Patient Safety and Nanomedicines

The need for a centralised regulatory procedure

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European Alliance for
Access to Safe Medicines

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Contents

Glossary of Terms

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BE	Bioequivalence of Two Drugs
CDER	The Center for Drug Evaluation and Research
CQAs	Critical Quality Attributes
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCRSR	Global Coalition for Regulatory Science Research
GMP	Good Manufacturing Process
ICH	The International Council for Harmonisation
IND	Investigational New Drug Application
IS	Iron Sucrose
ISS	Iron Sucrose Similar
NDA	New Drug Application
PD	Pharmacodynamic
PE	Pharmaceutical Equivalence
PK	Robust Pharmacokinetic
TE	Therapeutic Equivalence

Foreword

Maria da Graça Carvalho
Member of the European Parliament

Nanotechnology offers tremendous opportunities to address unmet medical needs. Its applications for clinical purposes have captured the attention of academia, researchers, governments, funding agencies and regulatory bodies. Nanomedicines have demonstrated significant therapeutic advantages for a multitude of applications. Notwithstanding this, their practical translation into treatments has not progressed as quickly as the plethora of positive preclinical results would have suggested.

A strong fit-for-purpose regulatory framework is needed, in order to build on all the current knowledge and expertise. Only then will we be able to have new treatment opportunities that will benefit patients in a timely and safe way.

The European Group on Ethics in Science and New Technologies (EGE) already highlighted, back in 2007, that nanomedicines offer new diagnostic and treatment options. However, there is still a need to verify the safety of nanomedical products through a proper assessment process.[1]

The European Medicines Agency's (EMA) 'Regulatory Science to 2025'[2] Strategy is designed to advance the agency's engagement with regulatory science over the next five to ten years, covering both human and veterinary medicines. In its efforts to enable and leverage research and innovation in regulatory science, one of the core recommendations aims at developing an understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals. This is to be welcomed.

With the new Pharmaceutical Strategy of the European Commission expected to be published soon, I believe this is the right time to raise awareness of nanomedicines and foster communication and collaboration with DG SANTE, DG JRC and MEPs in order to share knowledge and harmonise regulatory practices for the benefit of patients.

Nanomedicine can revolutionise the way we detect and treat diseases of the human body. In order to ensure their safety, quality and efficacy, it is therefore essential that a robust regulatory process exists and that all stakeholders, including health authorities, payers, pharmacists and prescribers are fully aware of their complexities.

Transparency, including openness about uncertainties and knowledge gaps in these technologies, is of the essence to achieve public trust in nanomedicine. The work carried out by the EAASM aims to help catalyse this and we wish them every success with their patient safety initiatives.

Foreword

Mike Isles
Executive Director,
European Alliance for
Access to Safe Medicines

European Alliance for
Access to Safe Medicines

Science and technology have never moved as fast as now. With personalised medicines and the advent of gene therapy, the standard rule book is clearly coming under pressure. It would appear that the same is true for the understanding and definitions behind the technology of nanomedicines.

Nanomedicines and their follow-on products, also referred to as nanosimilars, are complex molecules and so regulatory oversight must be scientifically fit for purpose. It is important to note that a survey[3] carried out in 2018 reported "…strong regional differences in the regulation of nanomedicines has confirmed the need for a harmonisation of information requirements on nano-specific properties". And so experts believe that the level of data for market authorisation is not sufficient or consistent across EU countries. In addition, protocols used in clinical trials are not of a level of detail to allow a full and consistent interpretation of clinical trial results and outcomes. Even with existing licensed nanosimilars then there is a question mark over the capability of the regulatory framework to adequately assess copies once the patent of the originator medicine has expired. There is evidence that such "follow-on copy" products do not deliver the same efficacy and safety. And although hindsight is a great thing, it has been admitted in circles that regulatory approvals in the past might have not been appropriate and have resulted in products that do not deliver the same efficacy and safety and so patients have been compromised. EU regulatory agencies are becoming more aware of the complex issues surrounding the correct criteria to ensure that follow-on nanomedicines are indeed truly similar. Within this context then a centralised regulatory process that addresses this is needed.

And so the EAASM would endorse the approach that all health agencies should adopt a regulatory approval process on the Hybrid Application process (10.3) and NOT the generics application process (10.1)[4] as this does indeed address the issue and would enable follow-on copies to exhibit therapeutically equivalent outcomes and thus ensure patient safety. The fact that the European Medicines Agency supports international harmonisation of regulatory science standards "…is to be applauded since it may prevent global divergence in the evaluation of these complex generic products".

The EAASM welcomes this and supports such collaborative actions which will help ensure that patients are not put in harm's way. Patient safety must always be the most important criteria when assessing the granting of a new product licence, whether it be for an originator medicine, or a follow-on nanosimilar. That is why we need to create a pan European medical agency consensus that enables an agreed cross-Europe robust regulatory framework. This not only applies to existing medicines but the plethora of new medicines that are in the pipeline.

In the absence of clarity on regulatory pathways and a legal definition, more scientific, policy and practice knowledge on the quality, safety, and efficacy of nanomedicines and nanosimilars must be gained among all stakeholders including payers and health care professionals. There is therefore a need to build a consensus dialogue as well as alignment between all players in Europe and beyond. This report aims to catalyse discussion and galvanise consensus so that existing as well as innovative nanomedicies can realise their full potential and thus take their place in this exciting and new field of medicine to the benefit of patients. I am pleased to say that this consensus is building and building fast. We hope very much that the EAASM's endeavours to highlight this area will indeed accelerate this process.

Expert views on the development and evaluation of nanomedinces

Jacques Rottembourg
Department of Nephrology, Groupe Hospitalier Pitie-Salpetriere-Paris-France

"The development of nanomedicines is progressing at an ever increasing pace. Such therapeutic advances will undoubtedly have a major positive effect on many types of hitherto unmet medical needs."

It is therefore imperative that the science being applied can be translated in to a workable, clear and fit for purpose regulatory framework. We can, I believe, reflect on the journey that biosimilars took and a successful outcome was certainly achieved. I have every confidence that innovative nanomedicines will share a similar successful pathway.

This is very important for two clear patient safety reasons. The first is that the safety, efficacy and quality must be properly and consistently determined and secondly that follow-on "similar" versions are adequately tested for their therapeutic similarity to the originator product through clinical studies.

We must not have a repeat of the issues that were experienced by patients with follow-on versions of IV iron preparations in terms of different efficacy and safety profiles and which eventually led the FDA to block their introduction in the US and the EMA to develop draft guidance.

Together by close scientific collaboration I am confident that we will build a robust regulatory framework and I believe that the European Medicines Agency along with a number of other EU institutions can lead the way to ensure that Europe is in the vanguard of this exciting field.

Maria Teresa Parisotto
Executive Director, European Specialist Nurses Organisation

Nursing, like any other, is a developing profession. The know-how of yesterday, today is probably not enough; an innovation of yesterday, today is probably obsolete. Therefore, the nursing skills and capabilities need a continuous professional development to be able to deal with new and innovative medicines such as the rapidly developing area of nanomedicines. A useful comparison to draw on is the biosimilars, which required a concerted collaborative effort to enable a new robust regulatory framework to be worked out and established in Europe; the same applies to nanomedicines.

I believe that this report and the work being catalysed by the EAASM will contribute positively to this goal and I look forward to adding to this endeavour, which will ultimately serve patients in all countries to get a sustainable personalised therapy.

Frédéric Destrebecq
Executive Director, European Brain Council

"Brain disorders are complex and most of them remain without a cure. Through the knowledge emerging from the advancing field of nanotechnology, there is hope that nanomedicines promise to develop significant new medical advances."

There are many diseases that, as yet, have not been addressed fully from a medical science perspective and this is particularly the case for brain disorders. This field must rightfully fill patients with new hope that more efficacious treatments are coming through the research pipeline.

However, like all new and emerging fields, new language and terminology need to be invented to accommodate new knowledge which, in itself, brings about challenges of understanding. This emphasises the need for a robust, well worked out and thus fit purpose regulatory framework. For it is essential that if medicines are to be authorised for use in patients, the regulations that govern this must ensure that quality, safety and efficacy are consistent and assured.

This applies equally to existing licensed nanomedicines as follow-on versions which, by their nature, can only ever be "similar". A number of nanomedicine products addressing neurological conditions such as multiple sclerosis and their "similars" are currently available in the European market.

For the European Brain Council it is of utmost importance that new innovative treatments can be assessed as quickly and efficiently as possible through a robust regulatory framework. It is therefore encouraging to know that the work carried out by the EAASM has the potential to catalyse important debate and ultimately actions that will achieve this goal.

Application of nanomedicines in the modern therapeutic setting

New nanomedicines currently under development

Nanotechnology is a compelling and growing scientific field that provides numerous opportunities for life science organisations to develop innovative medicines to address unmet medical needs and create alternatives for many therapeutic areas.

Modern nanotechnology is focused on developing nanoparticles (NPs) for prophylactic, diagnostic, and therapeutic applications.[5] Nanomedicines offer potential solutions for a number of the current treatment challenges such as cancer, cardiovascular, and neurodegenerative diseases, as well as other illnesses.[5]

Many nanomedicines and nanodiagnostics have already received product licences and are being used in the clinic, and many more are in clinical trials.[6,7] Currently, the most active areas of nanomedical research and product development are in cancer treatments, imaging contrast agents, and biomarker detection.[6,8,9]

The graph cleary shows the rapid progress being made in this recent field of medicines.

Submissions to the US FDA of Drug Products containing nanomaterials

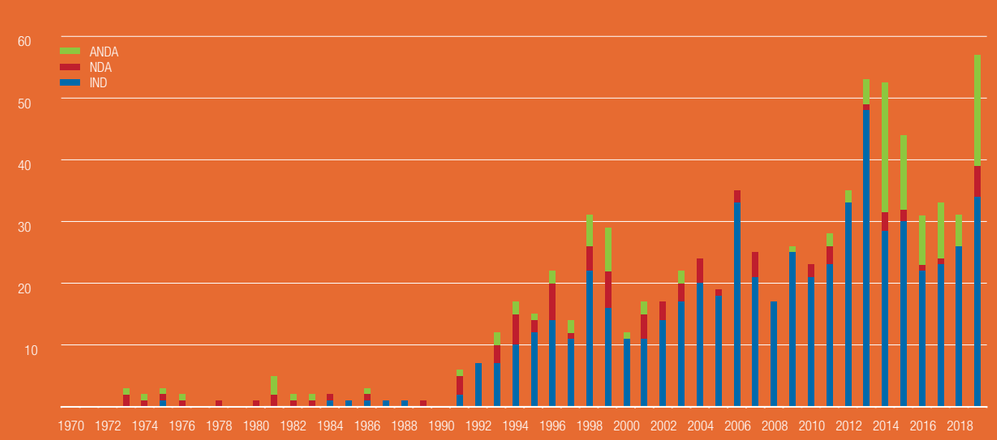


Figure 1 Human drug product submissions to FDA containing nanomaterials between 1970-2019. Nanotechnology: Over a Decade of Progress and Innovation at FDA, report by the US FDA, July 2020, https://www.fda.gov/media/140395/download

The application of nanotechnology is demonstrating the potential to significantly enhance treatments in many diseases, offering at the same time many future opportunities. It also holds the promise to provide new innovative diagnostic and therapeutic tools for serious diseases which are currently treated inadequately. Moreover, the use of nanoproducts will convey many benefits for all healthcare professionals and patients.

For patients, it will mean less frequent dosing, minimise invasive methods of administration and reduce adverse drug effects, leading to an enhanced quality of life. This will also benefit pharmacists in simplifying therapeutic procedures and provide personalised therapy. By increasing the drug efficacy and safety, this will reduce length of patient stay and subsequent costs of healthcare.

One field that is showing tremendous promise is that of gene therapy. Of particular note, was the FDA approval of patisiran, a first-in-kind targeted RNA-based therapy to treat the rare disease of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients. This new class of drugs is based on a lipid nanoparticle (LNP) system that facilitates small interfering ribonucleic acid (siRNA) delivery into the cytoplasm of target cells (hepatocytes) following intravenous (i.v.) administration. This peripheral nerve disease is a rapidly progressive disease which is normally fatal within 5 years. Patisiran halts the disease and actually reverses the accumulated damage.

"This peripheral nerve disease is a rapidly progressive disease which is normally fatal within 5 years. Patisiran halts the disease and actually reverses the accumulated damage."

Gene therapies using the LNP systems are making headway to produce proteins in hepatocytes (rare diseases) and for many vaccine applications (such as HIV, Zika, Universal influenza, Malaria) and also CRISPR (clustered regularly interspaced short palindromic repeats) Cas9 systems for gene editing applications.

Another line of research is where triple-negative breast cancer (TNBC) which is one of the most aggressive breast cancers with poor prognosis is treated with chemotherapy medicines where nanoparticles encapsulate tumour suppressive MRNA proteins. Early in vitro and animal results are showing great promise.

Clinical issues arising from the approved application of follow-on products

The realities of nanomedicines

Some of the most successful and well-established nanomedicines include AmBisome® (liposomal amphotericin B), Caelyx®/Doxil® (liposomal doxorubicin), Copaxone® (glatiramer acetate, a synthetic polypeptide), Venofer® (iron sucrose, a nanoparticular polymeric iron-carbohydrate) and Abraxane® (albumin-bound paclitaxel).

AmBisome®, the first liposomal nanomedicine approved by the EMA, is able to bind to fungal cell walls, where the liposome with the incorporated amphotericin B is disrupted.[10] Amphotericin B can remain bioavailable for several weeks following the initial treatment.[8] It has been proven to have a better safety profile than the conventional amphotericin B solution with respect to infusion-related toxicity and nephrotoxicity, while maintaining the same efficacy in patients.[10, 11] AmBisome®'s advantages are specific to this drug product, while other liposomal amphotericin B drug products do not show the same safety and efficacy profile.[11] This also demonstrates the importance of the specific composition and the corresponding manufacturing process.

Nanocolloidal solutions of iron carbohydrates for intravenous applications are another example of frequently used nanomedicines. The first nanotechnology-based intravenous iron product was introduced in the 1950s, and is now known as Venofer®. To overcome the high toxicity of iron (II) salts, iron in the form of polynuclear Fe(III)-oxyhydroxide core stabilised by a carbohydrate shell was developed.[12] Intravenously-applied Venofer® nanoparticles have been shown to be tolerated at more than 20-fold higher 50% lethal dose (LD 50) levels, compared to iron sulphate solutions in mice.[13]

After administration, the iron carbohydrate particles interact with the innate immune system for uptake and release of bioavailable iron.[14, 15] It is assumed that the characteristics of the nanoparticles affect the fate and disposition in the body.[16, 17, 18, 19, 20] There is a plethora of evidence showing that iron sucrose follow-on products from different manufacturers have different efficacy and safety profiles despite most of them complying with the USP monograph quality requirements.[21, 22, 23] Since the structural and functional relationships are not fully understood and hence the clinically meaningful critical quality attributes (CQAs) are not fully identified, the manufacturing process defines the product, and is crucial for the consistency and quality of the end product, and its clinical performance.[24] A robust manufacturing procedure needs to be in place and thoroughly sustained in order to ensure batch-to-batch consistency.

Nanomedicines gain all of their beneficial therapeutic properties from the way that they are manufactured. Therefore, nanomedicines produced by even a slightly different manufacturing process, but having the same chemical composition, might have undetected different physical structures leading to significant differences in their safety and efficacy profile.[25] It is important to note that nanomedicines such as iv iron products or liposomes cannot be characterised based on the active pharmaceutical ingredient (API) only. It is necessary to characterise the drug product with this complex combination of molecules which is highly dependant upon the manufacturing process.

Evidence for this is presented below whereby a number of iron carbohydrate compounds have been available on the market and among these, iron sucrose (IS) complex has a favourable safety profile when administered intravenously. However, their physico-chemical properties and biological properties depend on the manufacturing process as subtle structural modifications may effect the stability of the preparation.[26, 27] This is a crucial point as several iron sucrose similar (ISS) preparations have been introduced for the treatment of iron deficiency in a number of countries worldwide[26, 27] on the basis that they can be considered therapeutically equivalent in terms of safety, efficacy and quality to the originator. Alarmingly this has proven not to be the case. A study carried out in 2009[28] demonstrated that a "… switch from the originator IS to an ISS preparation led to destabilisation of a well-controlled populationof HD patients and incurred an increase in total anaemia drug costs. It can therefore be strongly argued that prospective comparative clinical studies are required to prove that ISS are as efficacious and safe as the originator i.v. IS".

Patient safety issues arising from nanosimilar interchangeability

In light of regulatory challenges, the vexed questions of interchangeability/substitutability/switching between originator nanomedicines and their 'similars' remain extremely pertinent.

Interchangeability

Due to their complex nature, nanomedicines cannot be replicated on a like for like basis. Minor changes in manufacturing can affect size and/or morphology of nanomedicines, and nanosimilars may exert clinically relevant differences compared with their originator products. These differences can substantially influence quality, biological properties and therapeutic profiles.

It is important for payers, pharmacists and physicians to recognise that nanosimilars are just that and be aware of the differences.

Therefore, nanosimilars should not automatically be considered to be interchangeable.

Automatic substitution

Automatic substitution between a nanomedicine and its nanosimilars at pharmacy level, should not be allowed under any circumstance given the complexity of nanomedicines - and all the more so in the absence of a harmonised regulatory approach for nanosimilars.

As nanosimilars are not identical copies of their reference products, automatic substitution should not take place. Automatic substitution at the pharmacy level is not even widely permitted for biologics/biosimilars, where a robust regulatory pathway is already in place.

Decisions involving the wellbeing of patients should not be made on cost-saving reasons, especially if clinical evidence points to potential issues of efficacy and safety.[29]

One of the biggest challenges with automatic substitution without the involvement of a healthcare professional should be discouraged to ensure traceability of the treatment of individual patients. EU pharmacovigilance legislation aims to ensure European-wide traceability of medicinal products. This is necessary for a root cause analysis in case an adverse drug reaction occurs.

The complexity of nanomedicines prevents sufficient proof of pharmaceutical equivalence, when comparing a follow-on product to a reference product. Automatic substitution of complex originator nanomedicines has the potential to make root cause analysis challenging and should be borne in mind.

Switching

Studies have shown that switching between a reference nanomedicine and its nanosimilar approved through a decentralised generic procedure has led to dramatic decrease in efficacy profile of the product.[30]

Therefore, switching should always be considered carefully by the prescriber, all the more so given the complexity of nanomedicines and the absence of a targeted regulatory approach for nanosimilars.

Regulatory awareness and activities in the EU

The European Medicines Agency (EMA) has long recognised the specific challenges posed by nanomedicines. They are thought leaders in facilitating discussion around the challenges presented in reviewing products that apply nanotechnology to medicines.

In this context the EMA established the Ad-Hoc Nanomedicines Expert Group in 2009 to pool quality, safety, and pharmacokinetics expertise to help inform evaluation and formulate guidelines. Later that year, the work of this cross-agency group was expanded with the creation of the International Regulators Subgroup on Nanomedicine, an initiative launched jointly by regulators from Canada (Health Canada), Europe (EMA), Japan (Ministry of Health, Labour and Welfare), and the US (FDA).

In 2010, EMA hosted the first international scientific workshop on nanomedicines. Regulators, academics, and industry representatives from 27 countries met to explore the science of nanomedicines and share their experience at an international level. The purpose being to better anticipate future needs. Proposed actions included expanding multidisciplinary regulatory platforms to share experiences, and facilitating early scientific dialogue and knowledge transfer among regulatory, academic, and industrial innovators to identify potential challenges and risks.

In 2011, EMA established a nanomedicine drafting group tasked with developing a series of reflection papers around nanosimilars and emerging nanotherapeutics. Issues around nanoparticles coating and block copolymer micelle medicinal products were discussed, recognising how differences in manufacturing and formulation between the follow-on product and innovator product may alter drug safety and efficacy profile.

The 2019 Global Summit on Regulatory Science (GSRS19)[31] was co-hosted by the Joint Research Centre (JRC) and the Global Coalition for Regulatory Science Research (GCRSR) at Ispra in Stresa (Italy), last September 2019. The congress attracted 200 scientists from around the world, from regulatory agencies, academia and industry, to discuss global regulatory science perspectives on nanotechnology and nanoplastics, and harmonise strategies via global collaboration.

Nanotechnology research and its role as fundamental background to enhance regulatory decision making, was extensively covered including methods, standards and applications. In addition, methods and approaches to better understand nanoplastics were also introduced. In plenary and parallel sessions, the following topics were addressed:

- ★ Global Regulatory Science Perspectives on Nanotechnology and Nanoplastics
- ★ Regulatory research needs for new and follow-on nanomedicines
- ★ Safety assessment of nanomaterials
- ★ Nanotechnology in the agri/food/feed sector
- ★ Documentary standards and reference materials
- ★ Challenges concerning nanoplastics

The JRC offered training opportunities and laboratory visits at its Ispra site. Everybody is looking forward to the GSRS20, which will convene 28-30 September 2020 at the National Institutes of Health (NIH) Bethesda, Maryland (USA) and deal with Emerging Technologies.

Furthermore, the EMA published its Regulatory Science Strategy to 2025[32] on 31st March 2020 and one of the core recommendations is designed to develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals. In line with this, the EMA proposes to implement the following actions:

- ★ Raise awareness of new nanomedicines and materials via the EU-Innovation Network, and foster collaboration with DG JRC and other international partners (e.g. IPRP), to share knowledge and harmonize regulatory practices:
- ★ Generate guidance addressing PK/PD (including modelling) requirements and long-term efficacy and safety;
- ★ Develop and standardise new testing methods related to the quality and safety assessment of nanomedicines;
- ★ Understand the critical quality attributes (CQA) of a given product and the relationship between those and the biological activity and in-vivo behaviour of the product

Regulatory challenges in Europe

The complexity, diversity and type of nanomedicines have given rise to significant regulatory challenges. Improved scientific knowledge of these compounds has raised new questions with regard to testing requirements to properly assess quality, safety, efficacy and risk management. Nanomedicinal products may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological as well as immunological properties.[33] Moreover, due to their size, related physicochemical properties and the resulting biological effects, nanomaterials require additional quality and safety testing compared with the products not using nanotechnology.[34]

Despite all the awareness and activities, Europe still faces significant challenges and inadequacies as many regional differences in the regulation of nanomedicines exist. This means that there is not a harmonised approach to assess the licensing process of nanomedicines. Hence, it is critical that a concerted effort to address this is coordinated with a sense of urgency as patient safety is at the core of correcting this important issue.

These regulatory challenges are summarised below:

Lack of a scientific consensus on definitions

A major barrier to a harmonised regulatory approach for nanomedicines is the current lack of a consistent terminology and categorisation of nanomedicines.

This has given rise to there being no specific nor consistent regulatory framework at a European level for the assessment and authorisation of nanosimilar products. It is important to note that the evolution of the new regulatory pathways for nanomedicines began its journey at a similar place to that of the biosimilars. And so there is much to be learned and taken from this process to potentially truncate the development of “fit for purpose” regulations for nanomedicines.

The need for clear regulatory criteria for the approval of follow-on (nanosimilar) products

Based on the scientific data, it is clear that prior to clinical trial work a robust pharmacokinetic (PK) and pharmacodynamic (PD) profile is required.

These analyses are crucial for the determination of the bioequivalence of the nanosimilar products. Nanomedicines are complex and so creating exact replicas is not possible.

In Europe, licence applications of nanosimilars remain infrequent. However, these new nanosimilars are claimed to be ‘similar’ to a reference (originator) licensed nanomedicine. Experts believe that the level of data on the biological characterisation for market authorisation is not sufficient or homogeneous across EU countries. In addition, protocols used in clinical trials are not of a level of detail to allow a full and consistent interpretation of clinical trial results and outcomes.

It is vital to point out that any drug developed to be substitutable to the reference originator product must show equivalence in terms of quality, safety and efficacy before a market authorisation can be granted.

In other areas, such as biosimilars, good manufacturing process (GMP) is now clearly marked. Similarly nanomedicines’ quality attributes must also be defined and written into the regulations. The refinement of the quality attributes of a given nanomedicine using strict criteria will be essential to ensure consistent manufacturing and therefore quality control of nanomedicines. Physicochemical parameters need to be agreed and should cover aspects such as stability, particle size (distribution), surface properties, and solubility, as they may change the pharmacokinetics, biodistribution, and toxicity of the formulation.[34]

A high level of manufacturing control must be therefore guaranteed as minor changes in manufacturing may lead to unknown changes of the product composition, which can affect the clinical performance. FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling.[35]

Recent advances in nanoscience have created even more complex, hybrid structures by both a new top-down fabrication combined with bottom-up manufacturing techniques. These products are seen as the next-generation nanomedicines and so robust methodologies for licensing assessment is essential to ensure long-term safety/risk management.[36] This should also include the environmental impact of all medicinal products.

Raising awereness of nanotechnology-based products in health care

Some products based on nanotechnology are classified as medical devices in Europe but as medicinal products in other countries (and vice versa). Clear differentiation of testing requirements of medicinal products and medical devices for nanotechnology-based products is of utmost importance. For instance, a clear regulatory pathway for borderline products (a product that does not fit easily in to an existing regulatory category) is currently not defined in the phase of preclinical development.[37] This requirement was determined as a priority in the EU Medicines Agencies Network Strategy 2020 document.[38]

It is important to establish and have accepted that complex products, such as borderline products or theranostics combining diagnostic and therapy agents (combination products) will require special regulatory awareness.[39, 40]

Recent studies have shown limited awareness of the specific properties of nanomedicines among the health care professionals community, leading to detrimental effects on patients. There is evidence that shows a lack of education.[41] Severe implications can arise if adherence to strict handling, storage (light and temperature) and administration protocols is not applied. Finally, monitoring and reporting activities should be in place to report adverse events and identify interactions with other medicines.

The need for a fit for purpose regulatory framework for nanomedicines and nanosimilars

The properties and features of nanomedicines have significantly challenged the process of development and consistency of manufacturing as well as the process for their regulatory approval. This particularly applies to nanosimimilar products.[42, 43] Manufacturers have experienced difficulties in copying these complex products as minor changes in manufacturing may lead to unknown changes of the product composition, which can affect the clinical performance.

The challenges can be described by the equation used to demonstrate therapeutic equivalence (TE) of generics: PE + BE = TE, where PE is the pharmaceutical equivalence and BE is the bioequivalence of two drugs.

The definition of PE requires the presence of the same active ingredients in the same composition. For nanomedicines, the active substance is not a homo-molecular structure, but rather consists of different, closely-related, nanoparticulate structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means.[44, 45] Nanomedicines are often designed with the intention of altering the pharmacokinetic and/or pharmacodynamic properties of the parenteral drug substance. Therefore, they cannot be considered simply a formulation, as the entire drug product is responsible for its in vitro and in vivo (PK/PD) profile; hence, the drug product must be considered as the drug substance.

Defining the clinically meaningful clinical quality attributes (CQA) also remains a challenge. In the absence of conclusive CQAs, it is impossible to know which parameters should be characterised for the demonstration of sameness. This means that the generic pathway is not appropriate for the approval of follow-on nanomedicines.

Additionally, PE implies that the two products should clearly show, in addition to the originator's physicochemical profile, the same strength, dosage form and route of administration, as well as comparable labelling.

BE can be shown by determining the PK/PD profile, through in vitro, in vivo, pre-clinical and clinical studies. For nanomedicines, this is complicated by the fact that nano-characteristics affect the bio-distribution and targeting, which cannot be addressed by a plasma drug profile only.

Because of this we believe that the existing regulatory framework for the approval of nanosimilars could be improved.

Recommendations for the harmonization of regulatory pathways for nanomedicines and nanosimilars

In order to guarantee the highest standard of patient safety in Europe we believe that a number of adaptations to the current regulatory system could bring about great improvements:

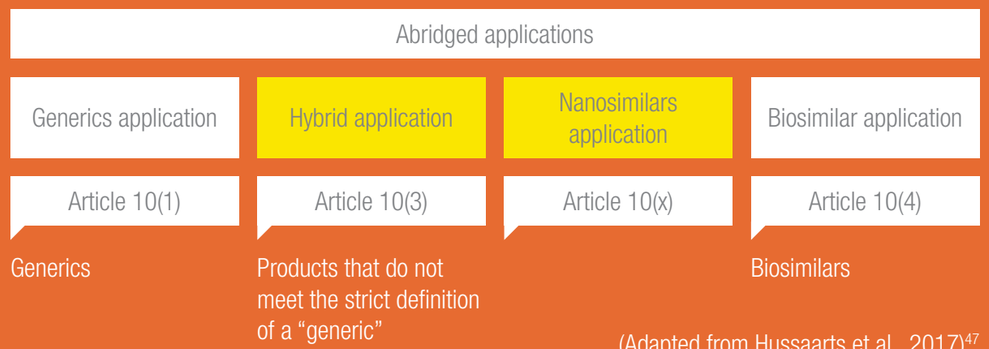
- The first step to ensuring consistency in how these products are treated throughout their regulatory assessment is for all nanomedicines and nanosimilars to be approved through the centralised procedure. By making the central authorisation of nanomedicines and follow on products by the EMA mandatory, as with biologics/biosimilars this would be avoid incoherence in the approaches taken by different national Member States. A mandatory centralised procedure could also offer clarity for developers and make the regulatory system more robust.

- The establishment of a separate, **dedicated pathway for follow-on nanomedicines (10(x))** would ultimately provide the highest degree of legal clarity and guidance for developers of originator and follow-on products. This new pathway could be based around the **concept of similarity (nanosimilars)** along the lines of the existing approach to biologics, including requirements for traceability. Regulatory clarity in this area coupled with appropriate monitoring, traceability and pharmacovigilance of follow-on products would help better ensure patient access to efficacious and safe copies of nanomedicines.

- **In the absence of such a dedicated pathway, follow-on nanomedicines should always be assessed via the Hybrid Pathway and, to make this pathway clearer, the EMA could improve its guidance for the implementation of the current regulatory framework.** For the hybrid pathway to function effectively for nanosimilars, EMA would need to develop broader guidelines covering all nanomedicines beyond the four specific scientific guidelines for product areas that have been developed to date.

If nanomedicines can be approved in a way that provides safe and effective treatments, patients will benefit through the improved safety profile of these products and manufacturers will also gain by having a clearer system for regulatory approval.

At the moment, a nanosimilar can be approved by the EMA in an abridged application process as a generic, a hybrid application or in some cases a biosimilar application [articles 10(1), 10(3), and 10(4) respectively].[46] In addition, these products can be approved through a centralised or a decentralised procedure depending on the type of product or the indication for which they have been developed.



(Adapted from Hussaarts et al., 2017)[47]

The need for international regulatory alignment for nanomedicines and nanosimilars

The challenges which European regulators have been facing when dealing with nanomedicines are shared by regulators across the globe and, currently, no international alignment exists while different agencies have been making attempts at improving their own systems.

Efforts to align regulatory processes for complex drug follow-ons could greatly benefit patients while at the same time decreasing the costs of development for manufacturers and unnecessary repetition of clinical trials. In turn this would lead to improved access to high-quality, affordable products for the global community.[48]

Globally, while the WHO has taken a lead in developing guidelines on the evaluation of similar biotherapeutic products which were published in 2009, it has not yet taken up the challenge to develop a global regulatory framework for nanomedicines and nanosimilars and this has created differerent approaches between geographies.

An illustrative case, taken from the article of Hussaarts et. al. from the Annals of the New York Academy of Sciences (2017) is the evaluation of follow-on versions of the nanomedicine Doxil/Caelyx (doxorubicin HCl liposome injection). Doxil and Caelyx are identical products but are marketed under different names by Johnson & Johnson in the United States and Europe,[36] respectively. Owing to a shortage of Doxil, the FDA decided in February 2012 to temporarily allow the import of Sun Pharma's Lipodox, which had not been approved in the United States. In February 2013, the FDA granted approval to another doxorubicin HCl liposome injection product by Sun Pharma, which was made the reference listed drug. Once sufficient supplies of this product are available, the FDA expects to stop the temporary import of the unauthorized Lipodox.[37] In Europe, the EMA assessed and rejected Sun's doxorubicin HCl liposome injection under Article 10(3) (through the centralized procedure) as a follow-on version of Caelyx.[38] Consequently, industries seeking to develop follow-on versions of Doxil/Caelyx are now required to undertake two separate comparative BE trials, using Sun's doxorubicin HCl liposome injection in the United States and Caelyx in Europe. In addition, the FDA and the EMA request different batteries of studies to demonstrate BE.

Such regulatory differences complicate requests for approval, and regulatory alignment will benefit all stakeholders. Such efforts could be pursued by the International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) or the Nanomedicines Working Group of the International Pharmaceutical Regulators Programme.

EAASM Call to Action

REGULATORY REFORM REQUIRED IN EUROPE

1 Need for scientific consensus on definitions for nanomedicines in Europe

- ★ A clear legal definition for nanomedicines is therefore essential for harmonisation across Europe

2 Improve education and foster awareness on the complexity and sophistication of nanomedicines among policymakers, prescribers, payers and patients

- ★ With the rapid development of innovative medicines greater awareness amongst all health stakeholders is paramount, notably policy makers, payers, prescribers and patients
- ★ Further education guidance and uptake of validated tests amongst decision makers, such as pharmacists, payers and physicians, to make informed decisions at country level

3 Need for a clear and robust regulatory pathway for all new nanomedicines as determined by the European Medicines Agency

- ★ Develop a clearly defined regulatory pathway by adopting an EMA centralised procedure. This is key to avoiding diverging approaches between Member States, minimising adverse events and guaranteeing the right to future personalised, innovative treatments that are safe for the patient. Robust scientific methodology that defines the process and criteria for the assessment of a nanomedicine is critical to ensure the long-term safety and risk management. The definition of the quality attributes of a nanomedicine using strict criteria will be essential to ensure consistent manufacturing and therefore quality control of nanomedicines.
- ★ The assessment criteria for the licensing of these medicines requires an equally robust regulatory process. Nanomedicines as nanosimilar/follow-on medicines have been proven not to be equivalent with patient safety issues arising. Manufacturing exact replicas of nanomedicines is not achievable. And so the highest possible standard of manufacturing control must be guaranteed and included in the licence application.
- ★ Minor changes in manufacturing may lead to unknown changes of composition, which can affect the clinical performance. In Europe, licence applications of follow-on/nanosimilar products are infrequent and so the experience and expertise require urgent attention.

4 Need for clear regulatory criteria for the approval of follow-on/nanosimilar medicines

- ★ The immediate compelling need to address the regulatory requirements of "follow-on copy" products, providing additional guidance for the entire product class as opposed to only selected products
- ★ Additional guidance to ensure safe market introduction of nanosimilars and that next generation nanomedicines enter clinical development and so the market in a safe and timely way for the benefit of public health
- ★ Ensure nanosimilars are not substituted or switched at country level
- ★ Ensure that if the hybrid pathway is used and follow-on products are only considered 'similars', then national authorities should warn against their interchangeability and substitution in order to avoid putting patients in harms way due to differing safety profiles of the follow-on products

Overview of key requirements and actions of all stakeholders

INDUSTRY	REGULATORS	KEYPLAYERS
• Clear guidance on regulatory requirements • Early dialogue with regulators	• Harmonisation definitions for nanomedicines and appropriate approval pathways • Alignment of regulation pathways for nanomedicines and follow-on products with those established for biosimilars	• Alignment and agreement • Collaboration • Transparency • Education

Visit the EAASM website to sign the Petition and endorse more collaborative actions for a new and robust regulatory framework for nanomedicines and nanosimilars in Europe.

In collaboration with other European associations, the EAASM has produced a leaflet calling upon DG SANTE, the EMA, Member States' health authorities and regulatory bodies to address unmet medical needs and enhance quality, safety and efficacy of nanomedicines and nanosimilars by addressing patient safety issues due to significant regulatory challenges across Europe.

https://eaasm.eu/en-gb/nanomedicines-petition

References

1. https://ec.europa.eu/commission/presscorner/detail/en/MEMO_07_32
2. EMA Regulatory Science to 2025 – Strategic reflection, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
3. Bremer-Hoffmann S, Halamoda-Kenzaoui B, Borgos SE, Jornal of Interdisciplinary Nanomedicine vol. 3, issue 1 March 2018
4. Nanomedicines: The magic bullets reaching their target?, B. Flühmann, I. Ntai, G. Borchard, S. Simoens, S. Mühlebach, https://doi.org/10.1016/j.ejps.2018.11.019
5. Ventola CL. The nanomedicine revolution: part 2: current and future clinical applications. P T. 2012;37(10):582–591.
6. Bawa R. Regulating nanomedicine: Can the FDA handle it? Curr Drug Deliv. 2011;8(3):227–234.
7. McGrady E, Conger S, Blanke S, Landry BJ. Emerging technologies in healthcare: Navigating risks, evaluating rewards. J Healthcare Manag. 2010;55(5):353–364.
8. Seigneuric R, Markey L, Nuyten DS, et al. From nanotechnology to nanomedicine: Applications to cancer research. Curr Mol Med. 2010;10(7):640–652.
9. Morigi V, Tocchio A, Pellegrini CB. Nanotechnology in medicine: From inception to market domination. J Drug Deliv. 2012 Mar 7.
10. J.P. Adler-Moore, R.T. Proffitt: Amphotericin B lipid preparations: what are the differences? Clin. Microbiol. Infect., 14 (Suppl. 4) (2008), pp. 25-36, 10.1111/j.1469-0691.2008.01979.x
11. J.R. Azanza, B. Sádada, J. Reis: Liposomal formulations of amphotericin B: differences according to the scientific evidence. Rev. Esp. Quimioter., 28 (6) (2015), pp. 275-281.
12. S. Mühlebach, B. Flühmann: Iron carbohydrate complexes: characteristics and regulatory challenges, D. Crommelin, J. de Vlieger (Eds.), Non-biological Complex Drugs, AAPS Advances in the Pharmaceutical Sciences Series, vol 20, Springer, Cham (2015).
13. P. Geisser, M. Baer, E. Schaub : Structure/histotoxicity relationship of parenteral iron preparations. Arzneimittelforschung, 42 (12) (1992), pp. 1439-1452.
14. T.S. Koskenkorva-Frank, G. Weiss, W.H. Koppenol, S. Burckhardt: The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: insights into the potential of various iron therapies to induce oxidative and nitrosative stress, Free Radic. Biol. Med., 06 (65) (2013), pp. 1174-1194, 10.1016/j.freeradbiomed.2013.09.001.
15. P. Geisser, S. Burckhardt: The pharmacokinetics and pharmacodynamics of iron preparations, Pharmaceutics., 3 (1) (2011), pp. 12-33, 10.3390/pharmaceutics3010012.
16. J.E. Toblli, G. Cao, L. Oliveri, M. Angerosa: Differences between the original iron sucrose complex Venofer® and the iron sucrose similar Generis®, and potential implications, Port J Nephrol Hypert, 23 (1) (2009), pp. 53-63.
17. J.E. Toblli, G. Cao, L. Oliveri, M. Angerosa: Differences between original intravenous iron sucrose and iron sucrose similar preparations. Arzneimittelforschung, 59 (4) (2009), pp. 176-190, 10.1055/s-0031-1296383.
18. J.E. Toblli, G. Cao, L. Oliveri, M. Angerosa: Comparison of oxidative stress and inflammation induced by different intravenous iron sucrose similar preparations in a rat model, Inflamm. Allergy Drug Targets, 11 (1) (2012), pp. 66-78.
19. J.E. Toblli, G. Cao, M. Angerosa: Nitrosative stress and apoptosis in non-anemic healthy rats induce by intravenous iron sucrose similars versus iron sucrose originator. Biometals, 28 (2) (2015), pp. 279-292, 10.1007/s10534-015-9822-3.
20. J.E. Toblli, G. Cao, J.F. Giani, F.P. Dominici, M. Angerosa: Markers of oxidative/nitrosative stress and inflammation in lung tissue of rats exposed to different intravenous iron compounds. Drug Des Devel Ther., 11 (2017), pp. 2251-2263, 10.2147/DDDT.S132612
21. J. Rottembourg, A. Kadri, E. Leonard, A. Dansaert, A. Lafuma: Do two intravenous iron sucrose preparations have the same efficacy?, Nephrol. Dial. Transplant., 26 (10) (2011), pp. 3262-3267, 10.1093/ndt/gfr024.
22. M.L. Agüera, A. Martin-Malo, M.A. Alvarez-Lara, V.E. Garcia-Montemayor, P. Canton, S. Soriano, P. Aljama: Efficiency of original versus generic intravenous iron formulation in patients on haemodialysis. PLoS One, 06 (10) (2015), p. 8 e0135967, https://doi.org/10.1371/journal.pone.0135967.
23. E.S. Lee, B.R. Park, J.S. Kim, G.Y. Choi, J.J. Lee, I.S. Lee: Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients. Curr. Med. Res. Opin., 29 (2) (2013), pp. 141-147, 10.1185/03007995.2012.760444.
24. Di Francesco T, Sublet E, Borchard G 2018. Nanomedicines in clinical practice: are iron sucrose ready-to-use solutions for infusions interchangeable? (This Issue).
25. Agüera ML, Martin-Malo A, Alvarez-Lara MA, Garcia-Montemayor VE, Canton P, Soriano S, et al. (2015) Efficiency of Original versus Generic Intravenous Iron Formulations in Patients on Haemodialysis. PLoS ONE 10(8): e0135967. https://doi.org/10.1371/journal.pone.0135967.
26. Goldberg LA, Iron sucrose similars, Hosp PharmEur, 2010, vol.48 (pg.21-22).
27. Toblli JE, Cao G, Oliveri L, et al. Differences between original intravenous iron sucrose and ironsucrose similar preparations, Drug Res, 2009 vol.59 (pg. 176 190).
28. Do two intravenous iron sucrose preparations have the same efficacy? Rottembourg J, Kadri A, Leonard E, Dansaert A, Lafuma, A Nephrol Dial Transplant Vol. 26, Issue 10 October 2011, (pg. 3262-3267).
29. Rottembourg, Jacques. (2018). Are Iron Sucrose and Iron Sucrose Similar Equivalent? Analytical, Experimental and Clinical Determinations. Nutri Food Sci J. 2018; 2(1): 116.
30. See above.
31. Global Summit on Regulatory Science 2019 on 'Nanotechnology and Nanoplastics' hosted by the JRC, EU Science Hub.
32. See reference 2.
33. Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines, Falk Ehmann, Kumiko Sakai-Kato, Ruth Duncan, Dolores Hernán Pérez de la Ossa, Ruben Pita, Jean-Marc Vidal, Ashish Kohli, Laszlo Tothfalusi, Alan Sanh, Sandrine Tinton, Jean-Louis Robert, Beatriz Silva Lima & Marisa Papaluca Amati (2013), https://doi.org/10.2217/nnm.13.68.
34. See reference 1.
35. Orange Book Preface, Food and Drug Administration Center for Drug Evaluation and Research: Approved Drug Products with Therapeutic Equivalence Evaluations, https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface
36. See reference 24.
37. See reference 1.
38. EU Medicines Agencies Network Strategy to 2020, December 2015.
39. Identification of regulatory needs for nanomedicines, Susanne Bremer-Hoffmann, Blanka Halamoda-Kenzaoui & Sven Even Borgos, March 2018, https://doi.org/10.1002/jin2.34.
40. See reference 1.
41. J. Knoeff, B. Flühmann, S. Mühlebach: Medication practice in hospitals: are nanosimilars evaluated and substituted correctly?. Eur J Hosp Pharm Sci Pract., 25 (2) (2018), pp. 79-84, 10.1136/ejhpharm-2016-001059.
42. F. Ehmann, K. Sakai-Kato, R. Duncan, Hernán Pérez de la Ossa D, R. Pita, J.M. Vidal, A. Kohli, L. Tothfalusi, A. Sanh, S. Tinton, J.L. Robert, B. Silva Lima, M.P. Amati. Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines. Nanomedicine (London), 8 (5) (2013), pp. 849-856.
43. E. Marden, I. Ntai, S. Bass, B. Flühmann: Reflections on FDA draft guidance for products containing nanomaterials: is the abbreviated new drug application (ANDA) a suitable pathway for nanomedicines? AAPS J., 20 (2018), p. 92, 10.1208/s12248-018-0255-0.
44. Lygature Non-Biological Complex Drugs (NBCD) Working Group, https://www.lygature.org/non-biological-complex-drugs-working-group, Accessed 9th Apr 2018.
45. H. Schellekens, S. Stegemann, V. Weinstein, J.S. de Vlieger, B. Flühmann, S. Mühlebach, R. Gaspar, V.P. Shah, D.J. Crommelin: How to regulate nonbiological complex drugs (NBCD) and their follow-on versions: points to consider. AAPS J., 16 (1) (2014), pp. 15-21, 10.1208/s12248-013-9533-z.
46. Klein et al. from 2019
47. L. Hussaarts, S. Mühlebach, V.P. Shah, S. McNeil, G. Borchard, B. Flühmann, V. Weinstein, S. Neervannan, E. Griffiths, W. Jiang, E. Wolff-Holz, D.J.A. Crommelin, J.S.B. de Vlieger: Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann. N. Y. Acad. Sci., 1407 (1) (2017), pp. 39-49, 10.1111/nyas.13347
48. Leonie Hussaarts, Stefan M¨uhlebach, Vinod P. Shah, Scott McNeil, Gerrit Borchard, Beat Fl ¨uhmann, Vera Weinstein, Sesha Neervannan, Elwyn Griffiths, Wenlei Jiang, Elena Wolff-Holz, Daan J.A. Crommelin, and Jon S.B. de Vlieger Equivalence of complex drug products: advances in and challenges for current regulatory frameworks Ann. N.Y. Acad. Sci. ISSN 0077-8923

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