


## REVIEW

View Article Online  
View Journal | View Issue



Cite this: *Biomater. Sci.*, 2020, **8**, 4653

# The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives

Rachel Foulkes,<sup>a</sup> Ernest Man,<sup>b</sup> Jasmine Thind,<sup>a</sup> Suet Yeung,<sup>a</sup> Abigail Joy<sup>a</sup> and Clare Hoskins <sup>\*a,b</sup>

The use of nanomaterials in biomedicine has increased over the past 10 years, with many different nano-particle systems being utilised within the clinical setting. With limited emerging success in clinical trials, polymeric, metallic, and lipid based nanoparticles have all found a place in medicine, with these generally providing enhanced drug efficacy or therapeutic effect compared to the standard drug treatments. Although there is great anticipation surrounding the field of nanomedicine and its influence on the pharmaceutical industry, there is currently very little regulatory guidance in this area, despite repeated calls from the research community, something that is critical to provide legal certainty to manufacturers, policymakers, healthcare providers and the general public. This is reflected in the lack of an international definition of what these materials are, with several bodies, including the National Institute of Health, USA, the European Science Foundation and the European Technology Platform, having differing definitions, and the FDA having no clear definition at all. The uncertainty created by the lack of consistency across the board may ultimately impact funding, research and development of such products negatively thus destroying public acceptance and perception of nano-products. This review aims to discuss the use of nanomaterials within the clinical setting, why regulation of these materials is so important, and the challenges faced in regulating these materials generally, as well as the current regulation used in different nations.

Received 8th April 2020,  
Accepted 9th July 2020  
DOI: 10.1039/d0bm00558d  
rsc.li/biomaterials-science

## Introduction

The broad definition of nanotechnology is based upon the use and application of materials within the nanometre range. This incredibly minute range provides many benefits across a wide range of applications<sup>1</sup> including for electronics,<sup>2</sup> sunscreens,<sup>3</sup> cosmetics,<sup>4</sup> energy storage<sup>5</sup> and drug delivery.<sup>6</sup> The size of these particles often confers unique and desirable properties when in their nanoscale form, including chemical, physical and biological properties, that may be beneficial over their larger equivalents.<sup>7</sup> Nanoscale medicines can be highly beneficial considering that many biological significant molecules such as water, antibodies, proteins, glucose, enzymes, haemoglobin and receptors all fit within this range (Fig. 1).<sup>8</sup> The application of nanotechnology within the field of medicine was expected to have a revolutionary impact on healthcare. Despite this, the expectation has not matched the initial hype,

though most working in the field contribute this to the fact that nanomedicine is still in its infancy and lack of clarity over regulation for clinical use is greatly hindering their translation.<sup>9,10</sup> Although we have very little knowledge or data regarding the pharmacokinetics, pharmacodynamics and toxicity of many nanomaterials in humans, there are several conceivable benefits of such technologies. There remains great anticipation surrounding the field of nanomedicine and its influence on the pharmaceutical industry, however regulatory guidance in this area is urgently required, which is critical to provide legal certainty to manufacturers, policymakers, healthcare providers and the general public.

## Properties of nanomaterials

Nanomaterials have several properties that make them suitable for a variety of clinical applications. One of the major benefits of nanoparticles is their small size of 10–200 nm allowing them to circulate the body without disrupting blood flow, as well as being able to avoid clearance by both the renal and complement systems.<sup>11</sup> The size of clinically used nano-

<sup>a</sup>School of Pharmacy and Bioengineering, Keele University, Keele, ST5 5BG, UK.  
E-mail: clare.hoskins@strath.ac.uk; Tel: +44 (0)0141 5482796

<sup>b</sup>Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1RD, UK



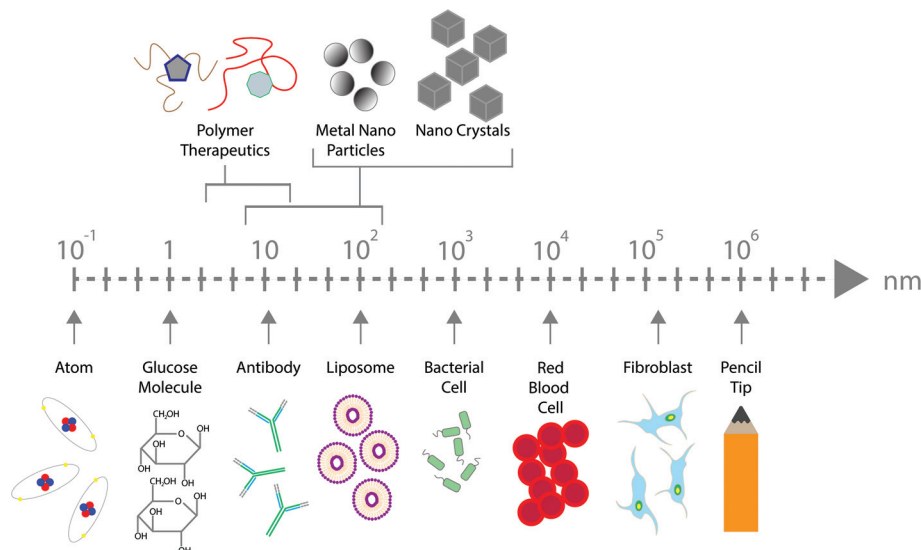


Fig. 1 Schematic representation of nanomaterial size in comparison to other biological molecules.

materials is also relevant in treatments for cancer, as it was first thought that the enhanced permeability and retention effect was one of the ways that nanoparticles could successfully penetrate tumour tissues.<sup>12</sup> However, this concept has been greatly contested within the scientific community, with very strong evidence emerging which suggests that active transport mechanisms dominating nanoparticle trafficking resulting in tumour accumulation.<sup>13</sup> Opinion on this is still divided amongst many in the community, however, as greater attention is paid to tumour microenvironment, it is becoming more clear that localised pressure within the tumour site would not be conducive to passive targeting through EPR, and is perhaps

the major limiting barrier to this phenomenon. Another key property of nanoparticles is their electronic and optical properties, particularly possessed by the metal nanoparticles. These properties are based on the principle of surface plasmon resonance; where free electrons in the metal nanoparticles oscillate.<sup>14</sup> Some metallic metal oxide nanoparticles are also magnetic, allowing them to be used for several applications such as imaging, cell separation, targeting and drug delivery. Nanomedicines are generally simple and cheap to manufacture on the small scale, however, difficulty with scale up and stability on large scale manufacture has been widely experienced.<sup>15</sup> Once manufactured, nanomaterials are relatively simple to sterilise before clinical use, with the majority being syringe filtered below the molecular cut off for biological contaminants such as bacteria.



Clare Hoskins

*Dr Clare Hoskins (FRSC, CSci) is a Reader in the School of Pure and Applied Chemistry, University of Strathclyde. She leads a vibrant interdisciplinary research group focussing on the development of a range of multi-functional nanoparticles and their translation into medical therapies and agricultural products. She has published >40 peer reviewed articles, 1 patent and her research has been supported with over £2 M funding.*

*Clare is the Elected Secretary of the RSC Chemical Nanosciences and Nanotechnology Network, and a Committee Member of the UK and Ireland Controlled Release Society. In 2019 Clare was awarded the Academy of Pharmaceutical Sciences 'Emerging Scientist' sponsored by Pfizer and also the North Staffordshire Medical Institute Researcher Award.*

## The need for nanomedicine regulation

Although there is a great deal of excitement surrounding the emerging field of nanomedicine, there is currently a lack of guidance in this field. Many nanomedicines work by direct interaction with genetic materials, or by interaction with biomolecules that are required for normal genome function and cell division,<sup>16</sup> all of which can cause genotoxicity and mutagenicity.<sup>17</sup> Such toxicity to nanomedicines is mediated by the inflammatory response of neutrophils and macrophages by the production of reactive oxygen and nitrogen species which cause oxidative and nitrosative stress.<sup>18</sup> The accumulation of such free radicals can cause extensive damage to the body.<sup>19</sup> There are several ways in which this damage can occur, including inducing oxidative DNA damage leading to strand breakage, protein denaturation and lipid peroxidation causing cancer, causing damage to mitochondrial membranes leading to cell death and necrosis, and transcription of genes respon-



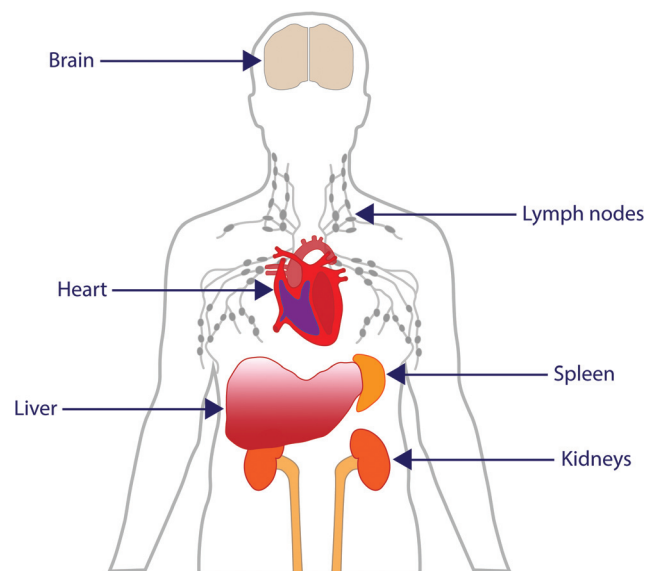


Fig. 2 Schematic representation of the main areas of nanoparticle translocation and accumulation after administration.

sible for carcinogenesis and fibrosis.<sup>20</sup> When administered intravenously, there is a wealth of data which shows accumulation of these particles within the liver, and translocation to areas such as the central nervous, cardiovascular and renal systems (Fig. 2).<sup>21</sup> For particles that have no ability for tracing after administration, there are simply too many unknowns which may pose potential threats against safety. Currently, the precise interactions of many nanomedicines with biological systems is not yet fully understood, therefore making understanding, identifying or drawing conclusions about the physicochemical and toxicological properties of nanomedicines difficult. However, without standardised regulatory gui-

dance in this area, very little is set to change. It has to also be acknowledged that 'one-size' certainly does not fit all in this process as the unique properties observed at the nano-scale are highly dependant upon nanoparticle type, surface properties, administration route and importantly nanoparticle morphology which can be diverse (Fig. 3) – something which is certainly holding up the regulatory process.

The regulatory agencies are right to be cautious, in the past, market approval has been gained for nanoparticles used in medical imaging, which subsequently have been withdrawn after the emergence of unanticipated patient events after administration.<sup>22</sup> Sinerem®, an ultra-small super paramagnetic iron oxide (USPIO) contrast agent for magnetic resonance imaging, was declined a recommendation for marketing authorisation and withdrawn from the market in 2008 by the European Medicines Agency (EMA) due to concerns raised in clinical trials. These concerns involved severe adverse reactions involving muscle pains, particularly in the lower back, and, more worryingly, allergic reactions which resulted in one death. It was therefore concluded that the risks associated with this particular nanomolecule far outweighed any potential benefits and so it was denied marketing authorisation.<sup>23</sup>

However, this over cautious approach appears to be manifesting as great inertia within the field, often the benchmark checks required for approval are still opaque and align with the regulation for small drug molecules (Fig. 4) which do not accurately reflect the nanomaterials potential. Guidance is critical as without it, manufacturers, healthcare providers, the public and policymakers are without clarity and legal certainty. The US Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and Health and Consumer Protection Directorate of the European Commission have taken initiatives in order to deal with potential risks posed by nanoparticles.<sup>24</sup>

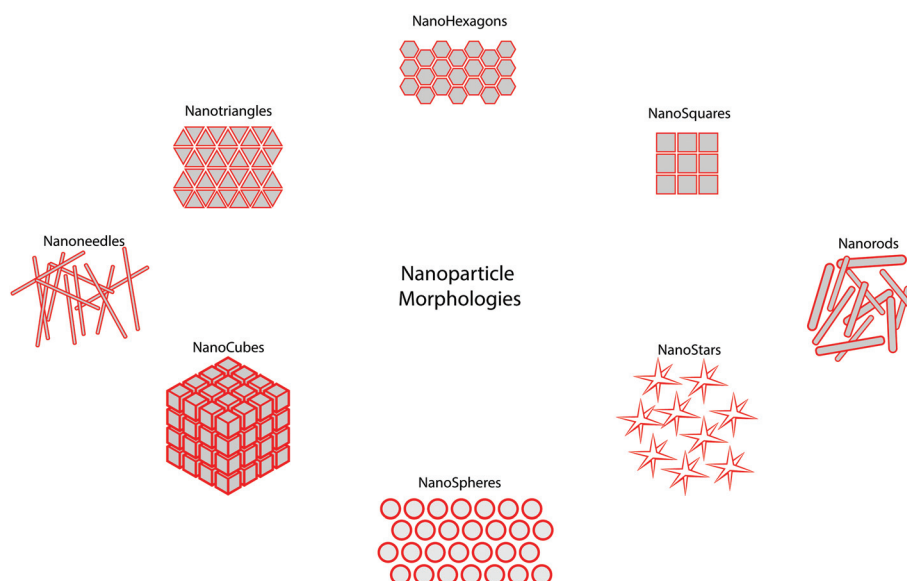


Fig. 3 Schematic representation of the diverse morphology of nanomaterials reported for clinical application.



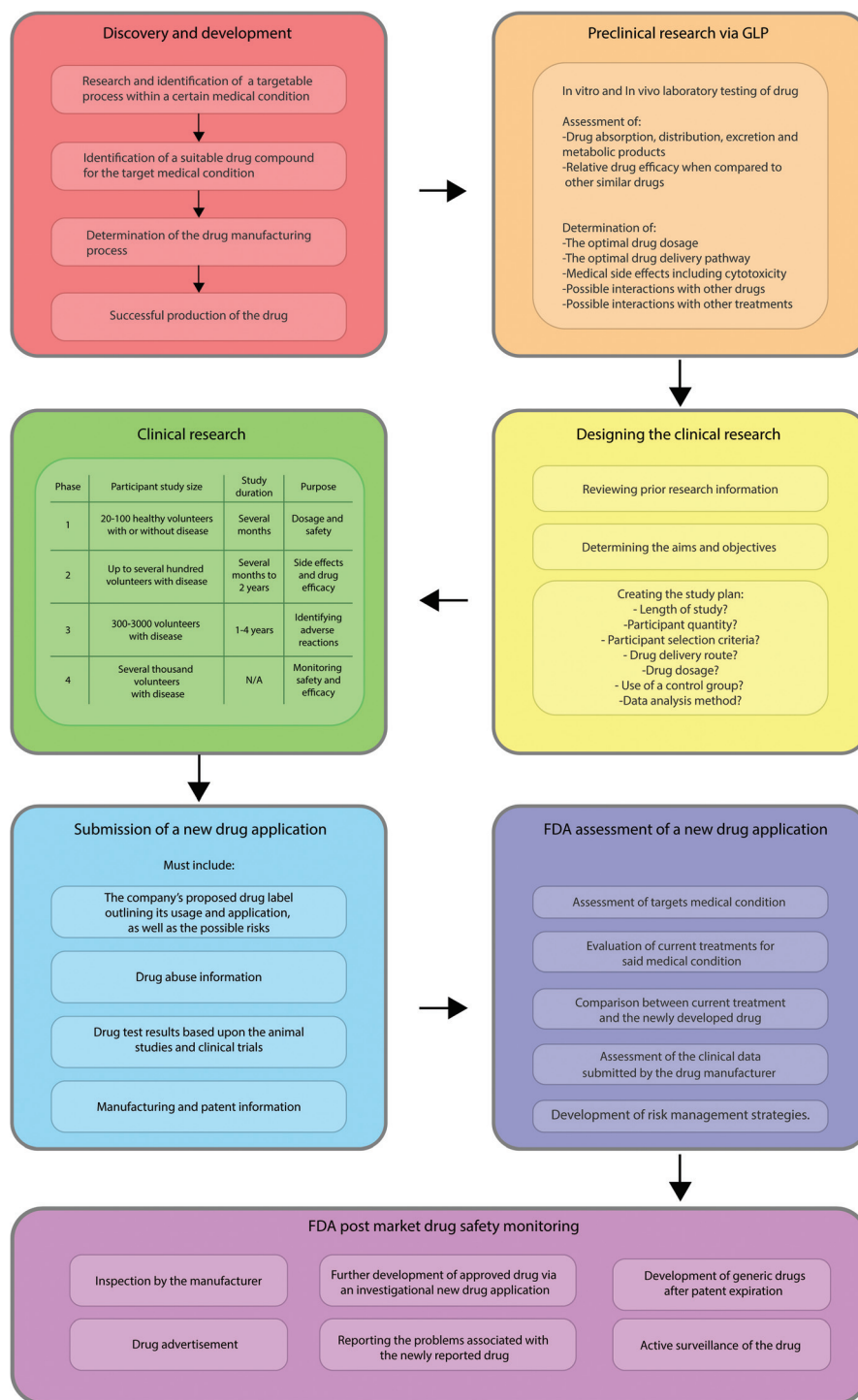


Fig. 4 Flow diagram showing well defined approval process for small drug molecules.

Initiatives within local (or semi local) communities have been put together and funded such as the REFINE project, which seeks to define the criteria for regulatory needs for nanomedicines and nanomaterials for clinical use.<sup>25</sup>

However, many feel that no firm and consistent lines have been drawn in order for the uniformity of regulation world-wide, or indeed guarantee that regulatory agencies will act

upon such guidance. In their white paper published in 2019, the REFINE project outlines their objectives, including 'Development and validation of new analytical or experimental methods'.<sup>26</sup> A sentiment of need which is echoed across the community, as those nano-based interventions reach clinical and subsequently fail due to lack of consistent or appropriate pre-clinical testing models.<sup>27</sup>





Another factor to consider when contemplating the impact of nanomedicines, is in their possible environmental impact, after use, upon disposal, and during production.<sup>28</sup> It is widely accepted that conventional pharmaceuticals are eventually recovered in the environment and so it is expected that nanomedicines will behave no differently, therefore there is a chance that they could negatively affect the environment.<sup>29</sup> The FDA cite the lack of data to determine the safety to humans and the environment, thus they are struggling to formulate a criterion to ensure safe and efficacious development of nano-products, whether they are a drug, device or biologic. The FDA released a first draft guidance in June 2011 as a response to criticism for their lack of nanoparticle regulation, however a final guidance document has not yet been generated for nanoparticles in medicine.<sup>30</sup> Despite the great need for a formal regulatory document, the FDA continues to ignore already collated data on toxicity profiles, rather they are taking a precautionary approach to the regulation of Nanomedicine, perhaps in hope to prevent future negative public opinion, treating them as an equal counterpart to their bulk equivalent. This is only negatively impacting the development of nanomedicine and inhibiting future use of these medicines as this uncertainty impacts future funding, research and development whilst destroying public acceptance. This may lead to a delay in the commercialisation of nano-products.<sup>31</sup> In the assessment of medical products in the USA and the EU, there are inclusion and exclusion criteria based on estimated environmental effects. In the EU, all marketing authorization applications are required to undergo an environmental risk assess-

ment and a pre-screening stage involving a rough estimation of the predicted environmental concentration for surface water with the acceptable limit being 0.01 ppb. Therefore, if the estimated environmental concentration is below this and no other environmental concerns are raised no further actions are taken for the product in terms of environmental risk assessment. In the USA, the FDA use an environmental assessment for new drug applications unless they are exempt from this, however, if the expected concentration in the environment exceeds 1 ppb, an exemption cannot be made.

## Regulatory challenges for nanomedicines

The main challenges faced in the regulation of nanomedicines is outlined in Fig. 5. Arguably, the biggest issue for the regulation of nanomedicines is the fact that regulatory bodies such as the FDA use safety data based on the bulk materials, which do not display the same pharmacodynamic and pharmacokinetic activity as nanomedicines.<sup>32</sup> This means data collected on safety and efficacy will not be representative of what could actually occur when the nanomedicine is used in clinical situations once they have achieved marketing authorisation. This leads to issues in creating regulations on safety and efficacy parameters of nanomedicines as a non-nano version may pass regulatory standards when a nanomedicine might not.<sup>31</sup>

Another huge challenge experienced is in the nanomedicine classification. They could be classified as medicines

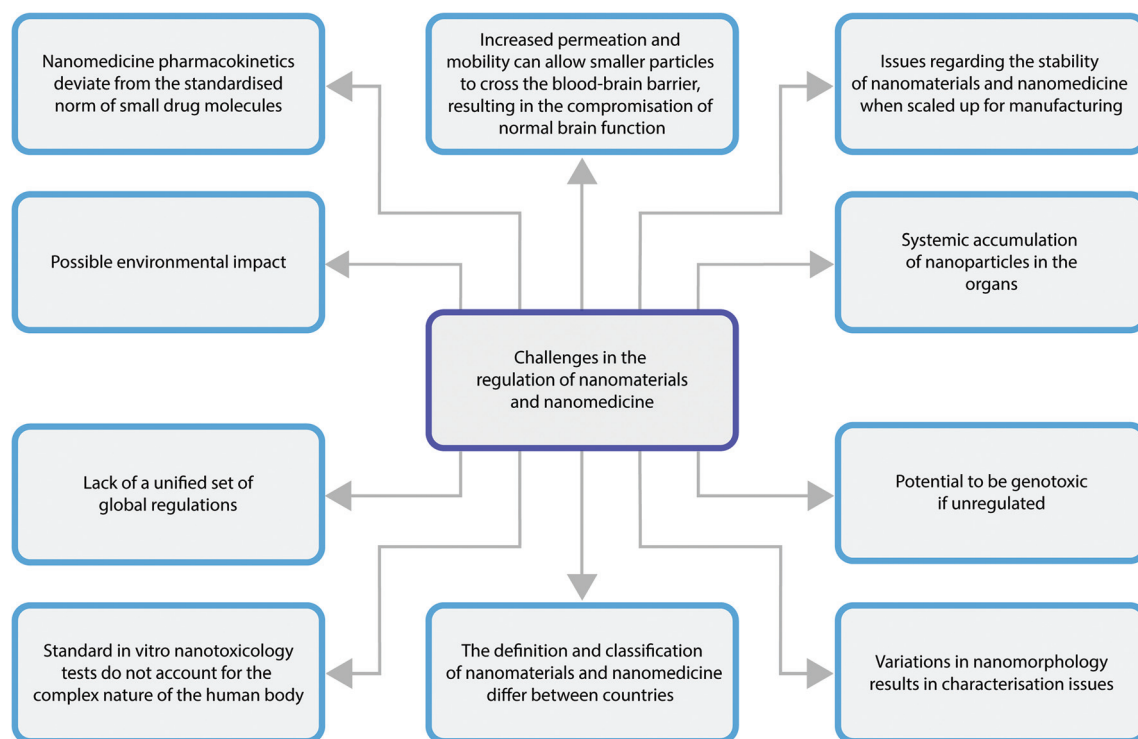


Fig. 5 Diagram highlighting the major challenges faced in the regulation of nanomaterials.



Nanotoxicology and cellular response is another challenge faced by regulators.<sup>42</sup> There have been many proposals on plausible ways to measure nanotoxicity. Traditional toxicity

Nanomedicines and their follow-ons, nanosimilars, have been introduced into the market over the last decade.<sup>40</sup> The challenges of pharmaceutical development and manufacturing process not only applies to nanomedicines but also their

An additional issue surrounding the regulation of nanomedicines is the question of who should hold the responsibility of formulating the guidelines for nanomedicines. This decision involves a consultative process that involves many stakeholders made up of academics and clinicians. In relation to this, there is a further immediate need to establish regulatory, high calibre laboratories to a federal level along with risk assessment of personnel, guidelines and technical standards needs to be developed. Often key bodies lack of scientific expertise around the topic due to how new the technology is and how diverse nanomedicines are in mode of action. It is difficult to create adequate regulations when there is limited knowledge of nanomedicines and so any regulations made may not be suitable to maintain patient safety and regulate the use of nanomedicines in a clinical setting.<sup>51</sup> In many ways, this infrastructure is already in place with strong national consortiums and national characterisation laboratories, however, the translation of information and guidance suggestions from these bodies is not yet integrated into regulatory frameworks.

## Nanomedicines already approved for clinical use

Amphotericin B is an antifungal agent that cannot be used alone due to poor water solubility, low tolerance and side effects exhibited by patients.<sup>55</sup> Amphotericin B was first formulated in deoxycholate, forming a mixed micellar dispersion (Fungizone).<sup>56</sup> Studies into the toxicity of Fungizone on human cells determined that this particular nanoparticle system may not be suitable for use. Forster, Washington and Davis determined that Fungizone showed toxicity towards erythrocytes and was determined to be due to the fast diffusion rate of Amphotericin B out of the micelles that it forms.<sup>57</sup> Dolberg and Bissell determined that Fungizone at the recommended dose was able to decrease the synthesis of DNA, reduce the number of cells and change the number of transport molecules in chick embryo fibroblasts at 10 days old.<sup>58</sup> Hence, other nanoparticle systems have been tested, with Fungizone often used as a standard for toxicity. Since then multiple studies into nanotechnology driven formulations of amphotericin B have entered clinical trial with success. These include Abelcet®, Amphotec® and AmBisome®, AmBisome®

Clinical use	Name	Approved for	Class of nanomedicine	Use
Cancer	Doxil	Ovarian cancer/HIV associated Kaposi's sarcoma	Liposome	Drug delivery
	NBTXR3/Hensify	Locally advanced sarcoma	Metallic	Radiation enhancer
	Vyxeos	Myeloid leukemia	Bilamellar liposomes	Combination therapy
	Abraxane	Pancreatic cancer, breast cancer, non-small cell lung cancer	Albumin bound	Drug delivery
	Onivyde	Pancreatic cancer	Liposome	Drug delivery
	DaunoXome	HIV associated Kaposi's sarcoma	Liposome	Drug delivery
Antifungal	Myocet	Breast cancer	Liposome	Drug delivery
	AmBisome	Cryptococcal meningitis, aspergillus, candida infections and visceral leishmaniasis	Liposome	Drug delivery
Other	Patisiran/ ONPATTRO	Transthyretin amyloidosis	Lipid	siRNA delivery
	Diafer	Iron deficient anemia	Metallic	Iron replacement
	Diprivan	Anaesthesia	Liposome	Anaesthetic

indicated for anaemia associated with chronic renal failure in adults.<sup>64</sup> Nanocrystals have also been licenced for clinical use as nanomedicines, Emend® is currently used as an antiemetic due to its increased dissolution rate and subsequent increased bioavailability compared to standard antiemetic formulations of aprepitant.<sup>64</sup> Metal-based nanoformulations such as FeraHeme® have also been licenced due to their prolonged steady release of the drug, allowing less frequent dosing for patients with anaemia in chronic kidney disease.<sup>68</sup>

As more knowledge was gained in the field, diversification of treatment condition and indeed cargo type were explored. In particular, nanomedicine has had great success in the delivery of small interfering RNA (siRNA). ONPATPRO® is one example of such success, with its approval for the treatment of the autosomal dominant disease hATTR amyloidosis.<sup>69</sup> ONPATPRO® are lipid based nanoparticles which were approved by the FDA in 2018 and were the first RNA based therapeutic approved for clinical use.<sup>70</sup> Given that siRNA are particularly difficult to administer alone, the use of nanotechnology within these formulations is the enabling factor. This approval has opened the field wide up to many applications where biologics may be used and delivered efficiently.

Nanomedicine approval and marketing has not come without criticism. There is still a wealth of unknowns when it comes to toxicity profiling, accumulation and clearance of many of the nanotechnologies. There are two potential risks based on this. The first, as commented on already, as was the case with Sinerem®, market approval and clinical use is not always plain sailing and new unknown adverse events can manifest within the patient population after widespread use which ultimately lead to withdrawal. This perhaps again due to the approval testing requirements following the route for small molecule drugs, where a more bespoke testing for nanomedicines are required. Secondly, there is a huge cost implication. Nanotechnologies for medicine have been widely criticised globally for their cost. For example, Abraxane® which was first approved in the USA and subsequently the UK, was not licenced by the UK National Health Service due to its high cost at point of need – despite its major clinical advantages in pancreatic cancer patients, who otherwise had a dismal prognosis. Gradually over time, this has been approved, however, lessons need to be learned from these experiences. As nanotechnologies pass through the clinical trial process and indeed enter the market. Late stage failure, results in huge costs which need to be recuperated elsewhere. If regulation was bespoke and appropriate, this would enable better refinement at preclinical study level, reducing failure rate either later in the clinical trials or indeed after marketing and clinical use.

The EMA applies General Medicinal Product legislation on regulating nanomedicines. At the same time, it creates a specialized multidisciplinary expertise to evaluate nanomedicines



using current risk/benefit-analysis principles. It has also established a definition of nanomedicine and published a list of specific guidance for nanomedicine which could be browsed on their guidance webpage. In 2009, the European Nanomedicines Expert Group was formed by the EMA to meet the increasing need for evaluation of nanomedicines from stakeholders. Established academics and regulatory science specialists from the Expert Group met with regulatory specialists from other regulatory agencies such as the FDA.<sup>71</sup>

## USA

Until now, the FDA are regulating nanotechnology products, including nanomedicines, using the current statutory and regulatory authorities as well as product-specific standards under its jurisdiction. Throughout the years, the FDA has issued guidance for nanomaterials on food, cosmetics and animal food. However, there is no published specific guidance for nanomedicine. In 2017, FDA produced a draft guidance on drug products, including biological products, that contain nanomaterials. In addition, the FDA does not attempt to categorize nanotechnology as safe or harmful but evaluate each nanotechnology on a case-by-case basis.<sup>72</sup> It should be noted that FDA identified several attributes concerning their regulatory approach. Nanomedicine products would be assessed in a product-specific way. Manufacturers are advised to consult with FDA when developing their nanotechnology products to establish a mutual understanding on regulatory issues. Consultation with the FDA is encouraged so that help on reviewing safety information and post-marketing safety designs could be given to manufacturers. Even after approval, post-market monitoring would be continued by FDA to protect consumers. Premarket review is required, and for nanotechnology that are not subject to premarket review, FDA would offer guidance and advice to corresponding manufacturers.<sup>72</sup> Ultimately, the responsibility to assure the safety of nanomedicines as well as their adherence to all applicable legal requirements lies on the manufacturers. Other institutes have also contributed to the regulation of nanomedicines, such as the Nanotechnology Characterization Laboratory of the National Cancer Institute (NCL-NCI) who have been contributing for more than 10 years.

The FDA formed the Nanotechnology Task Force and Nanotechnology Interest Group comprised of representatives from many regulatory centres in order to tackle the issue of regulating nanotechnology worldwide. Despite this, the FDA is yet to produce a clear set of guidelines, rather the Task Force has concluded that pre-existing regulations are comprehensive enough to ensure the safe production of nanomedicines as these products undergo pre-market testing and approval under the New Drug Application process. This conclusion is based upon the assumption that regulatory requirements already in place would detect toxicities in nano-products.<sup>31</sup> Despite this fact, the FDA has not changed their regulatory requirements and nanomedicines continue to be regulated according to existing guidelines for their larger counterparts. This lack of action in the changing landscape has resulted in great criti-

cism of the FDA. As a result, nano-formulations comprising of existing approved building blocks appear to fast track through the system not undergoing the new drug approval or full pre-market approval scrutiny. This strategy is extremely risky and only time will tell whether appropriate.

## UK

Medicines within the UK are regulated by the Medicines and Healthcare products Regulatory Authority (MHRA). No clear guidance has been published in relation to nanomedicine approval and in common with the FDA, these appear to be treated on a case-by-case basis. Researchers developing nanomedicines are encouraged to liaise with the MHRA Innovation Office for guidance and steering through the process. In common with the US, other organizations such as the European Nanomedicine Characterization Laboratory (EU-NCL) which are based across the UK and EU provide and constantly refine knowledge on preclinical characterization assays of nanomedicine.<sup>73</sup>

## EU

Within the EU, progress has been made with task forces and consortiums being put together to define the formal meaning of the word nanomaterial, with various reports and recommendations coming out from these which touch on food, environment and health. Other initiatives which have already been mentioned such as the EU-NCL and REFINE project have been funded through government awards to contribute to the advances within this field.<sup>74–76</sup> Unlike the UK, the regulatory body in the EU, the European Medicines Union (EMU) have published a range of specific preliminary guidelines for a range of nanomedicine preparation standards.<sup>71,73,77</sup> However, these are only at the public consultation stage and no formal regulatory guidance is currently in place. The EU-NCL work closely with the regulatory bodies as they do in the UK to inform and influence decision making on the regulation and potential danger of such products.

## Canada

Health Canada has established a Working Definition of Nanomaterials, where it “considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if it is at or within the nanoscale (1–100 nm) in at least one spatial dimension, or is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena”. Regarding the approval of nanotechnology products, Canada relies on existing regulatory frameworks. Health Canada advises manufacturers to consult with the responsible regulatory authority during the early development process to identify and assess the product's risks and properties.<sup>78</sup> Health Portfolio Nanotechnology Working Group is established in Canada for the gathering and discussion of issues related to nanotechnology, which consists of representatives from regulatory bodies like Health Canada and the Canadian Institutes of Health Research (CIHR). A general



- 1 <http://www.britishsocietyfornanomedicine.org/what-is-nano-medicine/> [accessed 14/06/19].
- 2 N.-C. Yeh, *Technovation*, 2013, **33**, 108.
- 3 D. Hanigan, L. Truong, J. Schoepf, T. Nosaka, A. Mulchandani, R. L. Tanguay and P. Westerhoff, *Water Res.*, 2018, **139**, 281–290.
- 4 A. Mihranyan, N. Ferraz and M. Strømme, *Prog. Mater. Sci.*, 2012, **57**, 875–910.
- 5 E. Pomerantseva, F. Bonaccorso, X. Feng, Y. Cui and Y. Gogotsi, *Science*, 2019, **366**, 6468.
- 6 Y. Min, J. M. Caster, M. J. Eblan and A. Z. Wang, *Chem. Rev.*, 2015, **115**, 11147–11190.
- 7 C. Ventola, *P. T.*, 2012, **37**, 512–517.
- 8 R. Seigneuric, L. Markey, D. Nuyten, C. Dubernet, C. Evelo, E. Finot and C. Garrido, *Curr. Mol. Med.*, 2010, **10**, 640–652.
- 9 J. P. Martins, J. das Neves, M. de la Fuente, C. Celia, H. Florindo, N. Günday-Türeli, A. Popat, J. L. Sanots, F. Sousa, R. Schmid, J. Wolfram, B. Sarmiento and H. A. Santos, *Drug Delivery Transl. Res.*, 2020, **10**, 726–729.
- 10 H. He, L. Liu, E. E. Morin, M. Liu and A. Schwendeman, *Acc. Chem. Res.*, 2019, **52**, 2445–2461.
- 11 N. Hoshyar, S. Gray, H. Han and G. Bao, *Nanomedicine*, 2016, **11**, 673–692.
- 12 S. K. Golombek, J. N. May, B. Theek, L. Appold, N. Drude, F. Kiessling and T. Lammers, *Adv. Drug Delivery Rev.*, 2018, **130**, 17–38.
- 13 S. Sindhvani, A. M. Syed, J. Ngai, J. B. R. Kingston, L. Maiorino, J. Rothschild, P. MacMillan, Y. Zhang, N. U. Rajesh, T. Hoang, J. L. Y. Wu, S. Wilhelm, A. Zilman, S. Gadde, A. Sulaiman, A. B. Ouyang, Z. Lin, L. Wang,

- M. Egeblad and W. C. W. Chan, *Nat. Mater.*, 2020, **19**, 566–575.
- 14 Y. Xia and J. Halas, *MRS Bull.*, 2005, **30**, 338–348.
- 15 R. Paliwal, R. J. Babu and S. Palakurthi, *AAPS PharmSciTech*, 2014, **15**, 1527–1534.
- 16 X.-Q. Zhang, X. Xu, N. Bertrand, E. Pridgen, A. Swami and O. C. Farokhzad, *Adv. Drug Delivery Rev.*, 2012, **64**, 1363–1384.
- 17 N. Singh, B. Manshian, G. J. Jenkins, S. M. Griffiths, P. M. Williams, T. G. Maffei, C. J. Wright and S. H. Doak, *Biomaterials*, 2009, **30**, 3891–3914.
- 18 B. Smolkova, M. Dusinska and A. Gabelova, *Food Chem. Toxicol.*, 2017, **109**, 780–796.
- 19 V. Lobo, A. Patil, A. Phatak and N. Chandra, *Pharmacogn. Rev.*, 2010, **4**, 118–126.
- 20 A. Manke, L. Wang and Y. Rojanasakul, *BioMed Res. Int.*, 2013, 942916.
- 21 A. Kermanizadeh, D. Balharry, H. Wallin, S. Loft and P. Møller, *Crit. Rev. Toxicol.*, 2015, **45**, 837–872.
- 22 M. Mioda, J. Kolosnjaj-Tabib, F. Nicholls, W. Linga, C. Wilhelm, O. Debargee, F. Gazeau and O. Clement, *Contrast Media Mol. Imaging*, 2013, **8**, 439–455.
- 23 [https://www.ema.europa.eu/documents/withdrawal-report/withdrawal-assessment-report-sinerem\\_en.pdf](https://www.ema.europa.eu/documents/withdrawal-report/withdrawal-assessment-report-sinerem_en.pdf) [Accessed 3 Feb. 2019].
- 24 R. Faulkner and N. Jasper, *Global Environ. Pollut.*, 2012, **12**, 30–35.
- 25 <http://refine-nanomed.eu/> [Accessed 10/06/20].
- 26 B. Halamoda-Kenzaoui, H. Box, M. van Elk, S. Gaitan, R. E. Geertsma, E. Gainza Lafuente, A. Owen, A. Del Pozo, M. Roesslein and S. Bremer-Hoffmann, *The REFINE White Paper*, Publications office of the European Union, Luxembourg, 2019.
- 27 D. Landesman-Milo and D. Peer, *Bioconjugate Chem.*, 2016, **27**, 855–862.
- 28 I. Mahapatra, J. R. A. Clark, P. J. Dobson, R. Owen, I. Lynch and J. R. Lead, *Environ. Sci.: Nano*, 2018, **5**, 1873–1889.
- 29 A. Baun and S. F. Hansen, *Nanomedicine*, 2008, **3**, 605–608.
- 30 Food and Drug Administration, Drug Products, Including logical Products, that Contain Nanomaterials Guidance for Industry, 2017. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-including-biological-products-contain-nanomaterials-guidance-industry> [Accessed 11/19/19].
- 31 R. Bawa, *Curr. Drug Delivery*, 2011, **8**, 227–234.
- 32 R. Bawa, G. F. Audette and B. Reece, *Handbook of Clinical Nanomedicine: Law, Business, Regulation, Safety, and Risk*, Pan Stamford Series on Nanomedicine, CRC Press, Taylor and Francis, Boca Raton, Florida, USA, 2016, vol. 2.
- 33 B. Kelly, 2010, *Nanomedicines: regulatory challenges and risks ahead*, [online] Cov.com. Available at: [https://www.cov.com/-/media/files/corporate/publications/2010/10/nano\\_medicines\\_regulatory.pdf](https://www.cov.com/-/media/files/corporate/publications/2010/10/nano_medicines_regulatory.pdf) [Accessed 5 Feb. 2019].
- 34 S. Rannard and A. Owen, *Nano Today*, 2009, **4**, 382–384.
- 35 A. N. Cleland, J.-L. Fraikin, P. Meinhold and F. Monzon, *Drug Dev. Delivery*, 2016, **16**(3), 20–26.
- 36 J. Y. Oh, H. S. Kim, L. Palanikumar, E. M. Go, B. Jana, S. A. Park, H. Y. Kim, K. Kim, J. K. Seo, S. K. Kwak, C. Kim, S. Kang and J.-H. Ruy, *Nat. Commun.*, 2018, **9**, 4548.
- 37 H. S. Leong, K. S. Butler, J. C. Brinker, M. Azzawi, S. Conlan, C. Dufes, A. Owen, S. Rannard, C. Scott, C. Chen, M. A. Dobrovolskaia, S. V. Kozlov, A. Prina-Mello, R. Schmid, P. Wick, F. Caputo, P. Boisseau, R. M. Crist, S. E. McNeil, B. Fadeel, L. Tran, S. Foss Hansen, N. B. Hartmann, L. P. W. Clausen, L. M. Skjolding, A. Baun, M. Ågerstrand, Z. Gu, D. A. Lamprou, C. Hoskins, L. Huang, W. Song, H. Cao, X. Liu, K. D. Jandt, W. Wen, B. Y. S. Kim, K. E. Wheeler, A. J. Chetwynd, I. Lynch, M. Moghimi Sayed, A. Nel, T. Xia, P. S. Weiss, B. Sarmiento, J. das Neves, H. A. Santos, L. Santos, S. Mitragotri, S. Little, D. Peer, M. M. Amiji, M. J. Alonso, A. Petri-Fink, S. Balog, A. Lee, B. Drasler, B. Rothen-Rutishauser, S. Wilhelm, H. Acar, R. G. Harrison, C. Mao, P. Mukherjee, R. Ramesh, L. R. McNally, S. Busatto, J. Wolfram, P. Bergese, M. Ferrari, R. H. Fang, L. Zhang, J. Zheng, C. Peng, B. Du, M. Yu, D. M. Charron, G. Zheng and C. Pastore, *Nat. Nanotechnol.*, 2019, **14**, 629–635.
- 38 M. S. Muthu and B. Wilson, *Nanomedicine*, 2012, **7**, 307–309.
- 39 S. Soares, J. Sousa, A. Pais and C. Vitorino, *Front. Chem.*, 2018, **6**, 360.
- 40 S. Muhlebach, *Adv. Drug Delivery Rev.*, 2018, **131**, 122–131.
- 41 V. Sainz, J. Conniot, A. Matos, C. Peres, E. Zupanoio, L. Moura, L. Silva, H. Florindo and R. Gaspar, *Biochem. Biophys. Res. Commun.*, 2015, **468**, 504–510.
- 42 J. Paradise, *AMA J. Ethics*, 2019, **21**, E347–E355.
- 43 A. Kroll, M. Pillukat, D. Hahn and J. Schneckeburger, *Eur. J. Pharm. Sci.*, 2009, **72**, 370–377.
- 44 R. Edmondson, J. J. Broglie, A. F. Adcock and L. Yang, *Assay Drug Dev. Technol.*, 2014, **12**, 207–218.
- 45 A. M. Dickinson, J. M. Godden, K. Lanovik and S. S. Ahmed, *Appl. In Vitro Toxicol.*, 2019, **5**, 114–122.
- 46 C. Hoskins, L. Wang, W. P. Cheng and A. Cuschieri, *Nanoscale Res. Lett.*, 2012, **7**, 77.
- 47 B. Fluhmann, I. Ntai, G. Borchard, S. Simoens and S. Muhlebach, *Eur. J. Pharm. Sci.*, 2019, **128**, 73–80.
- 48 S. Siegrist, E. Cörek, P. Detampel, J. Sandström, P. Wick and J. Huwyler, *Nanotoxicology*, 2019, **13**, 73–99.
- 49 H. S. Sharma, S. Hussain, J. Schlager, S. F. Ali and A. Sharma, *Acta Neurochir. Suppl.*, 2010, **106**, 359–364.
- 50 V. Agrahari and P. Hiremath, *Nanomedicine*, 2017, **12**, 819–823.
- 51 V. Limaye, G. Fortwengel and D. Limaye, *Int. J. Drug Regul. Aff.*, 2014, **2**, 33–41.
- 52 <https://www.accessdata.fda.gov/scripts/cder/daf/> [Accessed 10/06/20].
- 53 <https://products.mhra.gov.uk/> [Accessed 10/06/20].
- 54 A. C. Anselmo and S. Mitragotri, *Bioeng. Transl. Med.*, 2019, **4**, e10143.
- 55 F. Meunier, H. G. Prentice and O. Ringdén, *J. Antimicrob. Chemother.*, 1991, **28**, 83–91.
- 56 H. A. Gallis, R. H. Drew and W. W. Pickard, *Rev. Infect. Dis.*, 1990, **12**, 308–329.



- 57 D. Forster, C. Washington and S. S. Davis, *J. Pharm. Pharmacol.*, 1998, **40**, 325–328.
- 58 D. Dolberg and M. J. Bissell, *In Vitro*, 1974, **10**, 26–29.
- 59 T. Cooley, D. Henry, M. Tonda, S. Sun, M. O'Connell and W. Rackoff, *Oncologist*, 2007, **12**, 114–123.
- 60 <https://drugs.ncats.io/drug/ZS7284E0ZP> [Accessed 10/06/20].
- 61 <https://www.ema.europa.eu/en/medicines/human/EPAR/myocet-liposomal-previously-myocet> [Accessed 10/06/20].
- 62 <https://www.drugs.com/history/abraxane.html> [Accessed 10/06/20].
- 63 V. Weissig, T. K. Pettinger and N. Murdock, *Int. J. Nanomed.*, 2014, **9**, 4357–4373.
- 64 S. P. Chawla, V. S. Chua, L. Fernandez, D. Quon, W. C. Blackwelder, E. M. Gordon and F. L. Hall, *Mol. Ther.*, 2010, **18**, 435–441.
- 65 K. T. J. Chen, R. Gilabert-Oriol, M. B. Bally and A. W. Y. Leung, *Pharm. Res.*, 2019, **36**, 125.
- 66 <https://vyxeospro.com/clinical-data/efficacy/> [Accessed 07/07/20].
- 67 P. C. Nagle and J. C. Gerancher, *Tech. Reg. Anesth. Pain Manag.*, 2007, **11**, 9–18.
- 68 C. L. Ventola, *P. T.*, 2017, **42**, 742–755.
- 69 <https://www.onpattro.com/> [Accessed 07/07/20].
- 70 A. Akinc, M. A. Maier, M. Manoharan, K. Fitzgerald, M. Jayaraman, S. Baros, S. Ansell, X. Du, M. J. Hope, T. D. Madden, B. L. Mui, S. C. Semple, Y. K. Tam, M. A. Ciufolini, D. Witzigmann, J. A. Kulkarni, R. van der Meel and P. R. Cullis, *Nat. Nanotechnol.*, 2019, **14**, 1084–1087.
- 71 R. Pita, F. Ehmann and M. Papaluca, *AAPS J.*, 2016, **18**(6), 1576–1582.
- 72 FDA, *Nanotechnology Fact Sheet*, 2018. Available: <https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm402230.htm> [Accessed 12/12/19].
- 73 S. Bremer-Hoffmann, B. Halamoda-Kenzaoui and S. Borogs, *Join*, 2018, **3**, 1.
- 74 H. Rauscher, G. Roebben, V. Amenta, A. B. Sanfeliu, L. Calzolari, H. Emons, C. Gaillard, N. Gibson, T. Linsinger, A. Mech, L. Q. Pesudo, K. Rasmussen, J. R. Sintes, B. Sokull-Klüttgen and H. Stamm, *Towards a review of the EC Recommendation for a definition of the term “nanomaterial” Part 1: Compilation of information concerning the experience with the definition*, JRC Scientific Quality Report, Publications office of the European Union, Luxembourg, 2014.
- 75 G. Roebben, H. Rauscher, V. Amenta, K. Aschberger, A. B. Sanfeliu, L. Calzolari, H. Emons, C. Gaillard, N. Gibson, U. Holzwarth, R. Koeber, T. Linsinger, K. Rasmussen, B. Sokull-Klüttgen and H. Stamm, *Towards a review of the EC Recommendation for a definition of the term “nanomaterial” Part 2: Assessment of collected information concerning the experience with the definition*, JRC Scientific Quality Report, Publications office of the European Union, Luxembourg, 2014.
- 76 H. Rauscher, G. Roebben, A. B. Sanfeliu, H. Emons, N. Gibson, R. Koeber, T. Linsinger, K. Rasmussen, J. R. Sintes, B. Sokull-Klüttgen and H. Stamm, *Towards a review of the EC Recommendation for a definition of the term “nanomaterial” Part 3: Scientific-technical evaluation of options to clarify the definition and to facilitate its implementation*, JRC Scientific Quality Report, Publications office of the European Union, Luxembourg, 2015.
- 77 <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-nanomedicines> [Accessed 23/02/20].
- 78 Health Canada, *Nanotechnology-based Health Products and Food*, 2011, Available: <https://www.canada.ca/en/health-canada/services/drugs-health-products/nanotechnology-based-health-products-food.html> [Accessed 27/02/20].
- 79 Health Canada, *Current Issues with Nanomedicines in Canada*, 2010, Available: [https://www.ema.europa.eu/en/documents/presentation/presentation-nanomedicines-current-initiatives-canada-duc-vu-health-canada\\_en.pdf](https://www.ema.europa.eu/en/documents/presentation/presentation-nanomedicines-current-initiatives-canada-duc-vu-health-canada_en.pdf) [Accessed 23/01/20].
- 80 MHLW/PMDA, *Current Initiative in Japan for nanomedicines*, 2010, Available: [https://www.ema.europa.eu/en/documents/presentation/presentation-nanomedicines-current-initiatives-japan-kumiko-sakai-kato-toru-kawanishi-national/mhlw\\_en.pdf](https://www.ema.europa.eu/en/documents/presentation/presentation-nanomedicines-current-initiatives-japan-kumiko-sakai-kato-toru-kawanishi-national/mhlw_en.pdf) [Accessed 23/01/20].

