Comparison on toxicity testing in drug development and in present MNMs safety testing
Deliverable 6.3

Introduction

The safe by design concept has gained interest over recent years as it aims to reduce potential health and environmental risks at an early phase in the innovation process. In addition to its development and use in construction and engineering sectors, this concept has also had a long history of successful deployment in the domain of drug development. In early phase drug development, new chemical entities are screened in parallel for both their efficacy and their potential for toxicity. High throughput testing in this type of research serves the question of whether benefit-risk ratios will likely to be positive. Such an approach might therefore include relevant building blocks for the uptake and development of the safe by design concept for MNMs. The aim of deliverable 6.3 is to evaluate which aspects of the drug development approach can contribute to the safe by design concepts for MNMs.

Key questions and Approach

In the deliverable, the safe by design concept has been described, followed by the process of drug development (from discovery to market launch), MNM development (requirements for REACH) and finally the comparison between toxicity tests used for drug development and for MNM development was made. The key questions that have been addressed are:

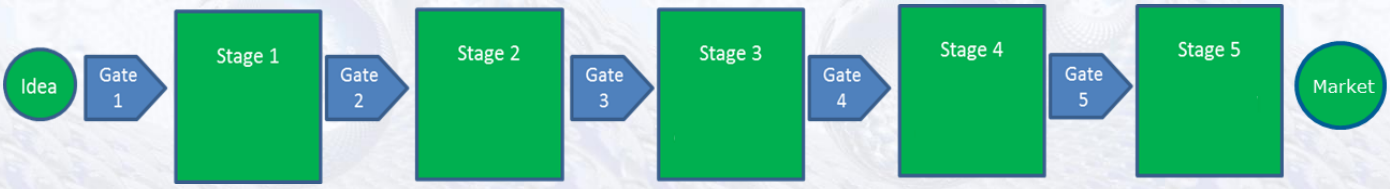
1. What are the similarities and differences in toxicity testing aims between drug and MNM development?
2. What are the critical safety questions in the drug development process and do they apply to the MNM process?
3. Could the toxicity tests for drug development be applicable for MNMs also?

Main Results

Safe by Design and Innovation model

Our approach of the Safe by Design concept is to develop new products where functionality and safety are tested in an integrated way through the development process phase. As a basis for the description of the development of both drugs and MNMs, the deliverable defines an “Innovation model” based on the widely implemented “Stage-Gate idea-to-launch” model. The Stage-Gate product innovation system is a conceptual and operational map for moving new product projects from idea to launch and beyond, a blueprint for managing the new product development process to improve effectiveness and efficiency.

Innovation model



The presented innovation model can give guidance to develop the Safe by Design concept within NANoREG. The structure of this innovation process will be used in this deliverable to make an overview of the toxicity test used for drug development and for MNM development.

Similarities and differences between drug and MNM development

Similarities throughout the drug and MNM development can be found in the goals that have to be achieved. Three main goals can be distinguished:

i) one compound (only) has to be developed and industrialised as product for the market,
ii) the compound has to be safe for humans and the environment and
iii) careful consideration and dataset have to be investigated and generated to predict and/or improve the overall safety across the many aspects to consider.

However, how these goals have to be achieved differs between drug and MNM development. Some distinct differences are presented in the table below.

	Drug development	**MNM development**
Starting position	5000-10000 test compounds	One or few compounds
	Library of similar compounds	Library not available
	Large suite of similar chemical compounds	One or a small suite of similar chemical compounds
	Clear specifications of application (drug for oral use)	Potential for applications
***In vitro* testing**	Huge library of screenings data	Library not available
	Clear criteria for HTS	Criteria for HTS not available
	Screening for severe toxicity	Identifying toxicity (potential)
	Screening for good absorption	
	Information supportive for *in vivo* studies	Partial proof for safety
***In vivo* testing**	Animal studies do not need to be conclusive	Animal studies need to be conclusive
	Human data	No human data
	Enormous amount of toxicity data	Relatively modest amount of toxicity data
Other	Insight into the relevance of test outcomes for business model	Unknown if MNM lead to product(s)

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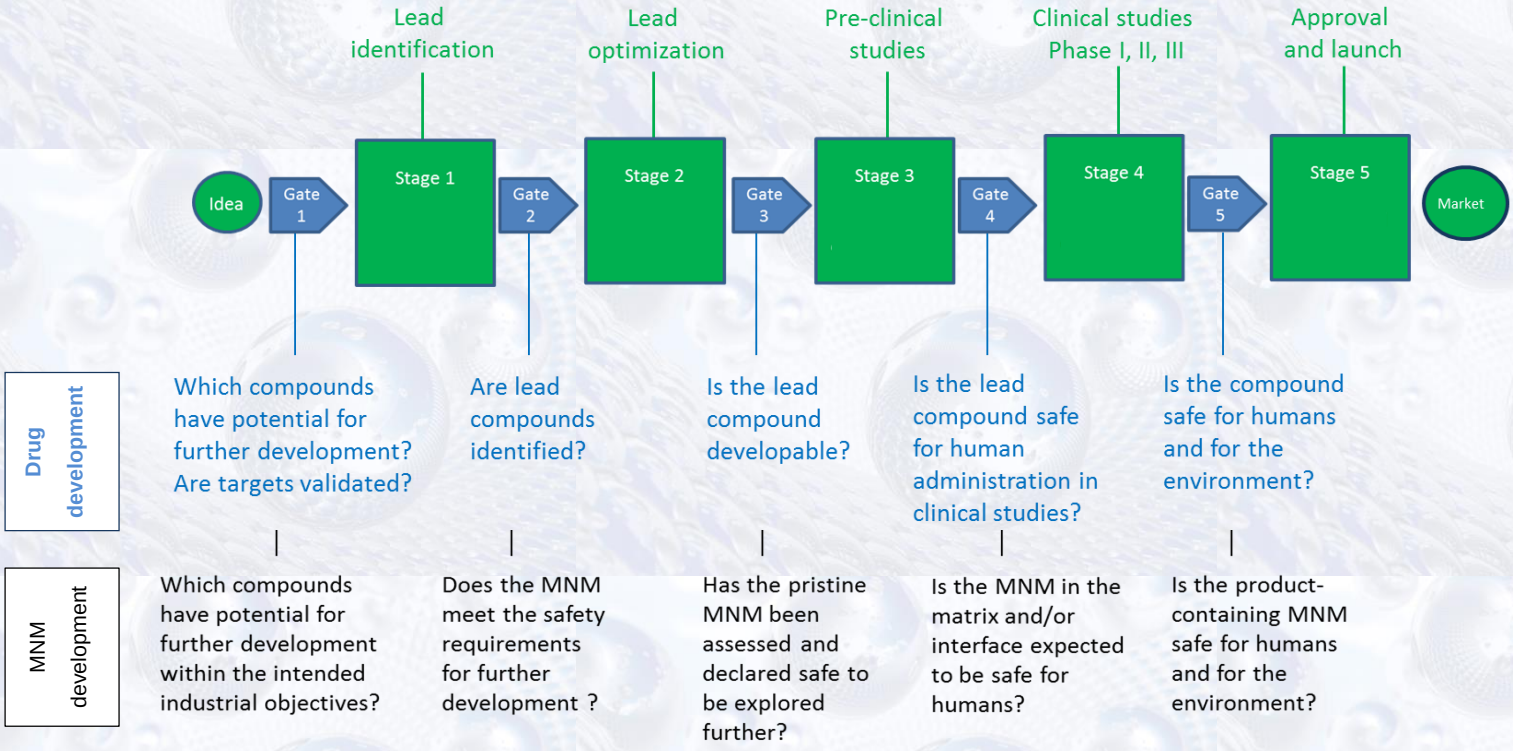
Critical safety questions

The critical safety questions in both drug and MNMs development processes have been linked to the "Gates" in the Innovation model that forms the basis for the deliverable.



Toxicity testing

Regarding the applicability of the toxicity tests used in drug development for MNMs development it is concluded that it is not possible to draw conclusions in general. What has been concluded is that some aspects of drug development may be further developed for a screening of risk potentials for MNMs. The following risk potentials for MNMs have been proposed:

Solubility/dissolution	Genotoxicity/carcinogenicity	Accumulation
Stability of coating	Immunotoxicity/Inflammation	Ecotoxicity

When focussing on these risk potentials of MNMs, parameters describing and quantifying such potential have to be defined. Furthermore, there is a need for the definition of the relationship between the parameters and the risk potentials. Once these parameters are identified and described in detail, then the next step will be the identification of the most satisfactory testing strategy to measure these parameters for qualitative and quantitative assessment. To this aim, the experiences from drug development could provide a great valuable and lesson learned experience.

For more details about NANoREG please visit the official website www.nanoreg.eu.

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