By means of SLI.DO polls, participants have been asked to answer specific questions on the needs and opportunities that DSSs can bring in their daily work. The results of the SLI.DO polls underlined that most of the respondents could be interested in using a DSS in their daily work to perform complex tasks such as choosing the correct regulatory path, deciding on a testing strategy, performing grouping and read across, assessing safety and risks, identifying Critical Quality Attributes, etc. However, most of them have never used this kind of tools. This could be triggered by the perceived complexity of these tools, the lack of available data and experts to run these systems and the need for appropriate training. Finally, all respondents agreed that there is a strong need to better include sustainability aspects when designing and developing nano-enabled products.

Assessment of the similarities of nanotechnology products

Session objectives

The first objective of Session 3 was to provide an overview of the current approaches for similarity assessment, grouping and read-across of nanoforms as developed in EU projects and industry-led initiatives with the participation of regulators. These developments formed a solid basis for the H2020 GRACIOUS project, and our second objective was to introduce the GRACIOUS highly innovative science-based framework to enable practical application of grouping of nanomaterials, leading to read-across of information for both safe by design and regulatory risk assessment purposes. In addition to focussing on the grouping of nanoforms used in consumer products, the third objective of Session 3 was to address the topic of nano/bio similars in the field of nanomedicine and provide the participants with first-hand information on the state-of-the-art developments in this area.

Session description

The session started with an overview of the current approaches for assessment of similarity between nanoforms for grouping purposes by Dr. Wendel Wohlleben from the large industrial company BASF. The grouping approaches were developed in several EU projects and industry-led initiatives such as the EU FP7 projects MARINA, NANoREG, GUIDEnano and ITS-NANO, as part of the ECETOC Nano Task Force and the ECHA's Partner Expert Group. These approaches formed the basis for the H2020 GRACIOUS project, which has developed an integrated framework for grouping of nanoforms to enable read across of information for safe by design and risk assessment purposes. The GRACIOUS framework was presented by Prof. Vicki Stone from Herriot Watt University in Scotland, who is the coordinator of the GRACIOUS project. This was followed by a presentation by Dr. Mario Pink from the German Federal Institute for Risk Assessment (BfR), which provided a regulatory perspective on the grouping of nanomaterials with a focus on the requirements and guidance for grouping by the European Chemicals Agency (ECHA). The fourth presentation in the session focused on the topic of biosimilars/nanosimilars in the context of the complexity introduced by the application of nano and biotechnologies in medicine.

Session Q&A, Poll, discussion

To engage the audience and to make the session more interactive, SLI.DO polls were used for discussion after the presentations. The discussion session focused on which changes are necessary to make in the sector-specific regulation (or regulatory guidance) to promote the application of similarity assessment, grouping and/or read-across. Several key sectors were covered in the discussion: i.e., chemicals, biocides, cosmetics, consumer products, and medicine. The participants discussed also the anticipated benefits for industry and the scientific changes that need to be overcome to successfully implement the grouping of nanoforms in practice.

Speakers and Rapporteur

Vicki Stone

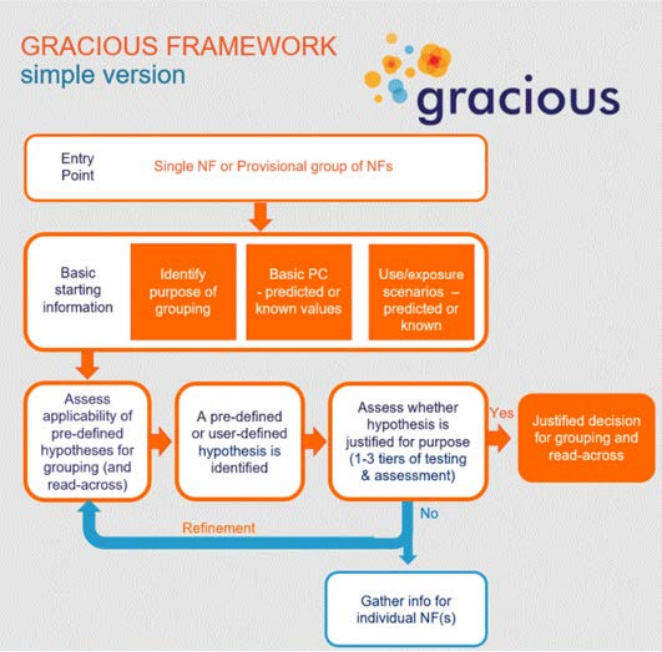
Wendel Wohlleben

Mario Pink

Gerrit Borchard

Danail Hristozov

Hubert Rauscher



The GRACIOUS Framework for grouping of nanoforms simplified

Presentations

GRACIOUS framework for grouping and read-across of nanoforms (V. Stone)
Similarity assessment of nanoforms (W. Wohlleben)
Regulatory perspective on the grouping of nanomaterials – REACH (M. Pink)
Nanosimilars/biosimilars in medical research (G. Borchard)

Conclusions

The discussions concluded that in the future nano-specific grouping and read-across strategies should be hypothesis-driven and must consider not only intrinsic properties and (eco)toxicological effects, but also extrinsic (system-dependent) descriptors of exposure, toxicokinetics and environmental fate. There are challenges that need to be addressed to enable similarity assessment of nanoforms as a basis for grouping. Some of these challenges include the access to sufficiently large FAIR (Findable, Accessible, Interoperable, and Reusable) datasets of acceptable quality. Moreover, it was concluded that in order to generate reliable data that would be accepted by regulators, more efforts should be invested into adapting the current standard test guidelines (e.g., OECD TGs) so that they can better address the unique properties and interactions of the nanomaterials. This is especially relevant for the new generations of “smart” and multicomponent advanced materials, which can be substantially more complex than the simple monoconstituent nanoforms and therefore their grouping can be a lot more challenging. To make effective use of the data, it was recommended that in silico modelling tools (e.g., machine learning approaches, QSARs) are adopted. It was stressed that there is a need for an integrated framework that brings these approaches and the data together in a way that is easily accessible to stakeholders. In this context, the relevance of software-based platforms and decision support systems was discussed.

Wrap-up Session

Speaker and Rapporteur

Adriele Prina-Mello

Simon Baconnier

Session objectives

The fourth session focus of the 2 half-day conference was to collect the key messages and actions of all sessions and draw down the concluding remarks towards securing the objectives of the KEC conference: sharing knowledge across stakeholders.

Session description

From the collective knowledge presented and shared in session 1 it was possible to build a framework towards the creation of a REFINE knowledge exchange space centred around the adoption of nanobiomaterials within medical technologies and products (i.e., nanotechnology-enable or nano-formulated), and not only limited to, their technical challenges, characterisation and regulatory gaps behind their risk and safe assessment.

Accordingly, Dr S. Bacconier summarised the regulatory requirements of the communities participating in the KEC2 and their need for a cross-community space as an easy accessible hub where to share collective knowledge, built on trust and scientific expertise and technical evidence. Such a hub will act as a connecting resource for enabling data capturing, data transfer and forum discussion. Bacconier presented existing options for knowledge hosting currently in use between customised and publicly available solutions.

Following to this overarching presentation, the concluding presentation from Dr. A. Prina-Mello consolidated on the concept of K-HUB by presenting case studies and existing networks where knowledge-hub models have been shared and developed to the benefit of the many stakeholder involved in the exchange exercise

Conclusions

The two-day Knowledge exchange conference brought together different communities around the discussion and objectives of conceptualising, creating and developing tools and knowledge exchange spaces where to present, discuss and have a forum for discussion around the use of nano-enabled or nano-formulated products. Through the four sessions regulatory challenges, gaps analysis, and the development of decision support tools to address some of challenges were presented. Similarities of products in different areas were then assessed and discussed with experts which have visibility and knowledge across different regulatory agencies (EMA, FDA, Canada, Korea, and others). This provided an opportunity for a broader discussion and also identification of needs for an "harmonised" knowledge.
The overall outcome of the KEC2 is the need for the creation of a common knowledge hub which will enable the cross-fertilisation, exchange and forum discussion of the needs, regulatory challenges and gaps existing across the different communities developing nanotechnology-enable or nano-products for industrial or societal applications.

Save the date 3rd KEC

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The KEC3 is organised back-to-back with the **Transregulatory Risk Analysis Summit 2022** of the Gov4Nano project which will provide a forum to discuss, from a regulatory perspective, risk assessment needs and expectations of stakeholders across disciplines and domains. It aims to find solutions to address the complexity of risk analysis for nanomaterials and to meet the ambitions of the Green Deal and the new Chemical Strategy for Sustainability. A joint session with REFINE KEC3 will be organized for awareness raising and the need to break down policy/regulatory silo's in acceptance of test methods.