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Identification of regulatory needs for nanomedicines

1st EU-NCL survey with the "Nanomedicine" working group of the international pharmaceutical regulators

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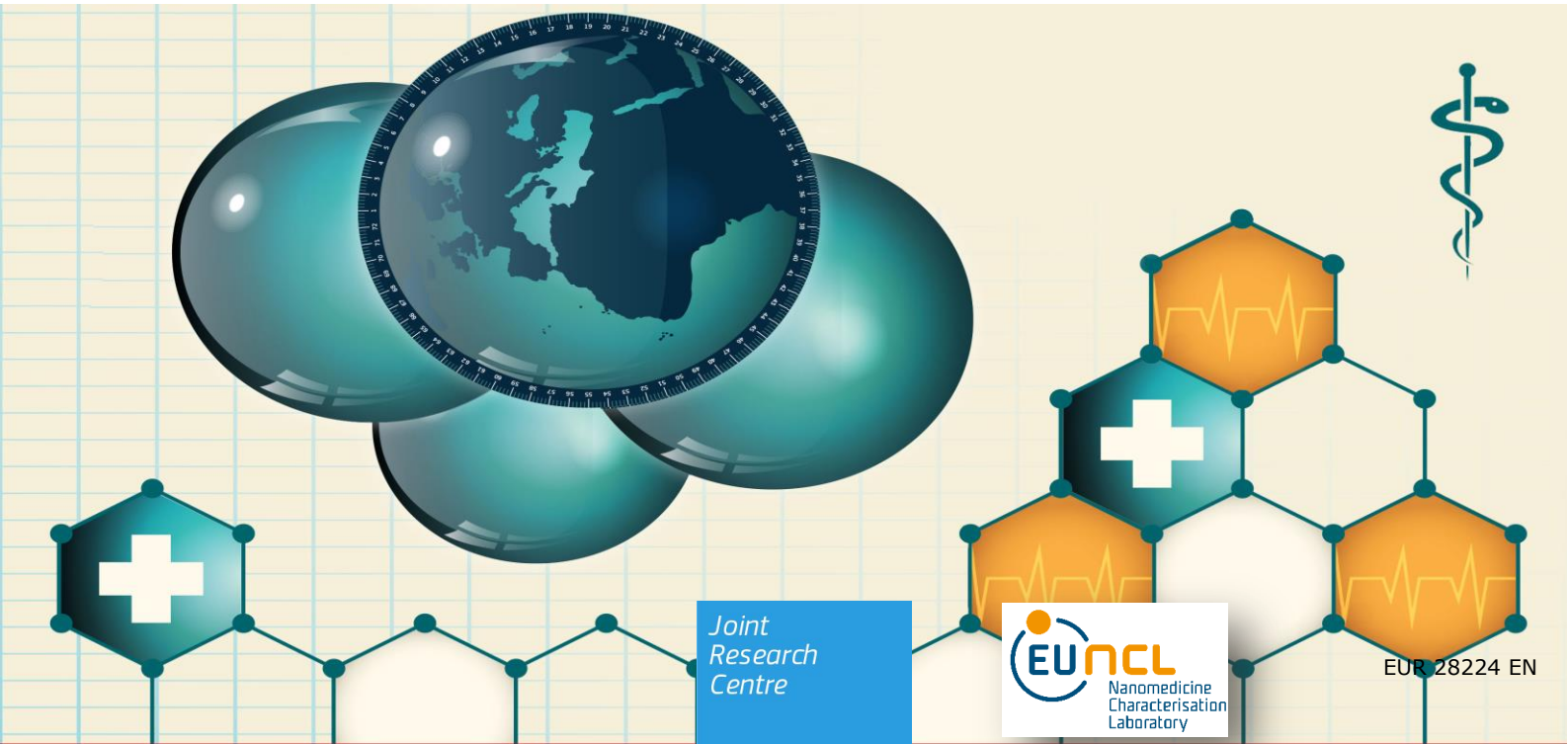

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Identification of regulatory needs for nanomedicines

Innovative products based on nanotechnology can challenge existing legislative frameworks. The present survey with regulatory scientists of nine international agencies elucidated their experiences with nanomedicines and identified information needs that allow the characterisation of the nano-specific properties. Finally future recommendations leading to the mutual acceptance of data are discussed.

Table of Contents

Foreword

Nanomedicines are emerging medicinal products which have to comply with the high standards of the medicinal product regulation. Due to their size related physicochemical properties and the sometimes resulting biological effects, nanomaterials can require additional quality and safety testing compared to products with standard size. For the safe evaluation and supervision of nanomedicines, critical quality attributes and safety parameter have to be identified and translated into standardised and regulatory accepted test methods/testing strategies. Standardised test methods will not only support regulatory decision making for the benefit of the patients but also reduce the uncertainty for product developer on regulatory information requirements during the different approval steps.

In order to ensure that methods developed/validated in the European Nanomedicine Characterisation Laboratory (EU-NCL) are relevant for regulatory purposes and the obtained information can assist the regulatory decision making, the EU-NCL project includes a series of questionnaires addressed to regulatory working groups that are involved in the evaluation of innovative medical products and/or nanomedicines. Due to its independence of national or commercial interests, its proximity to EU policy-makers as well as its expertise in nanotechnology, the Joint Research Centre of the European Commission has taken up the task to link the EU-NCL project to the regulatory community e.g the International Pharmaceutical Regulators Forum (IPRF) and the international conference "Global Summit on Regulatory Science (GSRS)". The presented survey is the first out of three surveys performed in close collaboration with the SINTEF Institute "Materials and Chemistry" that aims to identify the regulatory needs for the characterisation of the nanomaterials in medicinal products.

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- Bioanalytik - Gesellschaft für Bioanalytik Münster e.V. (Germany)
- CEA - Commissariat à l'énergie atomique et aux énergies alternatives (France)
- EMPA - Eidgenössische Material- und Prüfungs-Anstalt (Switzerland)
- ERS - European Research Services GmbH (Germany)
- LEIDOS - Leidos Biomedical Research, Inc. (USA)
- TCD - Trinity College Dublin (Ireland)
- UL - University of Liverpool (United Kingdom)

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- Health Canada, Canada
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- Food and Drug Administration, United States of America
- National Institute for Public Health and the Environment, The Netherlands
- Centre for Drug Evaluations, Taiwan
- Medicines and Biological Products Office, Brazil
- Pharmaceuticals and Medical Devices Agency, Japan
- Ministry for Food and Drug Administration, Korea

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Abstract

The application of nanotechnology in healthcare is widely accepted as a potential driver of biomedical innovation. By exploiting the unique physicochemical properties at molecular level, nanotechnology based products (also known as nanomedicines) can monitor, repair and control biological systems in order to address diseases for which currently no or only insufficient diagnostic and therapeutic tools are available. Nanotechnology will also play an enabling role in the implementation of personalised medicine as it provides tools for a better prediction and early diagnosis, the design of personalised treatments as well as for a close monitoring of the therapeutic success.

However, the opportunities of nanotechnologies in the health sector are coming along with challenges in the regulation of these products. Sufficient knowledge on their quality, safety and efficacy must be gained and standardised methods must be made available to support the regulatory decision making and allow a smooth translation towards clinical applications.

The current survey was performed within the *Nanomedicines Working Group* of the International Pharmaceutical Regulators Forum (IPRF) with the aim to get a general overview on the status and regulatory needs of nanomedicines and indicate some trends on future requirements.

The survey demonstrated strong regional differences in the regulation of nanomedicines and showed that in the last years, the European authorities have received fewer applications of nanotechnology based pharmaceuticals as e.g. the USA. However, a future increase of market applications must be anticipated in Europe as other regions are already facing challenges in the regulation of nanotech products. These expectations are supported by the fact that the last EC's framework programmes have invested hundreds of millions of Euro into nanomedicine development in order to make these promising products available to the patient. An intensive exchange of experience in the regulation of nanomedicines between regulatory bodies and discussions in numerous conferences e.g. European Foundation for Clinical Nanomedicine (Clinam), GSRS 2016, are now taking place in order to ensure a harmonised regulation of these products internationally. The respondents of the survey also confirmed the need for the harmonisation of information requirements on nano-specific properties. In addition, a number of critical physicochemical properties that have already been proposed in the scientific literature were verified in the survey as relevant for regulatory decision making. Some regulatory agencies also indicated the need for additional (eco)toxicological testing triggered by the nanospecific property of the product.

Finally, the survey demonstrated an interest of regulatory agencies in an independent nanomedicine characterisation testing facility that can support regulators in the evaluation of these systems and at the same time assess the performance of existing and new test methods for their application to the field of nanomedicine.

1. Introduction

The implementation of personalised medicine or precision/stratified medicine is currently worldwide on the political agenda. US President Barack Obama announced the Precision Medicine Initiative supporting biomedical researchers and clinicians with the development of new tools and knowledge to optimise treatments according to patient needs in 2015 [1]. In Europe, the Council of Employment, Social Policy, Health and Consumer Affairs adopted a number of conclusions and recommendations in December 2015 with the aim to realise patient-tailored treatment in Europe, to support the implementation of cross-sectorial research and to promote contributions to personalised medicine under the Horizon 2020 Programme in order to speed up the development of advanced preventive and diagnostic tools as well as better and safer medicines [2]. More specifically, the Commission staff working document on "the use of omics technologies in the development of personalised medicine" emphasized already a number of prerequisites necessary to implement personalised medicine. Among those recommendations, the document highlights the need to make use of *…new imaging technologies in order to understand better biological mechanisms, including toxicity, at the molecular, whole organ, and whole body level...* The regulation of the components of personalised medicine should be coordinated (e.g. medicines and diagnostics) by involving the EMA [3].

Amongst other emerging technologies, nanotechnology will play an enabling role in the successful implementation of personalised medicine as it can provide a variety of necessary tools including biosensing technologies for diagnostic purposes, targeted drug delivery systems or the online monitoring of therapeutic effects allowing the individualised adjustment of drug selection and dosage [4–6]. As such, nanotechnology based products will tackle different health policies including legislative frameworks of medicinal products, medical devices and *in vitro* diagnostics [7–9].

The rapidly growing field of nanotechnology in the health sector requires a close monitoring of scientific/technical developments in order to facilitate their evolution from concepts to products allowing a smooth transition into medicines that benefit patients in the EU and beyond. Identified needs should include the adequate characterisation of the nanomaterials using appropriate analytical methods, a detailed understanding of their critical quality attributes (CQAs), as well as a toolbox of standardised methods including toxicity tests preferably *in vitro* and based on human cells. A harmonised terminology and the development of additional guidance documents will further support the translation of nanomaterials into the clinical applications [10,11].

1.1 The European Nanomedicine Characterisation Laboratory

In order to fully exploit the potential of nanomedicines, the European Technology Platform on Nanomedicines (ETPN) has released a white paper in 2013 with an overall vision and concept for an effective translation of nanotechnologies for medical applications [12]. Among the proposed actions also the implementation of a European Nanomedicine Characterisation Laboratory has been suggested in order to support an early characterisation of the quality and safety of complex materials in the preclinical phase. The need and success of such a platform has been demonstrated by the Nanotechnology Characterization Laboratory of the US National Cancer Initiative (NCI-NCL) which has been founded in 2004 [13]. The NCI-NCL is supporting product developers by assessing critical physical, chemical and biological parameters under confidentiality agreement. At the same time the laboratory is also in close contact with

regulators from the Food and Drug Administration (FDA) discussing and practically tackling the regulatory needs for the next-generation nanomedicines.

In order to offer such service also for the growing market of nanomedicines in Europe, the European Union's Horizon 2020 research and innovation programme has launched the first trans-disciplinary testing infrastructure for the characterisation of medicinal products involving nanotechnology (EU-NCL) in 2015 [14]. The EU-NCL is a cooperative arrangement between six European Laboratories and the Nanotechnology Characterization Laboratory (NCI-NCL) of the United States. The facilities will offer access to their existing analytical services for public and private developers in order to characterise the quality and safety of nanomedicines that are aiming to enter into clinical trials or seeking for market authorisation. In order to ensure that methods developed/validated in the EU-NCL are relevant for regulatory purposes and the obtained information can support the regulatory decision making, the EU-NCL is performing a series of questionnaires addressed to different groups of regulatory scientists. The data presented here are the results of the first survey submitted by the scientists of regulatory bodies involved in the Nanomedicines Working Group of the International Pharmaceutical Regulators Forum (IPRF) [15]. The objectives of the survey were to get an overview on the experiences of regulators with nanomedicines in the various regions, their information needs as well as the identification of future priorities to support the translation of nanomedicines towards clinical applications.

2. Methodological Approach

2.1 The definition of questions

The questions have been defined according to recommendations of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [16], members of the EU-NCL consortium and EMA's reflection papers related to nanomedicine [17–20]. In addition, a similar questionnaire performed within the EU project "NANoREG" on manufactured nanoparticles has been taken into account [21]. In order to avoid any bias, responders had the possibility (and were encouraged) to include additional information not covered by the predefined questions.

2.2 Information on respondents

The IPRF has established a *Nanomedicines Working Group* in order to discuss emerging questions and anticipate regulatory needs for nanomedicines. This working group is acting as a platform to share non-confidential information and work related to nanomedicines/nanomaterials in pharmaceuticals, borderline and combination products. Furthermore, the group supports regulatory harmonisation and potential consensus finding on standards. Currently the IPRF group is chaired by the European Medicines Agency. 59 invitations to colleagues from 18 governmental institutions regularly participating in activities of the IPRF *Nanomedicines Working Group* were sent out (Table 1). 10 departments from 9 agencies responded to the questionnaire.

Table 1: Regulatory bodies invited to participate in the survey

No	Governmental organisation
1	Health Canada (market health products), Canada
2	European Medicines Agency
3	Swiss Agency for Therapeutic Products, Switzerland
4	Health Canada (health products and food branch), Canada
5	United States Food and Drug Administration, USA
6	Pharmaceuticals and Medical Devices Agency, Office of New Drug II; Japan
7	Brazilian Health Surveillance Agency, Brazil
8	Ministry of Food and Drug Administration, Korea
9	Center for Drug Evaluation, Taiwan
10	National Institute for Public Health and the Environment, Netherlands
11	Federal Institute for Drugs and Medical devices, Germany
12	The Medicines and Healthcare products Regulatory Agency, United Kingdom
13	National Health laboratory, Luxembourg
14	Spanish Medicines Agency, Spain
15	Ministry of Health, labour and welfare, Japan
16	Australian Government, department of Health therapeutic goods administration, Australia
17	National Agency for food and drug administration and control, Lagos
18	Health Science Authority, Singapore

2.3 Survey management

The survey has been performed by using the European Commission's management tool "EUSurvey". EUSurvey has been launched in 2013 in order to create official surveys of public opinion and forms for internal communication and staff management. The application, hosted at the European Commission's Department for digital services (DG DIGIT), is available free of charge to all EU citizens. The presentation of the results is anonymous and individual results will be kept confidential. The survey has been launched in October 2015 and has been finalised in November 2015. The responses have been evaluated by using basic result analysis capabilities and visualization of the data in histograms and chart views as offered by the European Commission tool (ANNEX 1).

3. Results

The obtained information can be classified into three categories: i) regulatory experience with nanomedicines, ii) information needs of regulators for the characterisation of nanomaterials and iii) further steps that can support the acceptance of nanotechnology based products in health care.

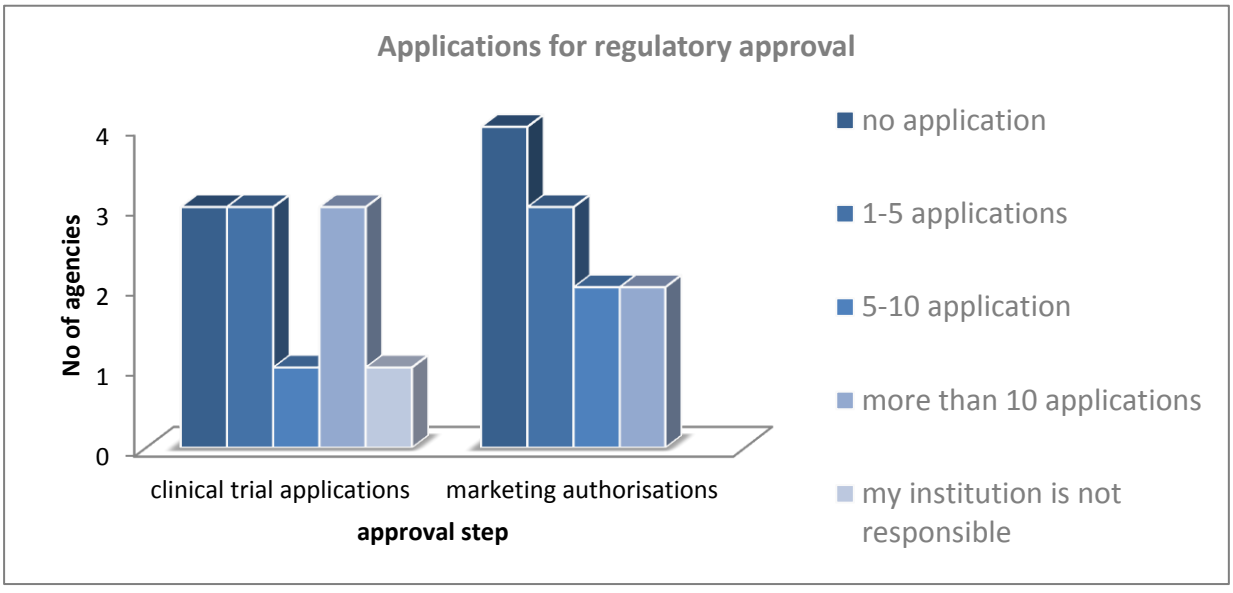
3.1 Regulatory experience with nanomedicine applications

The majority of competent authorities that responded to the survey had no or only few applications of nanomedicinal products. Out of 10 agencies only two agencies reported more than 10 market authorisations for medicinal products in the last 36 months and three agencies stated that more than 10 investigational products have been approved for clinical trials (Figure 1).

In order to get a better understanding whether the submitted products were innovative products or products claiming to be similar to an innovator product, the respondents were asked to quantify their applications for follow-on products ("nanosimilars"). Only one agency reported more than 10 applications for these products (Figure 2). Additional four agencies had few applications of so called "nanosimilars".

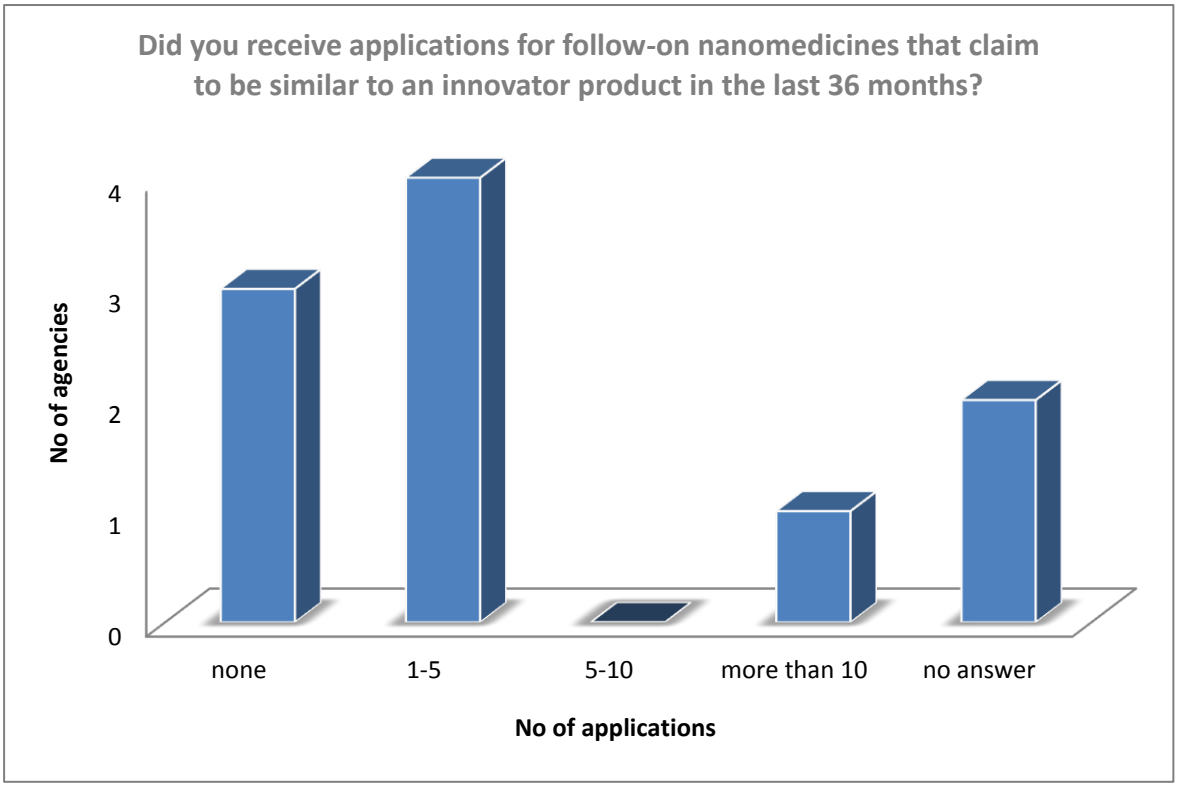
The respondents were asked how many nanotechnology involving products were classified as medical device (Figure 3). Very few products were regulated as medical devices but the decision making on their regulatory path triggered discussion in three agencies (Figure 4).

Figure 1: Current status of products involving nanotechnology that have applied for clinical trials or market authorisation



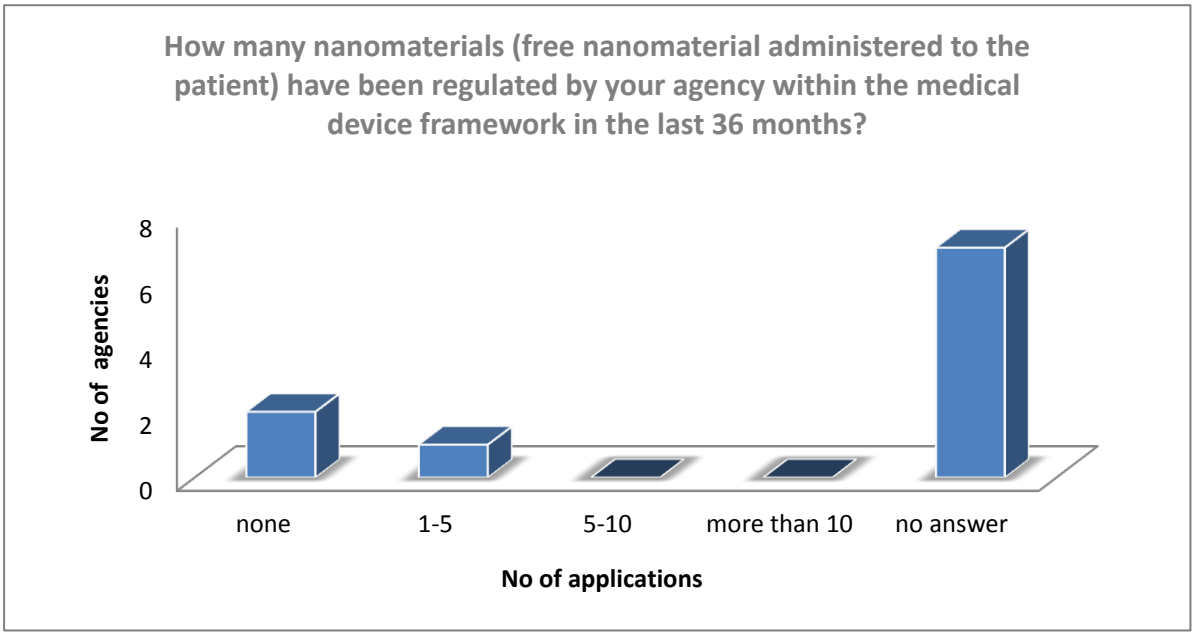
The graph demonstrates regional differences of nanomedicine applications requesting the approval of clinical trials or market authorisation.

Figure 2: Number of applications similar to an innovator product/agency



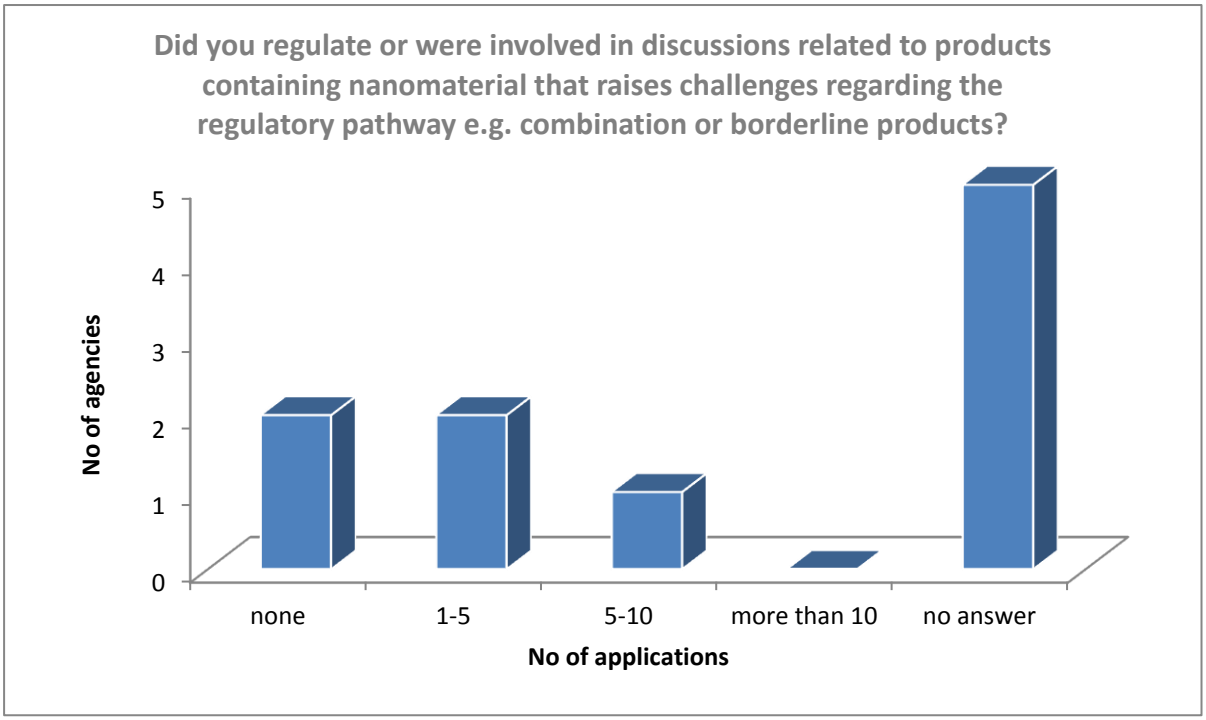
One agency reported more than 10 applications of products that are similar to an innovator product.

Figure 3: Number of nanomaterials regulated as medical device



The agencies did not report on many applications related to freely administered nanoparticles that were regulated as medical devices. (Please note that the EMA is not responsible for regulating medical devices.)

Figure 4: Number of products raising discussions regarding the regulatory pathway/agency



Three agencies were reporting their involvement in discussion about borderline and combination products that require special regulatory awareness

Table 2 and 3 are summarizing the satisfaction of agencies with the data provided by product developer. Two agencies receiving up to 10 applications for market authorisation responded that the information on the physicochemical characterisation was not sufficient (Table 2). One of these agencies also reported insufficient data on the biological characterisation for market authorisation (Table 2). Another agency with up to five clinical trial applications indicated unsatisfactory data on the biological characterisation (Table 3). It should also be noted that a considerable number of agencies have not responded to the question. Table 2 and 3 demonstrate a correlation with number of applications and responses to specific questions.

Table 2: Summary table on the sufficiency of information submitted for market authorisation

No of market authorisations	No. of agencies	Satisfied		Non-satisfied		No answer	
		Phys. Chem. Charact.	Biol. Charact.	Phys. Chem. Charact.	Biol. Charact.	Phys. Chem. Charact.	Biol. Charact.
0	3					3	3
1-5	3	3	3				
5-10	2		1	2	1		
>10	2	2	2				

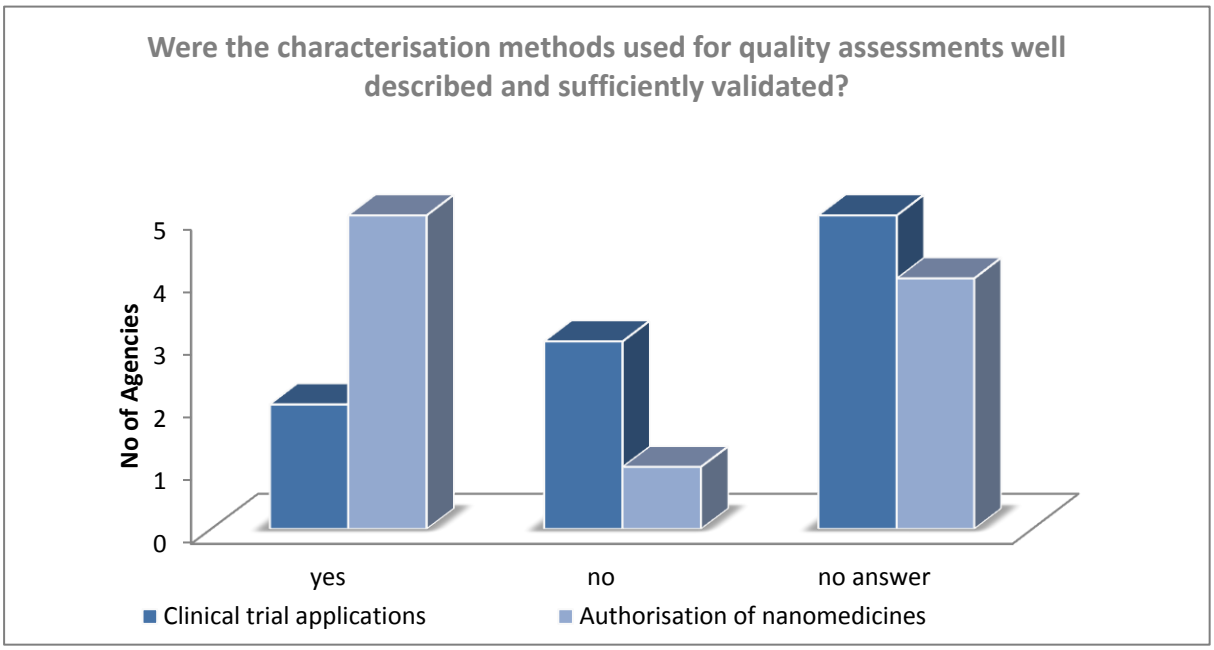
Table 3: Summary table on the information submitted for clinical trial authorisation

No of clinical trial approvals	No. of agencies*	Satisfied		Non-satisfied		No answer	
		Phys. Chem. Charact.	Biol. Charact.	Phys. Chem. Charact.	Biol. Charact.	Phys. Chem. Charact.	Biol. Charact.
0	1					2	2
1-5	3	2	1		1	1	1
5-10	1	1					1
>10	3	3	3				

** one agency was not responsible for the authorisation of clinical trials and was included.*

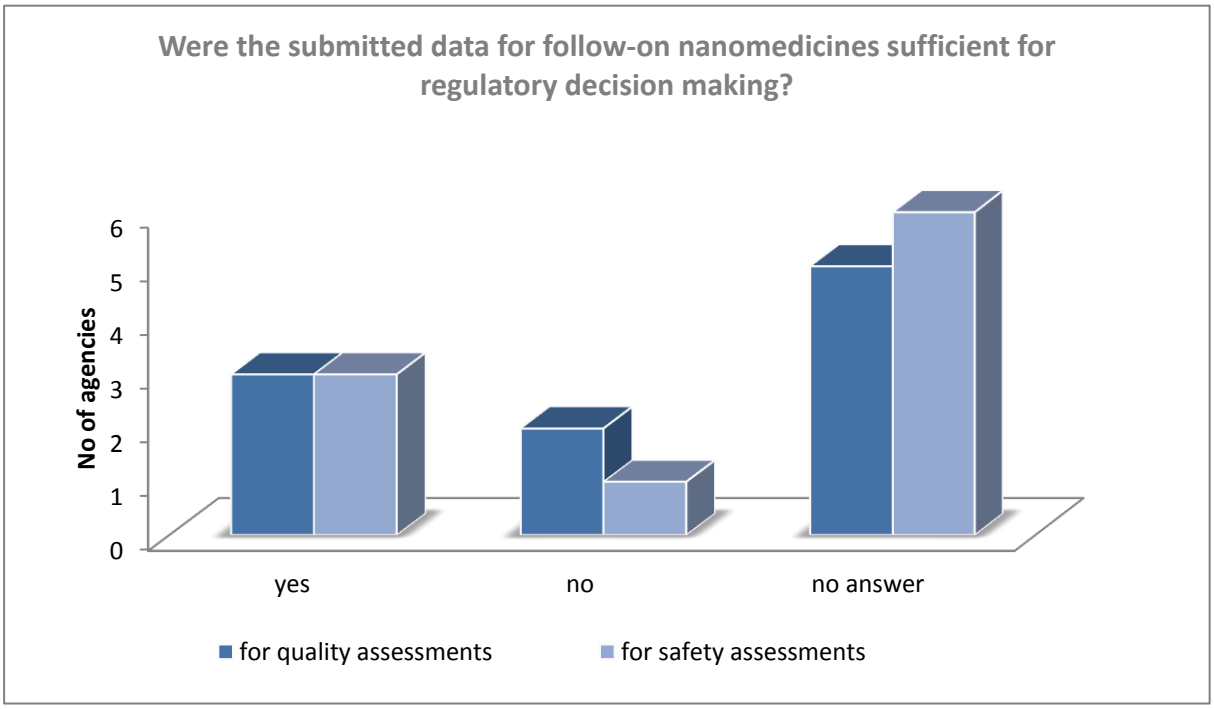
Furthermore, the agencies were asked whether test methods used for the physicochemical characterisation were suitable for their decision making. One agency with more than 10 applications reported that the agency received applications with test methods that were not suitable for quality assessments (Figure 5). In addition, two agencies reported insufficient information for assessing the quality of follow-on products (Figure 6). Most of the agencies did not report on the data sufficiency of medical devices involving nanotechnology. Only one agency stated that the received data were sufficient whereas another agency gave a negative opinion (Figure 7).

Figure 5: Validation status of characterisation methods for quality assessments



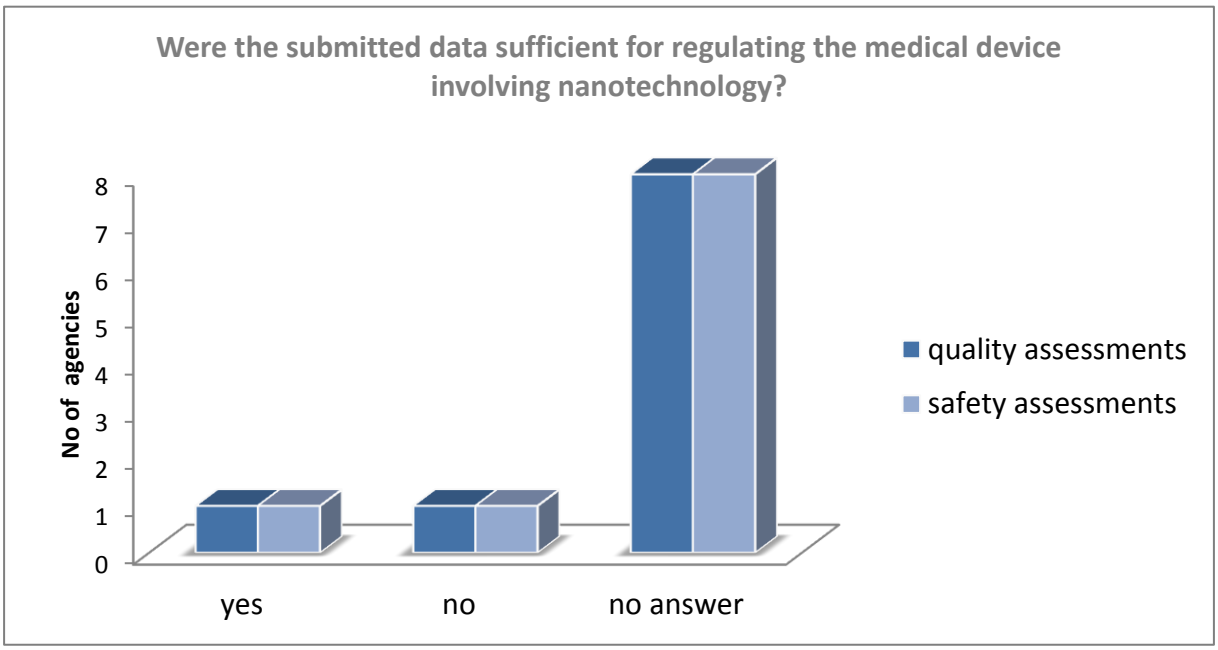
Only very few standards specifically addressing the application of nanotechnology in the health sector are available, therefore the regulators have to evaluate the suitability of the used characterisation methods. Methods used in the application for clinical trials were judged as not sufficiently validated by three agencies.

Figure 6: Sufficiency of data provided for nanosimilars evaluations (quality and safety)



Two agencies report insufficient data for quality assessment of follow-on products whereas one agency reported insufficient data for safety assessment.

Figure 7: Adequacy of data submitted for medical device evaluation

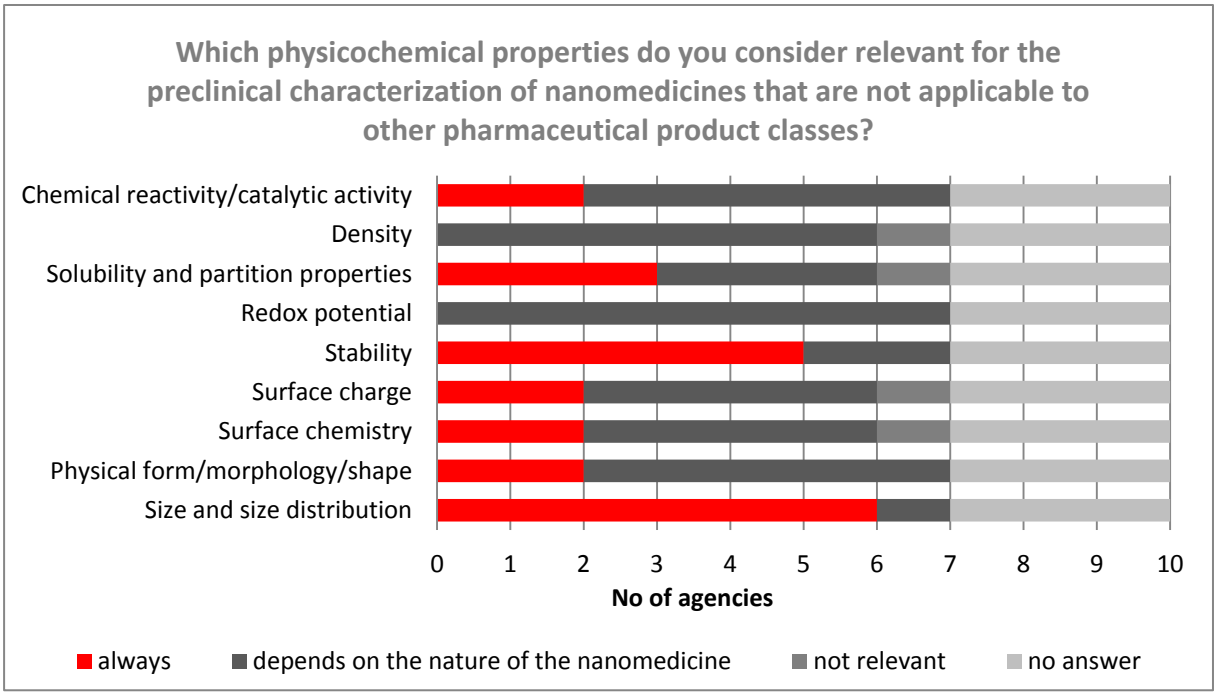


One agency reported insufficient data for medical device evaluations. However, the majority of the agencies did not provide any answer. (Please note that the EMA is not involved in the regulation of medical devices)

3.2 Relevance of information needs for the preclinical characterisation of nanomedicines

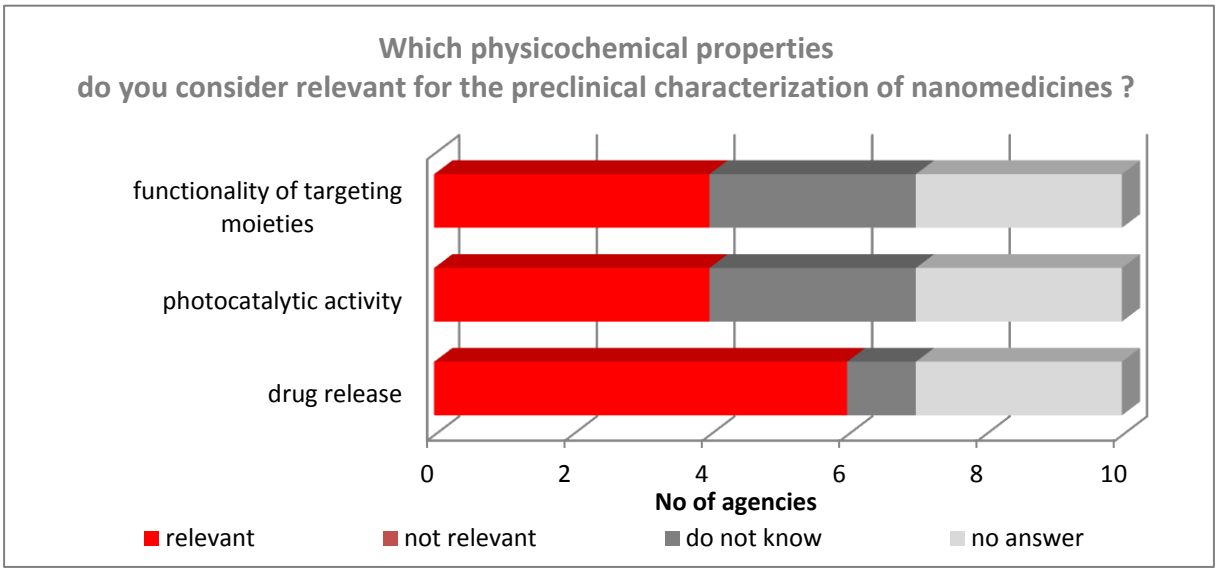
The questions regarding the relevance of various physicochemical parameters aimed to get an overview on information requirements needed to assess the properties of nanomaterials for regulatory decision making. These parameters e.g. stability, particle size (-distribution), surface properties as well as information on drug release may change the pharmacokinetics, biodistribution and toxicity (Figure 8). Nevertheless, the relevance of each parameter is strongly depending on the evaluated nanomedicine which holds also true for the assessment of the nanomedicine functionalities as shown in Figure 9. As already demonstrated in the table above, agencies with no or only a few applications have not responded to this set of questions as it requires hands-on experience with regulating nanotechnology based products (data not shown).

Figure 8: Relevant physicochemical parameters for preclinical characterisation



Relevance of selected physicochemical parameters for regulatory decisions.

Figure 9: Relevance of the assessment of functional properties for preclinical evaluations

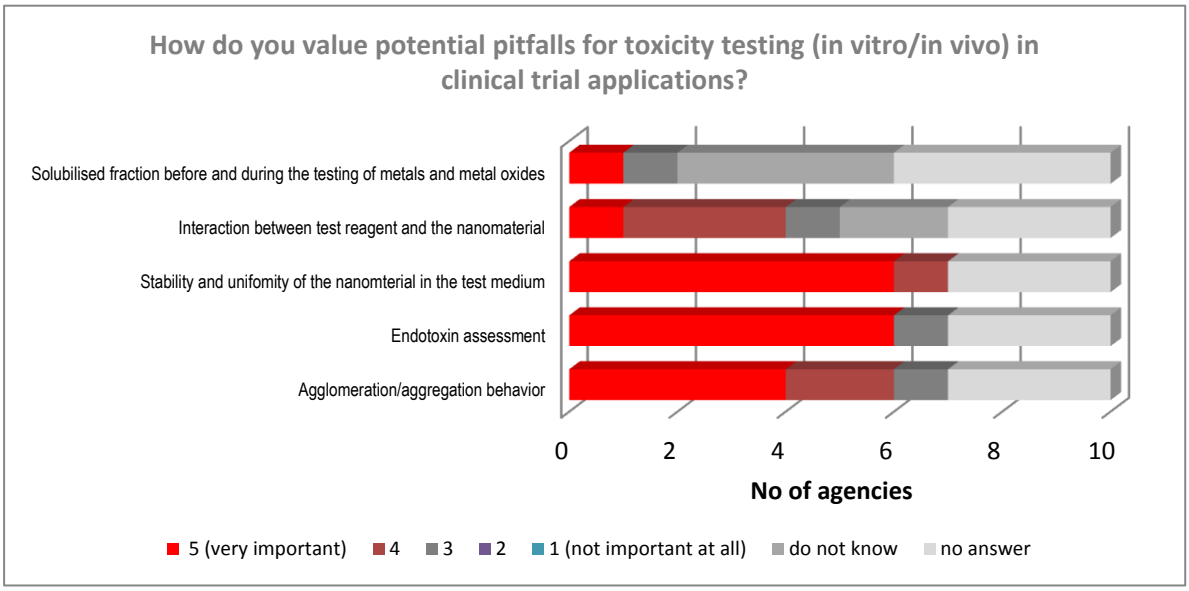


The assessment of the functionalization is an important aspect of quality control as it can be directly linked to the performance of the product.

Adequate characterization of CQAs that may impact drug safety and efficacy is essential for product development and quality control. In addition, since slight changes in the manufacturing process can lead to products with different behaviour, the understanding of the manufacturing process and its critical steps and their impact on the CQAs should be carefully evaluated.

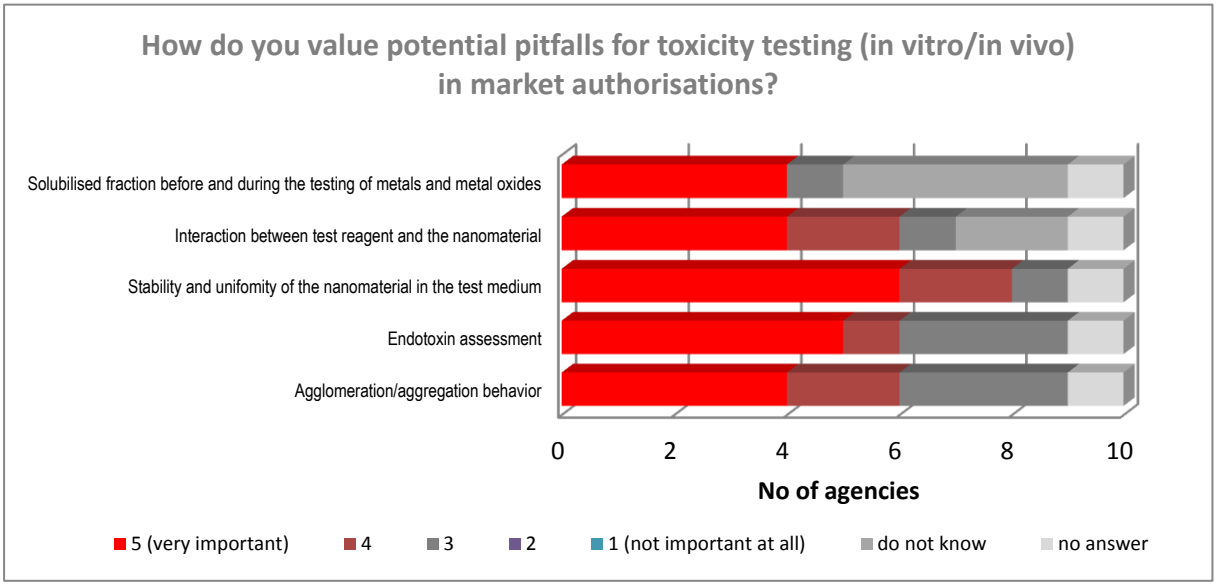
A number of potential pitfalls for toxicity testing are widely discussed in the scientific literature and a selection of questions related to these pitfalls aimed to obtain a regulatory point of view. The agencies have highlighted the need for assessing the stability, uniformity (dispersibility), endotoxin testing and agglomeration behaviour as highly relevant before entering into clinical trials. Additional information such as the assessment of the solubilised fraction before and during the testing of metals and metal oxides seems to be more relevant at a later stage of the product development (Figure 10).

Figure 10: Pitfalls related to the toxicity testing of nanomaterials for clinical applications



A number of pitfalls for toxicity testing have already been identified and should be considered in toxicity testing when applying for the approval of clinical trials.

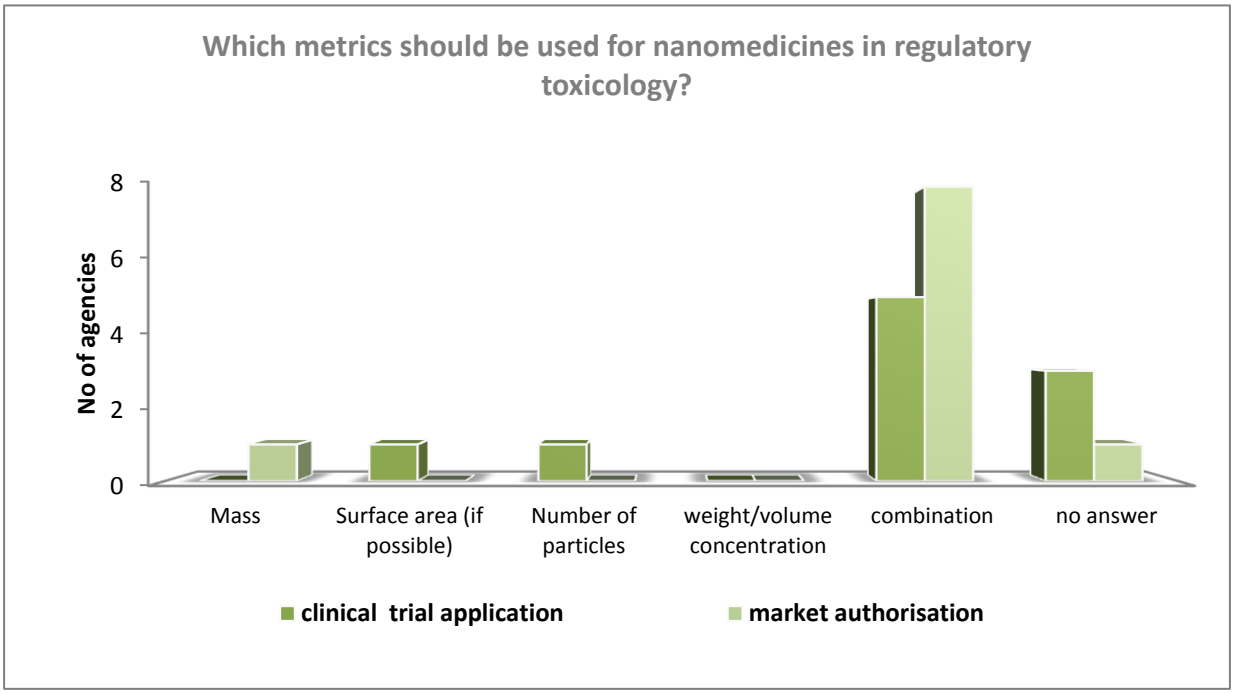
Figure 11: Pitfalls related to the toxicity testing of nanomaterials for market authorisation



A number of pitfalls for toxicity testing have already been identified and should be considered in toxicity testing when applying for market authorisation.

The effective cellular dose is another widely discussed topic in the area of *in vitro* toxicity testing. The dosage should be preferably described as a combination of metrics (Figure 12).

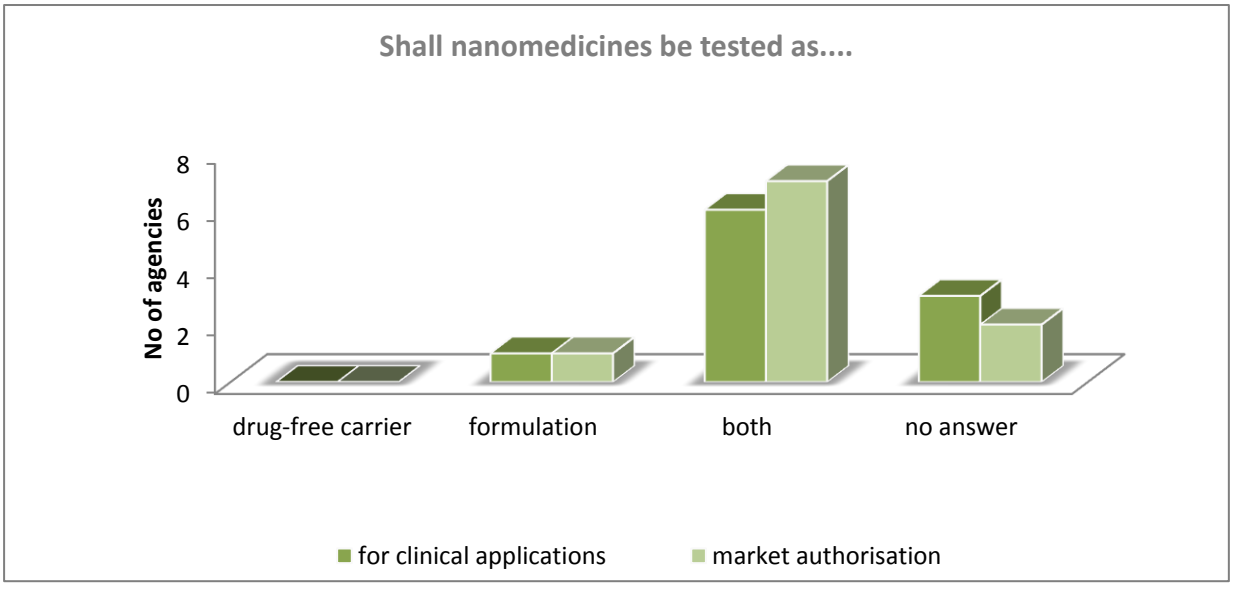
Figure 12: Metrics for nanomedicines



The agencies preferred a combination of different metrics'.

There was also a concurrence among the authorities on the need to test the empty carrier in addition to the formulation for assessing inherent toxicities (Figure 13).

Figure 13: Testing requirements

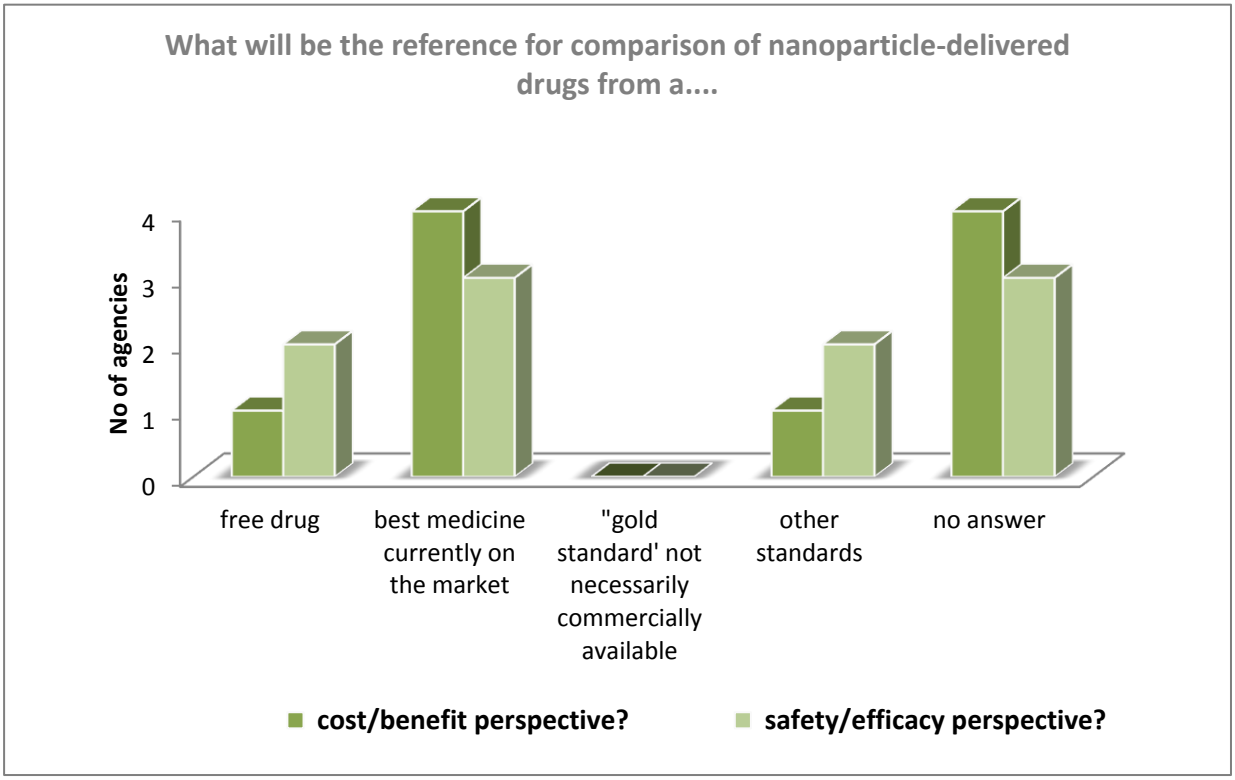


The agencies preferred to test the drug free carrier as well as the complete carrier.

The agencies agreed that a new nanomedicine should be compared to the best medicine currently on the market in terms of cost/benefit but also in terms of benefit/risk.

Nevertheless, two agencies with higher regulatory activities in the field of nanomedicines are suggesting "other standards" (Figure 14).

Figure 14: Reference of nanoparticle delivered drugs

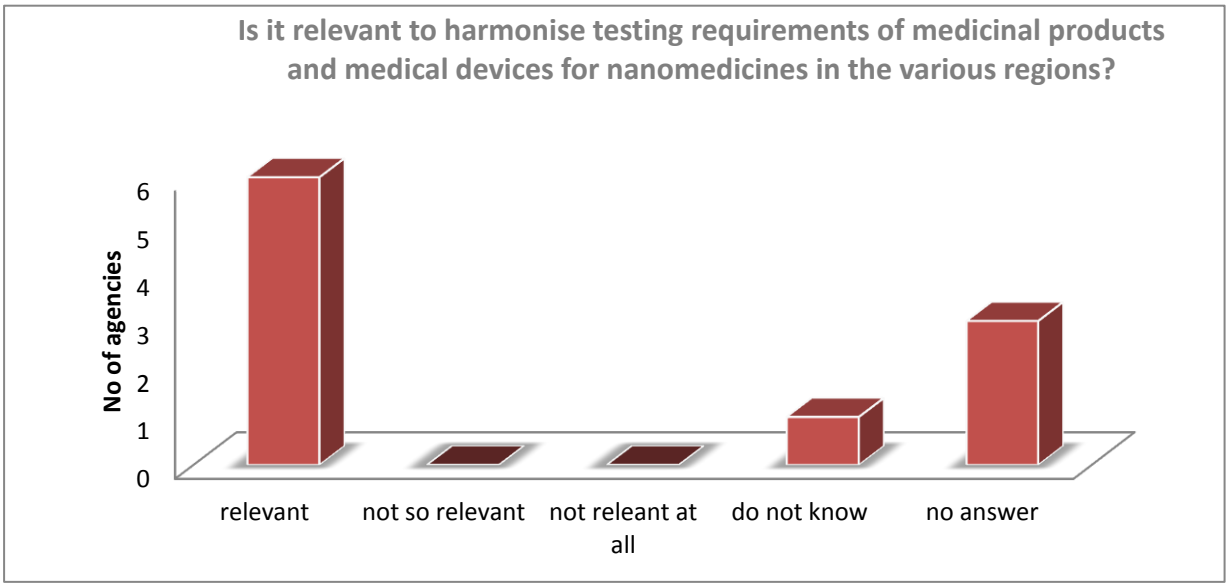


The agencies favored that the nanotechnology based pharmaceutical should be compared with the best medicine on the market.

3.3 Supporting the acceptance of nanotechnology based products in the health sector

Some products based on nanotechnology are classified as medical devices in Europe and as medicinal product in other regions (and vice versa). The respondents were asked whether a harmonisation of testing requirements of medicinal products and medical devices for nanotechnology based products in the various regions is relevant. Six out of nine agencies confirmed the need of such a harmonisation activity (Figure 15).

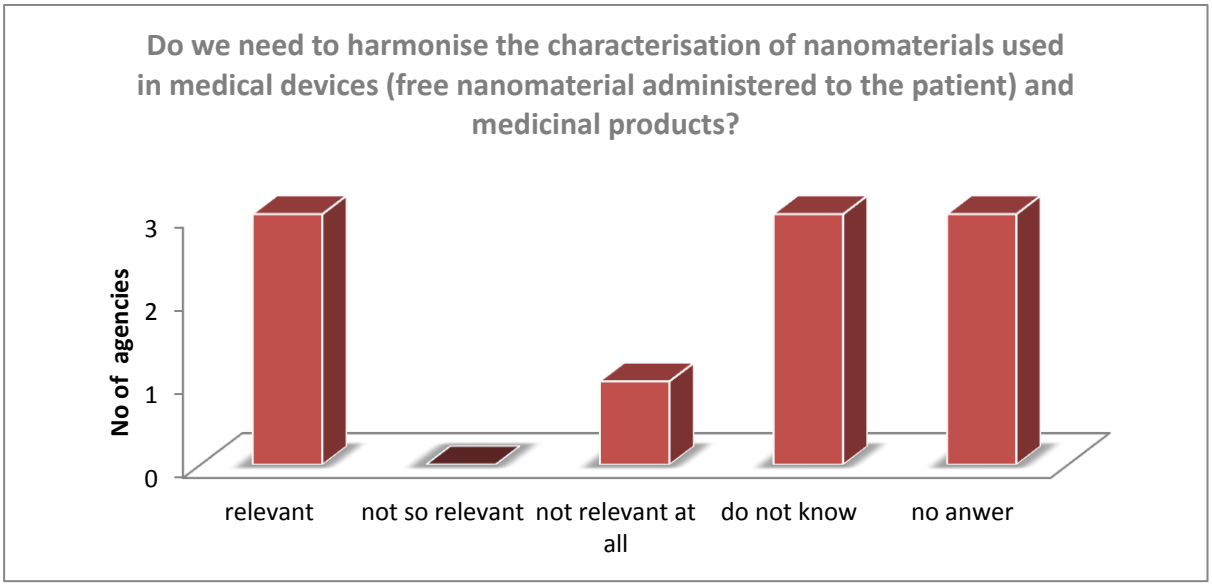
Figure 15: Harmonisation of testing requirements of medicinal products and medical devices for nanomedicines in the various regions



The harmonisation of testing requirements should be harmonised between the different regions.

The need to harmonise also characterisation of nanomaterials used in medical devices and medicinal products might be of interest in particular for borderline products for which the regulatory path is not defined in the phase of preclinical development. A number of materials e.g. metal oxides currently in the phase of development might fall in this category as they use mainly physical means to exert the therapeutic actions. Three agencies considered such activities as relevant. However, the majority of respondents have not replied to the questions or had no opinion on this need (Figure 16).

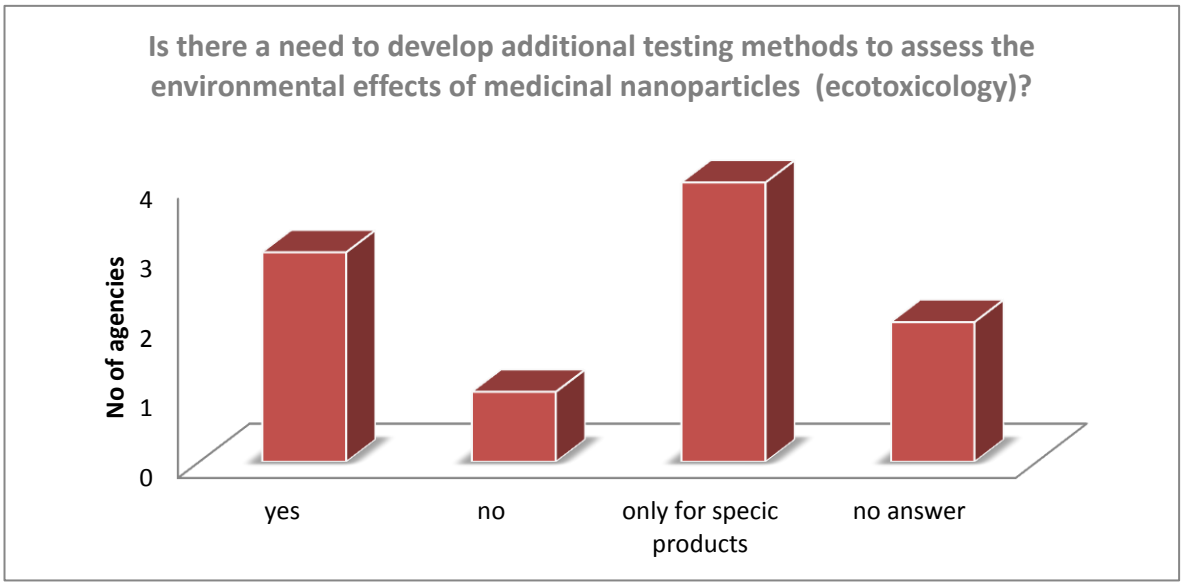
Figure 16: Harmonisation of characterisation needs of nanoparticles that will either be regulated as medicinal products or medical devices (borderline products).



Three agencies supported the need to harmonise the characterisation of nanoparticles regulated as medicinal product or medical devices.

In order to assess the impact of nanomedicines on the environment, some agencies felt a need to make additional methods available (Figure 17).

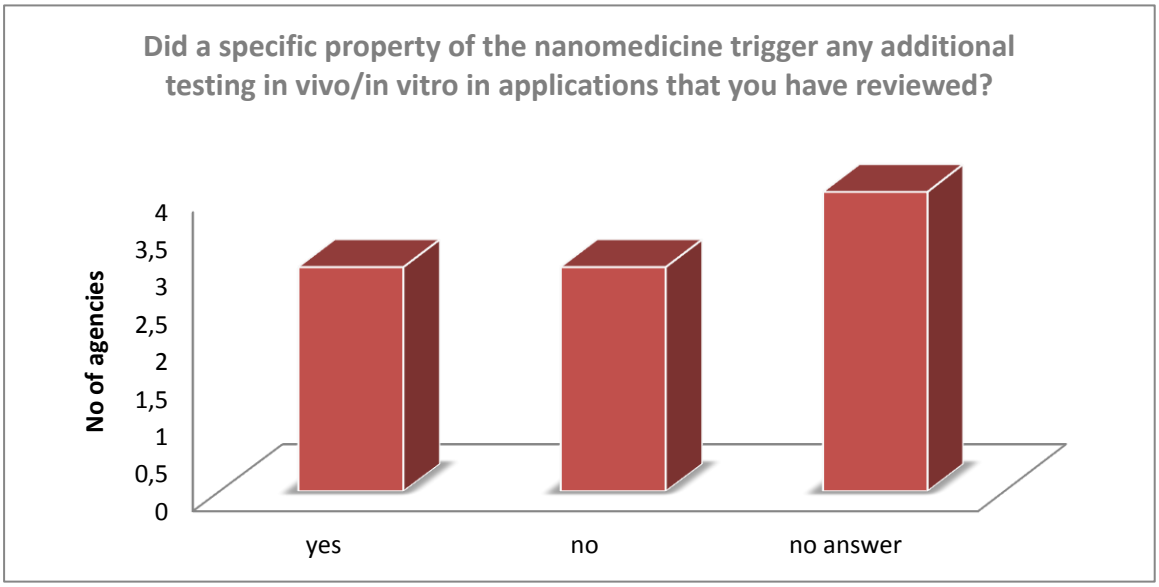
Figure 17: Development of specific test methods for ecotoxicology



The agencies agreed that testing methods for assessing effects on the environment might be needed.

An important question when characterising nanomedicines was related to additional toxicity testing requirements. Three agencies reported that they experienced additional toxicity testing needs due to the involvement of nano-specific characteristics (Figure 18).

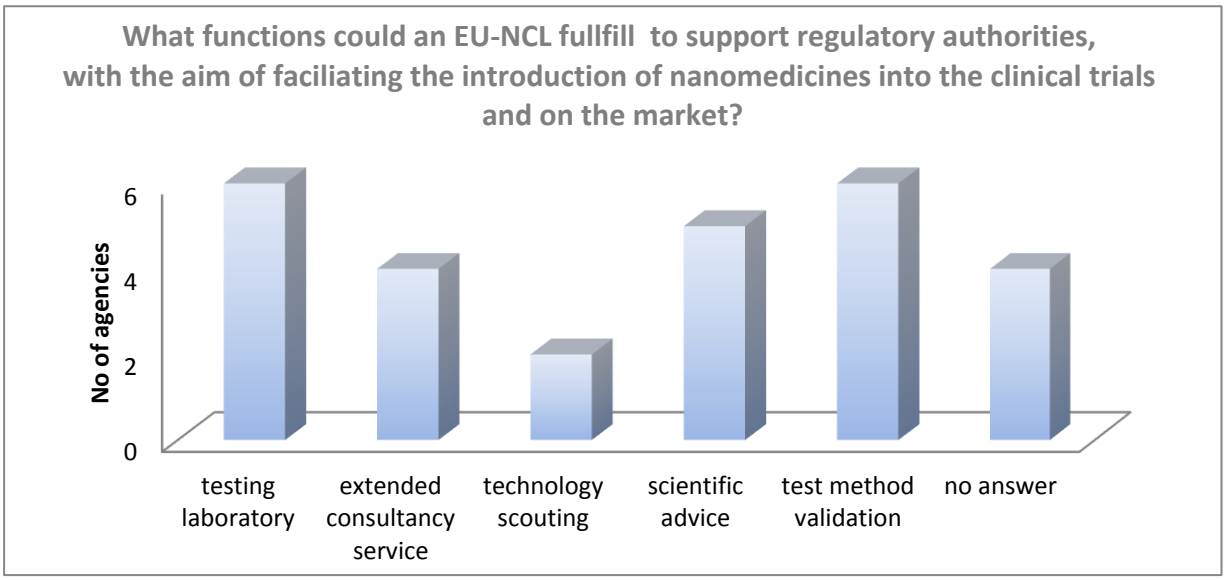
Figure 18: Additional toxicity testing due to nano-specific properties



Three agencies reported that the nano-specific property has triggered additional toxicity testing.

Finally, the agencies provided their opinion on how the EU-NCL could support their work in regulating nanomedicines (the respondents were allowed to tick several tasks) (Figure 19).

Figure 19: Functions of an EU-NCL to support regulatory authorities



The agencies understand that a European Nanomedicine Characterisation Laboratory can support regulators in the validation of tests methods and as a testing facility.

4. Discussion

4.1. Regional differences in the regulation of nanomedicines

The first set of questions revealed the current experience of regulators with nanomedicines. Previous studies evaluated that nearly 250 nanomedicines are approved or in various stages of clinical studies worldwide [22]. Though, the European Medicines Agency (EMA) only reported on 11 marketing authorisation applications for nanomedicines and approximately 50 nanomedicines and nanoimaging agents in the phase of clinical development (Phase I–III) in Europe [23,24]. However, it should be stressed that the EMA is not responsible for authorising clinical trials and for national or decentralized marketing authorisations. The significant regional differences of nanomedicine applications for market authorisation were confirmed in the recent survey and raised the question why the ecosystem of some regions is more suitable for the marketing of nanomedicines even if they seem to address relevant markets such as oncology. Several economic analyses have forecasted the growth of the nanomedicine market at global level [25]. In this context, the United States is the most successful region making nanomedicines available to the patient [22].

In the view of the still limited number of approved nanomedicines in most countries and the heterogeneity of the product class, it is very difficult to obtain robust data sets allowing making general conclusions on the information requirements related to their quality and safety [26]. The restricted amount of experience of most agencies might also explain the overall response rate to the questionnaire of 50% and the low response rates in particular to those questions that require "hands-on" experiences with the regulation of nanomedicines. In this context, it is of particular importance to share knowledge among the regulatory bodies in order to train regulators of those regions where an increasing rate of approval requests must be expected in the future. The sharing of regulatory experience is also of high relevance for a harmonized regulatory governance of nanotechnology products and was considered as an important objective of the IPRF *Nanomedicines Working Group*.

Another caveat for a harmonized regulation of nanomedicines is the current lack of a consistent terminology and categorization of nanomedicines which complicates the communication between agencies and eventually also explains the response rate to the survey. The establishment of a common language is often a challenge for emerging products and should be addressed at an early stage [26–28]. The need for an agreed terminology was identified as another important objective for the IPRF working group [29,30].

According to the scientific literature, the so called follow-on products ("nanosimilars") will pose additional challenges for the regulation of nanomedicines [23,31]. Follow-on products are similar to an innovator products for which the patent has expired. Currently there is no specific regulatory framework for "nanosimilars" but regulatory bodies have provided initial guidance in reflection papers. However, the survey demonstrated that only a few so called "nanosimilars" have requested a market authorization. But also for this question, the survey indicated regional differences demonstrating that follow-on products might be an upcoming challenge for the European regulators. A prominent example is the drug "Doxorubicin SUN" which is accepted as a generic drug of the reference product "Doxil" in the US. "Doxorubicin SUN" was presented in Europe as a generic liposomal formulation of doxorubicin referring to the European innovator product

Caelyx®. The assessment report on "Doxorubicin SUN" of the Committee for Medicinal Products for Human use recommended: *"… is not approvable since there are outstanding major non-clinical and clinical objections which preclude a recommendation for marketing authorisation at the present time ….*The product was not recommended to be authorised for the European Market due to major non-clinical and clinical objections [32].

The selection of the regulatory path for certain products involving nanotechnology has triggered the attention of regulatory scientists and lawyers [33,34]. In particular, sophisticated products for which the regulatory path is blurry (borderline products) or complex products such as theranostics combining diagnostic and therapy agents (combination products) will require special regulatory awareness. These issues have to be quickly addressed since uncertainties of the regulatory information requirements might affect investments that are needed for further product development. The challenge of regulating borderline products is widely recognised and already flagged as a priority in EU Medicines Agencies Network Strategy to 2020 document [35]. Nevertheless, the number of nanomaterials which are freely administered to the patients and are proposed as medical devices is still low. In any case, six agencies indicated a need to harmonise the requirements related to the characterisation of nanomaterials in medicinal products and medical devices since the information requirements might differ between the concerned legislative frameworks of health products (Figure 16). In addition, certain products might follow different regulatory paths in the various regions. As the EU-NCL will characterise nanomaterials independently of the regulatory path that the products will follow at a later stage, the EU-NCL will provide protocols and testing strategies that are tailored to particle categories, compositions and functionalization. Furthermore, the strong collaboration between the US NCI-NCL and the EU-NCL will allow a harmonisation of testing methods and the characterisation strategies which will support the mutual acceptance of data at both sides of the Atlantic.

4.2 Identification of information needs for regulating nanomedicines

The definition of information needs related to the nano-specific properties of a medicinal product which can have an impact on the quality, safety and efficacy is one of the biggest challenges ahead. Currently only very few accepted methods from standardisation bodies specifically addressing the application of nanotechnology in the health sector are available (Table 4), which can contribute to national and regional variations in the information needs. The survey of Satalkar et al (2016) [36] supports this hypothesis as respondents confirmed regional and national differences of individual requirements leading to significant challenges for researchers running multicentrical international clinical trials.

Table 4: Standards specifically addressing the application of nanotechnology in the health sector

Test method	Endpoint	Reference	Comments
Determination of silver nanoparticles potency by release of muramic acid from Staphylococcus aureus [37]	Antimicrobial efficacy	ISO/TS 16550:2014	Not only pharmaceutical products but also textile products, other consumer products
Standard Test Method for Analysis of Hemolytic Properties of Nanoparticles [38]	Biocompatibility, hemolytic properties	ASTM E2524 - 08(2013)	Similar to Practice F756 but modified to accommodate nanoparticulate materials
Standard Test Method for Evaluation of Cytotoxicity of Nanoparticulate Materials in Porcine Kidney Cells and Human Hepatocarcinoma Cells [39]	Cytotoxicity assessment using MTT and LDH assays	ASTM E2526 - 08(2013)	
Standard Test Method for Evaluation of the Effect of Nanoparticulate Materials on the Formation of Mouse Granulocyte-Macrophage Colonies [40]	Immunological response	ASTM E2525 - 08(2013)	
New Test Method for Measuring the Size of Nanoparticles in Aqueous Media Using Batch-Mode Dynamic Light Scattering [41]	Size measurement	ASTM WK54872	Under development; designed for NPs for biomedical applications

In order to support the identification and development of new standards, some regulatory bodies have started to collect the available knowledge e.g. by reviewing submissions of the agencies and published initial guidance [17–20,42]. Within a series of workshops, regulators currently discuss and seek for consensus on standardisation needs for example under the umbrella of the Global Summit on Regulatory Science [43]. Based on their 10 years' experience in testing nanomedicines, the US NCI-NCL collaborates with the US Federal Drug Administration (FDA) in order to support the identification of standardisation needs. The need of a similar nanocharacterisation and toxicological testing laboratory in Europe was also stressed by Saltakar et al (2016) [36]. The recently established EU-NCL aims to provide additional trend analysis and contribute to the enlargement of a knowledge base that allows the anticipation of regulatory needs in Europe. An initial list of parameter for the characterisation of nanoparticles and their toxicity used as medical devices has been proposed by the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [16]. The European Medicines Agency published a number of reflection papers on selected categories of nanomedicines indicating physicochemical properties that should be considered when developing nanomedicines and preparing the marketing authorisation

[17–20]. Finally, also the EU flagship project NANoREG organised a virtual workshop to identify, formulate and prioritize relevant issues and questions related to the safety of nanomaterials in consumer products [21]. The recommendations of the various activities demonstrated a similarity of information requirements of various sectors using nanotechnology and were mostly confirmed within this survey (see Figure 8). A significant number of characteristics are already addressed in the existing EU-NCL testing cascade and options to further expand the list to requirements that are not covered yet have been proposed by the EU-NCL consortium (Table 5).

Table 5: Mapping of critical information needs for preclinical evaluation proposed by regulatory scientists and EU-NCL testing cascade

Information needs to nanospecific characteristics (not exhaustive)	No of agencies considering information as relevant for the approval of clinical trials (n=7)	EU-NCL testing cascade	Could be further developed
Size and size distribution	7	DLS, FFF-MALS, TEM	
Physical form/morphology/shape	7	TEM	
Surface chemistry	6		e.g.TOF/SIMS, SPR
Surface charge	6	Zeta potential	
Stability	7	DLS	
Redox potential	7	-	
Solubility and partition properties	6		e.g. Hydrophobicity
Density	6		Ultracentrifugation
Chemical reactivity/catalytic activity	7	-	
Drug release	7	LC-MS, HPLC-UV	
Photocatalytic activity	7	-	
Functionality of targeting moieties	7		Circular dichoroism, SPR
Agglomeration/aggregation behavior	7	DLS	
Endotoxin assessment	7	Kinetic turbidity LAL assay	
Interaction between test reagent and the nanomaterial	5		UV spectrophotometer
Solubilised fraction before and during the testing of metals and metal oxides	2		ICP-MS

Beside the need for accurate characterisation of physicochemical properties allowing the monitoring of the quality of nanomedicines, a number of articles have investigated the relevance of additional toxicity assessments for nanomedicines [44–46]. Also the present survey indicated that specific properties of nanomedicines can trigger additional *in vitro* and *in vivo* testing (Figure 19). The scientific literature has focussed in particular on the interaction of the nanomaterials with the blood and immune system since the latter can recognise intravenously administered materials as foreign and trigger different kind of immune responses. Furthermore, the materials can be hazardous to the blood system as it is the first target organ that is exposed to the highest concentration [47–51]. A better understanding of nano-specific effects on target tissues will support the identification of the hazardous potential already in the preclinical phase. Furthermore, such knowledge can inform decision maker on the need for additional toxicity assessments. Specific *in vitro* tests should be made available before introducing additional laborious and expensive animal experiments in biomedical research and preclinical testing. Furthermore, most of the currently available *in vitro* tests have been developed/validated for small molecules and the question of their suitability for nanoparticles has to be proven.

Further investigations are also necessary to understand which product classes have to demonstrate the safety for the environment and what kind of environmental tests could be of interest in this context.

The availability of standardised methods and relevant guidance documents addressing the regulatory perspective on nano-specific properties can provide more confidence for product developer to further invest in innovative nanomedicines.

5. Conclusions

The recent survey confirmed that some regions are more advanced in marketing nanomedicines than others. These regional differences call for a close collaboration of various regulatory bodies in order to share experiences in the assessment of nanotechnology based products. It will allow training scientists who will be confronted with more nanomedicine applications in the future. One prerequisite for such collaborations is the availability of a consistent terminology and categorization of nanomedicines facilitating the communication between agencies. In addition, also particular challenges such as the evaluation of "nanosimilars", borderline and combination products will require special regulatory awareness and are already on the agenda of international working groups such as the Nanomedicines Working Group of the IPRF.

Regulatory scientists working for different legislative frameworks outlined a number of crucial information requirements allowing assessing the quality and safety of nanotechnology based products. A selection of such physicochemical parameters resulted from this survey. However, for most of the proposed parameters no standards are available yet and the reliability and relevance of the analytical methods should be assessed and be available for their use in regulatory testing. Special emphasis should be given to the identification of *in vitro* tests that have the potential to identify toxic effects triggered by the nano-specific property of the formulation. Such tests can contribute to the reduction of animal experiments in biomedical research and non-clinical testing and will support product development by an early detection of hazards.

The strategic partnership of the EU-NCL and the NCI-NCL can support such discussions by providing scientific/technical expertise on information needs, technology scouting as well as the development and validation of new test methods in particular related to the physicochemical characterisation and *in vitro* testing. A concerted action between the NCLs would promote the marketing of products on both sides of the Atlantic.

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List of Figures

List of Tables

Abbreviations

CLINAM	European Foundation for Clinical Nanomedicine
DLS	Dynamic Light Scattering
EMA	European Medicines Agency
ETPN	European Technology Platform on Nanomedicines
EU-NCL	European Nanomedicine Characterisation Laboratory
FDA	Food and Drug Administration
FFF	Field Flow Fractionation
GSRS	Global Summit on Regulatory Science
IPRF	International Pharmaceutical Regulators Forum
LC-MS	Liquid Chromatography-Mass Spectrometry
MALS	Multi-Angle-Light Scattering
NANoREG project	"A common European Approach to the regulatory testing of nanomaterials" funded by the European Union's 7th Framework Programme
NCI-NCL	National Cancer Institute-Nanotechnology Characterization Laboratory
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SPR	Surface Plasmon Resonance
TEM	Transmission Electron Microscopy
TOF/SIMS	Time-of-Flight Secondary Ion Mass Spectrometry

ANNEX 1 Statistics: Current status of regulating nanomedicines

The full text of the questionnaire – including the introductory text – is given below, for reference.

General Information

Background

On May 1, 2015, the European Union's Horizon 2020 research and innovation programme has launched the first trans-disciplinary testing infrastructure for the characterisation of medicinal products involving nanotechnology, EU-NCL (https://ec.europa.eu/jrc/en/news/eu-ncl-launched). The Laboratory is a cooperative arrangement between six European Laboratories and the Nanocharacterisation Laboratory (NCI-NCL) of the United States (http://ncl.cancer.gov/) fostering the development of new or improved analytical tests and the quality management of medicinal nano-products. The facilities will offer access to their existing analytical services for public and private developers in order to characterise the quality and safety of nanomedicines* that are aiming to enter into clinical trials.

Aims

As nanomedicine is an emerging product class with additional safety testing requirements, critical quality attributes and safety parameter needs to be identified and translated into suitable test methods and testing strategies. In order to ensure that methods developed/validated in the EU-NCL are relevant for regulatory purposes and the obtained information can support the regulatory decision making, the project proposal has included a series of questionnaires addressed to competent authorities that are approving clinical trials and authorising the product for marketing.

Due to its independence of national or commercial interests, its proximity to EU policy-makers as well as its expertise in nanotechnology, the Joint Research Centre of the European Commission is involved in the identification of the regulatory needs for the characterisation of the nanomaterial in medicinal products.

Methodology

The survey is the first out of three surveys within the next 4 years aiming to ensure the relevance of the testing cascade for regulatory purposes.

The questions have been defined according to recommendations of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)[1], the NCI-NCL, the expert team of the EU-NCL and EMA's reflection papers related to nanomedicine. In addition, a similar questionnaire performed within the EU project "NanoReg" on manufactured nanoparticles has been taken into account. In order to avoid any bias, interviewees have the possibility (and are encouraged) to include additional information not covered by the predefined questions. The first survey will be performed within the International Pharmaceutical Regulators Forum (IPRF) "Nanomedicine" working group. Members of the working group have already indicated their interest in the survey and

offered advice to further improve the questions. It is of high relevance to include information that is considered relevant at international level before a second questionnaire will be submitted to regulators of the competent authorities in the European Memberstates. (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2008_01_CTFG_Mandate.pdf). As such the survey will also contribute to the standardisation and harmonisation of testing requirements for nanomedicines.

[1] Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices (2015)

Disclaimer

This survey is intended to facilitate and assist the establishment of the EU-NCL supporting the translation of nanomedicines towards clinical trials and marketing authorisation. This requires an improved understanding of the regulatory authorities' needs and wishes. The answers given here are not presumed to be either limiting or formally binding for the respondents nor will they be published.

Contact information

For questions or comments not entered in the survey, please contact either Susanne Bremer-Hoffmann (JRC ; email: Susanne.BREMER-HOFFMANN@ec.europa.eu; phone +39 0332785914) or Sven Even Borgos (SINTEF; email: Sven.E.Borgos@sintef.no; phone +47 959 91 348).

Identifier

Information on name, organisation, department and email address was requested here.

Questionnaire

Approval of clinical trials

1. How many clinical trial applications have been submitted to your institution/department in the last 5 years?

		Answers	Ratio
None		3	27.27%
< 5		3	27.27%
5-10		1	9.09%
More than 10		3	27.27%
My Institution/department is not responsible for the approval of clinical trials (please proceed with question 10)		1	9.09%
No Answer		0	0%

2. Were the submitted data on the quality of the formulations sufficient for the approval of first-in-man studies?

		Answers	**Ratio**
yes		5	45.45%
no		0	0%
No Answer		6	54.55%

3. Which physicochemical properties do you consider relevant for the preclinical characterisation of nanomedicines that are currently not applicable to other pharmaceutical product classes e.g. small molecules (nanomedicine-specific knowledge gaps)? Size and size distribution

		Answers	Ratio
always		6	54.55%
depends on the nature of the nanomedicine		1	9.09%
not relevant		0	0%
No Answer		4	36.36%

Physical form/morphology/shape

		Answers	Ratio
always		2	18.18%
depends on the nature of the nanomedicine		5	45.45%
not relevant		0	0%
No Answer		4	36.36%

Surface chemistry

		Answers	Ratio
always		2	18.18%
depends on the nature of the nanomedicine		4	36.36%
not relevant		1	9.09%
No Answer		4	36.36%

Surface charge

		Answers	**Ratio**
always		2	18.18%
depends on the nature of the nanomedicine		4	36.36%
not relevant		1	9.09%
No Answer		4	36.36%

Stability (Chemical/enzymatical/integral)

		Answers	**Ratio**
always		5	45.45%
depends on the nature of the nanomedicine		2	18.18%
not relevant		0	0%
No Answer		4	36.36%

Redox potential

		Answers	Ratio
always		0	0%
depends on the nature of the nanomedicine		7	63.64%
not relevant		0	0%
No Answer		4	36.36%

Solubility and partition properties

		Answers	Ratio
always		3	27.27%
depends on the nature of the nanomedicine		3	27.27%
not relevant		1	9.09%
No Answer		4	36.36%

Density

		Answers	Ratio
always		0	0%
depends on the nature of the nanomedicine		6	54.55%
not relevant		1	9.09%
No Answer		4	36.36%

Chemical reactivity/catalytic activity

		Answers	Ratio
always		2	18.18%
depends on the nature of the nanomedicine		5	45.45%
not relevant		0	0%
No Answer		4	36.36%

Drug release

		Answers	Ratio
relevant		6	54.55%
not relevant		0	0%
do not know		1	9.09%
No Answer		4	36.36%

Photo catalytic activity

		Answers	Ratio
relevant		4	36.36%
not relevant		0	0%
do not know		3	27.27%
No Answer		4	36.36%

Functionality of targeting moieties

		Answers	Ratio
relevant		4	36.36%
not relevant		0	0%
do not know		3	27.27%
No Answer		4	36.36%

4. Were the characterisation methods used for quality assessments in the applications for clinical trials, well described and sufficiently validated for the assessment of the nanomaterial?

		Answers	Ratio
yes		2	18.18%
no		3	27.27%
No Answer		6	54.55%

5. Were the submitted data on the biological characterisation (toxicity/biocompatibility) sufficient for the approval of clinical trials?

		Answers	Ratio
yes		4	36.36%
no		1	9.09%
No Answer		6	54.55%

6. How do you value potential pitfalls for toxicity testing (in vitro/in vivo) that may impact the correct judgement on the interaction with the biological system: Agglomeration/aggregation behaviour

		Answers	Ratio
5 (very important)		4	36.36%
4		2	18.18%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		0	0%
No Answer		4	36.36%

Endotoxin assessment

		Answers	Ratio
5 (very important)		6	54.55%
4		0	0%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		0	0%
No Answer		4	36.36%

Stability and uniformity of the nanomaterial in the test medium ensuring the maintenance of the applied concentration/dose

		Answers	Ratio
5 (very important)		6	54.55%
4		1	9.09%
3		0	0%
2		0	0%
1 (not important at all)		0	0%
do not know		0	0%
No Answer		4	36.36%

Demonstration of a lack of interaction between the test reagents and the nanomaterials (e.g. colorimetric assays)

		Answers	Ratio
5 (very important)		1	9.09%
4		3	27.27%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		2	18.18%
No Answer		4	36.36%

Determination of the solubilised fraction before and during the testing of metals and metal oxides

		Answers	Ratio
5 (very important)		1	9.09%
4		0	0%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		4	36.36%
No Answer		5	45.45%

7. Which metrics (metrology) should be used for nanomedicines in regulatory toxicology?

		Answers	Ratio
mass		0	0%
Surface area (if possible)		1	9.09%
number of particles		1	9.09%
weight/volume concentation		0	0%
combination		5	45.45%
No Answer		4	36.36%

8. Shall nanomedicines be tested as:

		Answers	Ratio
drug-free carrier		0	0%
formulation		1	9.09%
both		6	54.55%
No Answer		4	36.36%

Market Authorisation

9. How many applications on nanomedicines seeking for market authorisation have been submitted to your institution in the last 5 years?

		Answers	Ratio
None		4	36.36%
<5		3	27.27%
From 5 to 10		2	18.18%
More than 10		2	18.18%
No Answer		0	0%

10. Were the submitted data on the physicochemical characterisation of the nanomedicine sufficient for market authorisation?

		Answers	Ratio
yes		5	45.45%
no		2	18.18%
No Answer		4	36.36%

11. Were the characterisation methods used for quality assessments in the applications sufficiently described and validated for the assessment of the nanomedicine?

		Answers	Ratio
yes		5	45.45%
no		1	9.09%
No Answer		5	45.45%

12. Was the obtained information on the biological characterisation (toxicity/biocompatibility) sufficient for the authorisation of the nanomedicine?

		Answers	Ratio
yes		6	54.55%
no		1	9.09%
No Answer		4	36.36%

13. The impact of medicinal products on the environment has to be demonstrated: Is there a need to develop additional testing methods to assess the environmental effects of medicinal nanoparticle (ecotoxicology)?

		Answers	Ratio
yes		3	27.27%
no		1	9.09%
only for specific products		4	36.36%
No Answer		3	27.27%

14. Did a specific property of the nanomedicine trigger any additional testing in vivo/in vitro in applications that you have reviewed?

		Answers	Ratio
yes		3	27.27%
no		3	27.27%
No Answer		5	45.45%

15. How do you value potential pitfalls for toxicity testing (in vitro/in vivo) that may impact the correct judgement of toxicological data: Agglomeration/aggregation behaviour

		Answers	Ratio
5 (very important)		4	36.36%
4		2	18.18%
3		3	27.27%
2		0	0%
1 (not important at all)		0	0%
do not know		0	0%
No Answer		2	18.18%

Stability and uniformity of the nanomaterial in the test medium ensuring the maintenance of the applied concentration/dose

		Answers	Ratio
5 (very important)		6	54.55%
4		2	18.18%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		0	0%
No Answer		2	18.18%

Endotoxin assessment

		Answers	Ratio
5 (very important)		5	45.45%
4		1	9.09%
3		3	27.27%
2		0	0%
1 (not mportant at all)		0	0%
do not know		0	0%
No Answer		2	18.18%

Demonstration of a lack of interaction between the test reagents and the nanomaterials (e.g. colorimetric assays)

		Answers	Ratio
5 (very important)		4	36.36%
4		2	18.18%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		2	18.18%
No Answer		2	18.18%

Determination of the solubilised fraction before and during the testing of metals and metal oxides

		Answers	Ratio
5 (very important)		4	36.36%
4		0	0%
3		1	9.09%
2		0	0%
1 (not important at all)		0	0%
do not know		4	36.36%
No Answer		2	18.18%

16. Which metrics (metrology) should be used for nanomedicines in regulatory toxicology?

		Answers	Ratio
mass		1	9.09%
surface area (if possible)		0	0%
number of particles		0	0%
weight/volume concentration		0	0%
combination		8	72.73%
others		0	0%
No Answer		2	18.18%

17. Should the nanomedicinal product be tested as

		Answers	Ratio
drug free carrier		0	0%
only in the final product		1	9.09%
both		7	63.64%
No Answer		3	27.27%

18. Did you receive applications for follow on nanomedicines that claim to be similar to an innovator product in the last 36 months?

		Answers	Ratio
none		3	27.27%
<5		4	36.36%
5-10		0	0%
more than 10		1	9.09%
No Answer		3	27.27%

19. Were the submitted data for follow-on nanomedicines sufficient for regulatory decision making? For quality assessments

		Answers	Ratio
yes		3	27.27%
no		2	18.18%
No Answer		6	54.55%

For safety assessments

		Answers	Ratio
yes		3	27.27%
no		1	9.09%
No Answer		7	63.64%

20. How many nanomaterials (free nanomaterial administered to the patient) have been regulated by your agency within the medical device framework in the last 36 month

		Answers	Ratio
none		2	18.18%
<5		1	9.09%
5-10		0	0%
more than 10		0	0%
No Answer		8	72.73%

21. Were the submitted data sufficient for regulating the medical device involving nanotechnology? for quality assessments

		Answers	Ratio
yes		1	9.09%
no		1	9.09%
No Answer		9	81.82%

For safety assessments

		Answers	Ratio
yes		1	9.09%
no		1	9.09%
No Answer		9	81.82%

22. Do we need to harmonise the characterisation of nanomaterial properties used in medical devices (free nanomaterial administered to the patient) and medicinal products?

		Answers	Ratio
relevant		3	27.27%
not so relevant		0	0%
not relevant at all		1	9.09%
do not know		3	27.27%
No Answer		4	36.36%

23. Some products containing nanomaterials are classified as medical devices in Europe and as medicinal product in the US (and vice versa). Is it relevant to harmonise testing requirements of medicinal products and medical devices for nanomedicines in the various regions?

		Answers	Ratio
relevant		6	54.55%
not so relevant		0	0%
not relevant at all		0	0%
do not know		1	9.09%
No Answer		4	36.36%

24. Did you regulate or were involved in discussions related to products containing nanomaterial that raises challenges regarding the regulatory pathway e.g. combination or borderline products?

		Answers	Ratio
none		2	18.18%
<5		2	18.18%
5-10		1	9.09%
more than 10		0	0%
No Answer		6	54.55%

25. What will be the reference for comparison of nanoparticle-delivered drugs from a cost/benefit perspective?

		Answers	Ratio
free drug		1	9.09%
best medicine currently on the market		4	36.36%
'gold standard' not necessarily commercially available		0	0%
other standards		1	9.09%
No Answer		5	45.45%

26. What will be the reference for comparison of nanoparticle-delivered drugs from a safety/efficacy perspective?

		Answers	Ratio
free drug		2	18.18%
best medicine currently on the market		3	27.27%
'gold standard' not necessarily commercially available		0	0%
other standards		2	18.18%
No Answer		4	36.36%

27. What functions could the EU-NCL fulfil to support regulatory authorities, with the aim of facilitating the introduction of nanomedicines into the clinical trials and on the market (tick all that apply)?

		Answers	**Ratio**
testing laboratory		6	54.55%
extended consultancy services to companies		4	36.36%
technology scouting		2	18.18%
scientific advise		5	45.45%
test method validation (ring trials)		6	54.55%
No Answer		4	36.36%

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