EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality aspects of Nano-based medicines

SME Workshop: Focus on quality for medicines containing chemical entities

London, 4 April 2014

Presented by: Dolores Hernán Pérez de la Ossa Ph.D.
EMA Specialized scientific disciplines, Quality

Agenda

I. Introduction-EMA experiences in nanomedicines

II. Challenges of nanotechnology

III. Regulatory developments

IV. Further support

V. Conclusions

What are nanomedicines?

What are nanomedicines?

In 2011 the EC published a recommendation on the definition of nanomaterial predisposing size as the critical factor (1-100 nm)

- Acknowledged that an upper limit of 100 nm is not scientifically justified across the whole range of nanomaterials.

  Commission Recommendation of 18 October 2011 on the definition of nanomaterial
  http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF

- Noted the 'special circumstances prevailing in the pharmaceutical sector' and stated that the Recommendation should 'not prejudice the use of the term "nano" when defining certain pharmaceuticals and medical devices'.

  European Union 004-EN-N. Scientific Committee on Emerging and Newly Identified Health Risks.
  Scientific Basis for the Definition of the Term "nanomaterial"; 2010;
  BN 978-92-79-12757-1; doi:10.2772/39703 ND-AS-09-

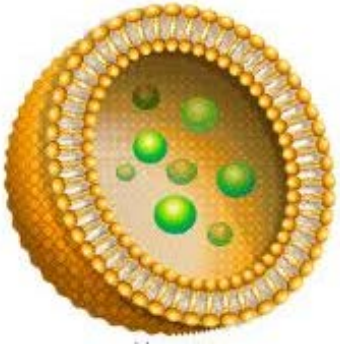
EMA working definition of Nanomedicines

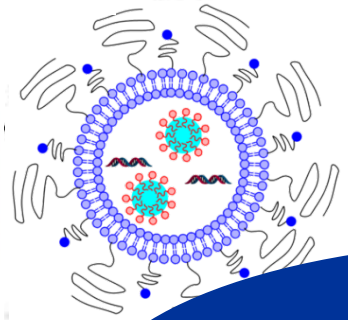
- ✓ Purposely designed systems for clinical applications
- ✓ At least one component at nano-scale size
- ✓ Resulting in definable specific properties and characteristics
  - related to the specific nanotechnology application and characteristics for the intended use (route of admin, dose)
  - associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution)

And needs to meet definition as a **medicinal product** according to European legislation.

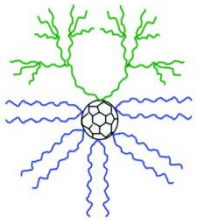
Nanomedicines

Liposomes
Caelyx
Myocet

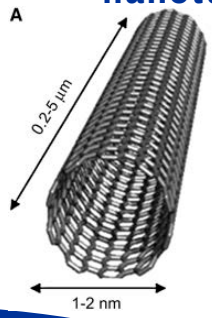




Fullerenes

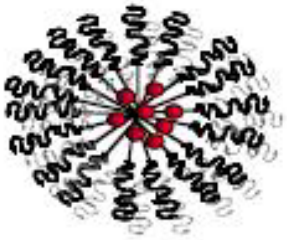


Carbon nanotubes

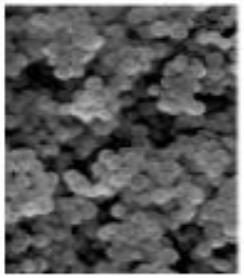


Viral and non-viral vectors

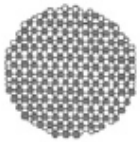
Polymeric micelles



Nanoparticles
Abraxane



Magnetic NP



Gold NP

Quantum dots

Dendrimers

The term “nanomedicines” can cover a wide variety of materials and structures.

Unique and distinctive features -> Case-by-case approach

Purpose of nanomedicines

Address unmet medical needs

- Integrate efficacious molecules that otherwise could not be used because of their high toxicity (e.g. Mepact)
- Exploit multiple mechanisms of actions (e.g. Nanomag, multifunctional gels, polymers in development)

Maximise efficacy and reduce dose and toxicity

- Drug targeting
- Controlled and site specific release
- Preferential distribution within the body (e.g. in areas with cancer lesions)
- Improved transport across biological barriers

Experience in the Centralised Procedure

1. Liposomes:

- **Caelyx** *(metastatic breast cancer, AIDS related Kaposi's syndrome, …)*

  Doxorubicin in sterically stabilised (Stealth®) long circulating **pegylated** liposomes.

  Formulation allows preferential release at KS lesions reducing general toxicity

- **Mepact** *(high-grade non-metastatic OS)*

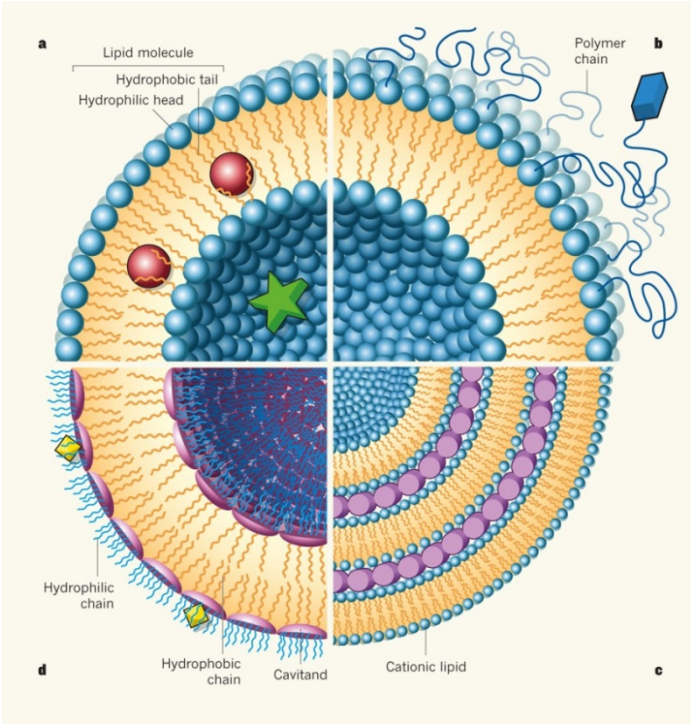
  Mifamurtide in multilamellar liposomes.

  Formulation facilitates targeting macrophages and RES

- **Myocet** *(BC)*

  Doxorubicin in self assembling ***lamellar liposomes***.

  Formulation reduces cardiac toxicity



Experience in the Centralised Procedure

2. Nanoparticles:

- **Abraxane** *(metastatic breast cancer)*

  Paclitaxel albumin bound spherical nanoparticles

  Formulation aimed at solving solubility issues

- **Rapamune** *(organ rejection in renal transplant)*

  Sirolimus particles in nanocrystal colloidal dispersion.

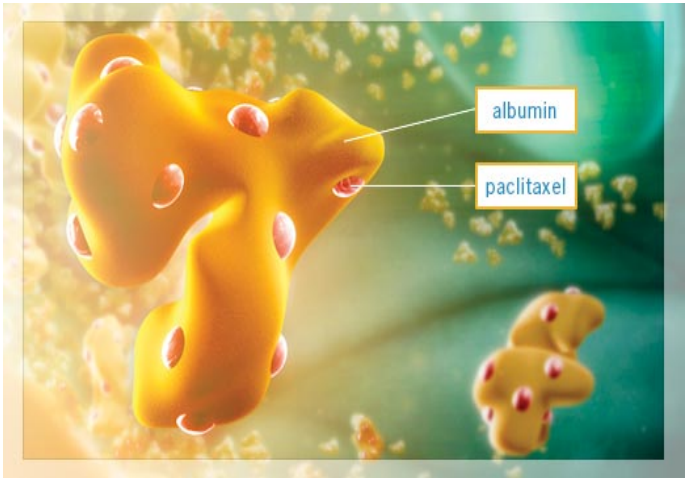
  Improve stability and bioavailability

- **Sinerem*** (diagnostic agent)

  Super-paramagnetic iron oxide *coated nanoparticles* (30 nm) in-vivo characterisation of lymph nodes

  Formulation aimed at increasing uptake by RES.

Source: ww.abraxane.com/professional/moa.aspx)



Evaluation of nanomedicines

B / R

Q/S/E

Potential benefits

Promise of improved:

-Prevention

-Detection

-Treatment of disease

⇧ Solubility

Overcoming biological barriers (BBB)

Targeted delivery (EPR, ligands)

⇧ Bioavailability

Controlled release

Contervailing concerns

Potential safety risks

- infusion reactions
- hypersensitivity reactions
- oxidative stress
- altered body distribution
- …

Risk minimization and management

"As for any medicinal product, the EU competent authorities will evaluate any application to place a nanomedicinal product on the market, utilising established principles of benefit/risk analysis, rather than solely on the basis of the technology *per se" (including RMP and enviromental risk assessment)*

Reflection paper on nanotechnology-based medicinal products for human use

Agenda

I. Introduction-EMA experiences in nanomedicines

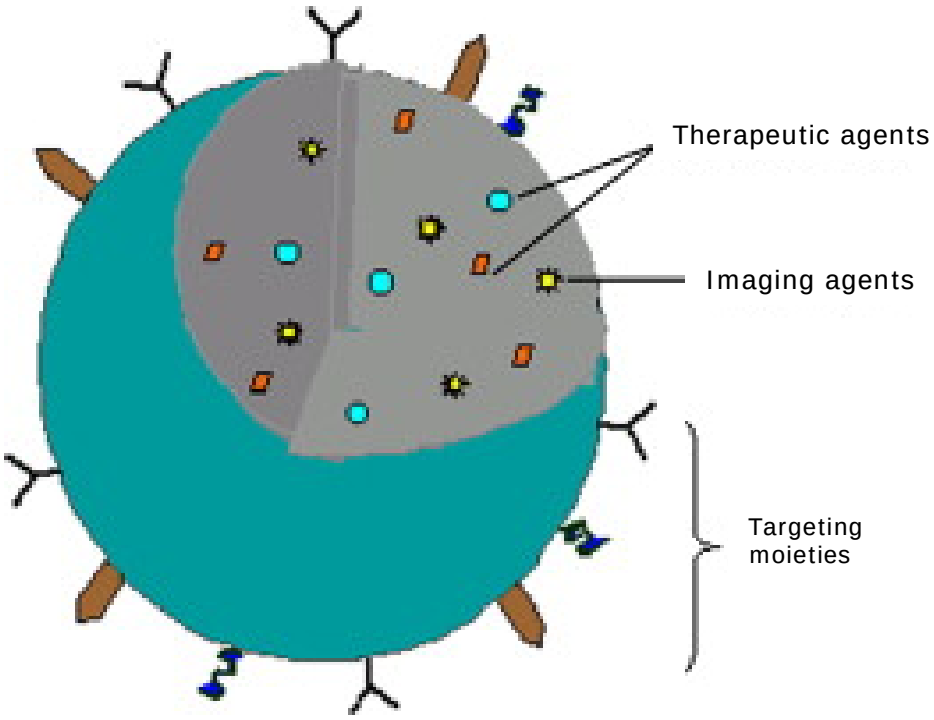
II. Challenges of nanotechnology

III. Regulatory developments

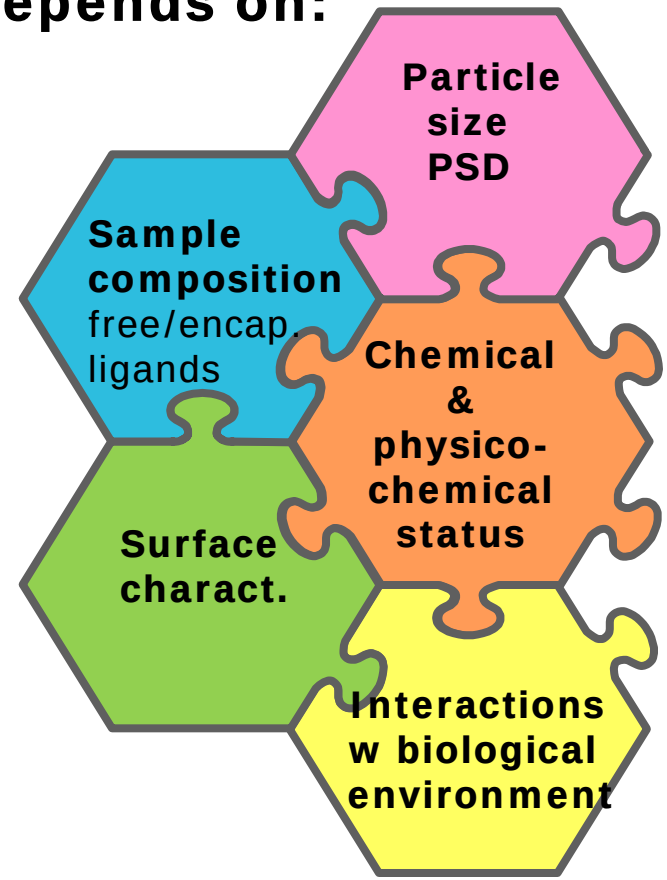
IV. Further support

V. Conclusions

Scientific challenges - CMC considerations (1)



Quality and performance depends on:



The better one can understand these products in **early development**, the more likely it is that a successful reproducible manufacturing process will be achieved.

Scientific challenges- CMC considerations (2)

Understanding of critical components & their interactions

Identification of key characteristics and their relation to performance

- PSD ➔ PK, BD, safety
- Surface properties ➔ interactions, stability, opsonization, PK, BD, cell uptake
- drug loading, release kinetics…
- aggregation

Identification of appropriate analytical tests to fully characterize nanomedicines

- ✓ Sensitive and specific to the desired parameter
- ✓ Physicochemical and biological tests sensitive enough to identify differences that could affect performance.
- ✓ Not change the sample characteristics and cause artifacts (e.g. dilution, dispersing medium)
- ✓ Validated?

PSD - Often spherical shape assumed, but anisotropic shapes are present
Not all parameters for exact analysis known

Understanding of critical manufacturing steps

Reproducibility & scale-up

In vitro & in vivo stability

Sterility*

Nanosimilars

EMA Liposomal RP

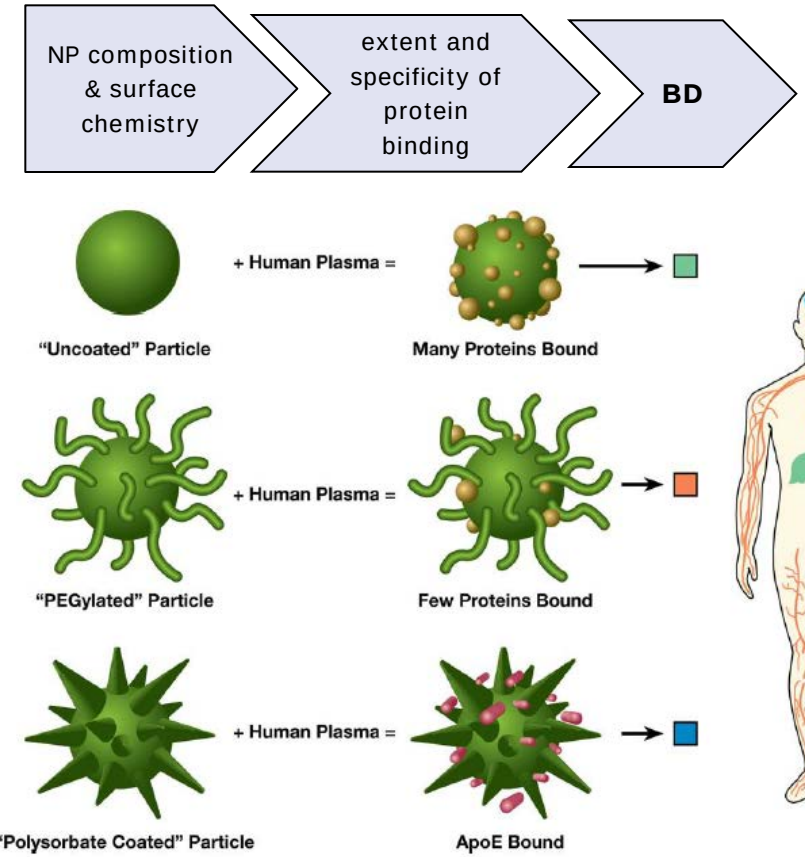
"Comparative investigations should be undertaken when a **change** is introduced **into the manufacturing process** during development but also after marketing authorisation (e.g. for **scale up**)".

FDA liposomal guidance:

"Liposome drug products are **sensitive to changes in the manufacturing conditions**, including changes in **scale**. This *should be considered during the development process*, and critical manufacturing parameters (e.g., scale, shear force, temperature) should be *identified and evaluated*".

Scientific challenges –Safety & Efficacy

Subtle changes in composition and/or physicochemical characteristics of nanomedicines could result in substantial changes in the pharmacology and toxicity.



Aggarwal P et al Adv Drug Deliv Rev. Jun, 2009; 61(6): 428–437. Review

- ✓ Understanding the interaction of nanoscale material with biological systems → PK
- ✓ Biodistribution and permanence
- ✓ Biodegradability? How are they cleared?
- ✓ Physicochemical properties associated with toxic responses
- ✓ Impact on the immune system
- ✓ Potential unexpected toxicity effects:
  - i. Increased reactivity (> surface area)
  - ii. Increased potential to cross biological barriers, get into tissues and cells
- ✓ Need to develop a multidisciplinary integrated science-based approach.
- ✓ …. …

Regulatory challenges

- 'Nanosimilars' - evaluation of follow-on nanomedicine products
  - Step-wise comparability studies
- 'Next generation' nanomedicines
  - Advances in nanoscience leading to creation of more complex, hybrid structures
  - Wave of new pharmaceuticals, imaging agents and combination products

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Nanotechnology

Nanotechnology is the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties. Nanotechnology is an **emerging field in science** that is used in a wide range of applications, from consumer goods to health products.

In medicine, nanotechnology has only partially been exploited. It is being investigated as a way to improve the properties of medicines, such as their solubility or stability, and to develop medicines that may provide new ways to:

- deliver medicines to the body;
- target medicines in the body more accurately;
- diagnose and treat diseases;
- support the regeneration of cells and tissues.

Activities at the European Medicines Agency

The European Medicines Agency follows the latest developments in nanotechnology that are relevant to the development of medicines. Recommendations from the Agency's Committee for Medicinal Products for Human Use (CHMP) have already led to the approval of a number of medicines based on nanotechnology. These include medicines containing:

- liposomes (microscopic fatty structures containing the active substance), such as Caelyx (doxorubicin); Mepact (mifamurtide) and Myocet (doxorubicin);
- nano-scale particles of the active substance, such as Abraxane (paclitaxel), Emend (aprepitant) and Rapamune (sirolimus).

The development of medicines using newer, innovative nanotechnology techniques may raise new challenges for the Agency in the future. These include discussions on whether the current regulatory framework is appropriate for these medicines and whether existing guidelines and requirements on the way the medicines are assessed and monitored are adequate.

The Agency also needs to consider the acceptability of new testing methods and the availability of experts to guide the Agency's opinion-making.

Ad-hoc expert group on nanomedicines

In 2009, the CHMP established the *ad-hoc* expert group meeting on nanomedicines.

This group includes selected experts from academia and the European regulatory network, who support the Agency's activities by providing specialist input on new scientific knowledge and who help with the review of guidelines on nanomedicines. The group also helps the Agency's discussions with international partners on issues concerning nanomedicines.

The group held its first meeting on 29 April 2009.

International workshops on nanomedicines

Related information

Reflection paper on nanotechnology-based medicinal products for human use (29/06/2006)

Contact point:

itfsecretariat@ema.europa.eu

Regulatory developments

Regulators from EU, US, Canada, Japan and Australia started in 2006 a forum for dialogue to share experience and understanding.

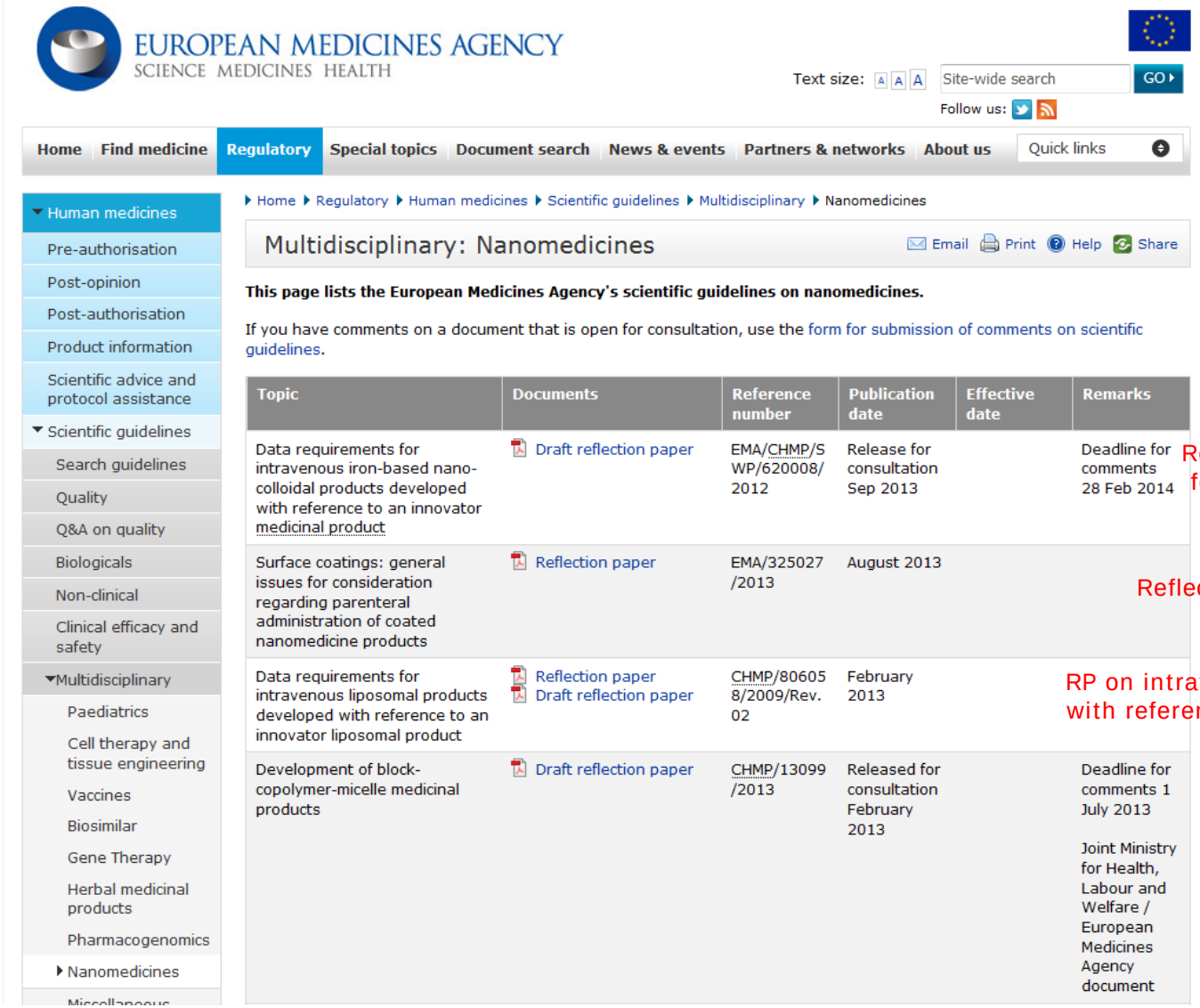
Need for additional guidance?

In EU there is a highly evolved system for the evaluation of benefit risk of medicinal products that has accommodated effectively in the past new technologies (eg. new diagnostic modalities, PET) and even some nanosize products

However….

Specific guidance on quality, toxicology and clinical development and monitoring aspects might be required in this area once sufficiently focused and identified sub-technologies have emerged and sufficient scientific experience is established.

CHMP nanopharmaceuticals multidisciplinary drafting group



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Multidisciplinary: Nanomedicines

Email Print Help Share

This page lists the European Medicines Agency's scientific guidelines on nanomedicines.

If you have comments on a document that is open for consultation, use the form for submission of comments on scientific guidelines.

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product	Draft reflection paper	EMA/CHMP/SWP/620008/2012	Release for consultation Sep 2013		Deadline for comments 28 Feb 2014
Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products	Reflection paper	EMA/325027/2013	August 2013		
Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product	Reflection paper Draft reflection paper	CHMP/806058/2009/Rev.02	February 2013		
Development of block-copolymer-micelle medicinal products	Draft reflection paper	CHMP/13099/2013	Released for consultation February 2013		Deadline for comments 1 July 2013 Joint Ministry for Health, Labour and Welfare / European Medicines Agency document

Reflection paper on non clinical studies for iron oxide Nanoparticles

Reflection paper on nanoparticles coating

RP on intravenous liposomal products developed with reference to an innovator product

Joint EMA/MHLW reflection paper on block copolymer micelles

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EMA support to nanomedicines developers

- **Innovation Task Force (ITF)** itfsecretariat@ema.europa.eu
  - Briefing meetings

    http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9

- **CHMP Scientific Advice and novel methods qualification (e.g. biomarkers)** scientificadvice@ema.europa.eu
  - Option of Parallel Scientific Advice with FDA

    http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

- **CHMP Expert and Drafting Groups on Nanomedicines**
  - Support to core procedure
  - Reflection papers to prepare the way forward
  - Joint activities with FDA and MHLW

- **EMA SME office** smeoffice@ema.europa.eu

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&mid=WC0b

Content

CONCLUSIONS

- Nanotechnology is an emerging science with great potential in a wide range of applications including drug delivery, diagnostics, theranostics and regenerative medicine.
- Due to the complex nature of nanomedicines it is important to take special CMC considerations during **early development** of these systems, i.e.
  - Identification of the CQAs of the drug product essential for its activity and safety;
  - Identification of appropriate analytical methods (physical, chemical, biological) for its **characterization;**
  - Identification of CPPs, evaluation of batch to batch consistency & scale up considerations to ensure a successful reproducible manufacturing process is achieved.
- Applicants are encouraged to contact the EMA from the early stages of the development through the Scientific Advice procedure or through the informal briefing meetings with the ITF.
- The focus of the EMA is to facilitate the development of such products.

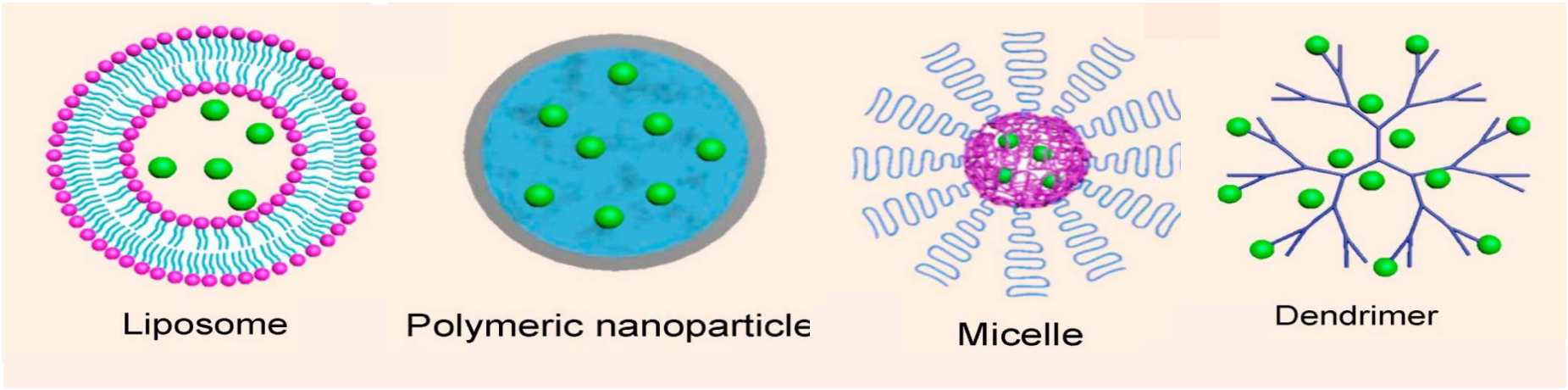
Need more information?

EMA website (nanotechnology page):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac05800baed9

Useful guidance:

- EMA guidance for companies requesting SA or PA
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9
- Qualification of novel methodologies for drug developments
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0
- Scientific guidelines
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb



Thank you for your attention!

Questions?

Acknowledgements:

CHMP Nano Drafting Group

ITF-Nano

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Back up slides

Reflection paper on data requirements for iv liposomal products developed with reference to an innovator liposomal product

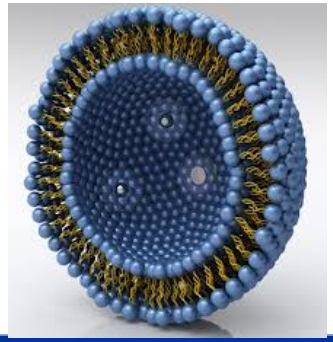
Background

Article 10 – BE guideline: liposomes require special considerations.

≠formulation & manufacture ⇨ S/E (cell interactions, distribution)

Scope

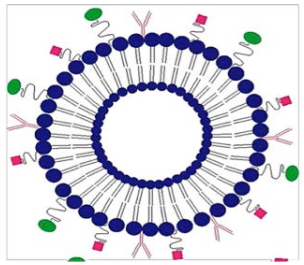
- Assist in the generation of relevant **quality**, **non-clinical** and **clinical** data to support a marketing authorisation of **intravenous liposomal** products developed **with reference to** an innovator liposomal product.
- The principles are valid to **"liposome-like"** and vesicular products which may be **under development** including those administered by routes other than intravenous administration
- Only where the PK of the active substance is affected.
- **Not product specific** ⇨ ***Product specific SA**

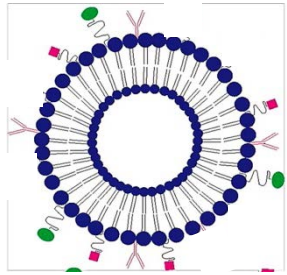


Pharmaceutical comparability

Quality characterisation

Compare





- Lipidic components & critical excipients
- Active susbtance/lipidic moiety ratio
- Liposome morphology, mean size and size distribution, aggregation
- Fraction of encapsulated active substance (amount of free/entrapped)
- Stability of AS, lipids, f(x)al exicipients, critical degradation products
- *in vitro* drug substance release rate from the liposome in physiologically/clinically relevant media
- Stability
- Reconstitution
- Maintenance of liposomal formulation integrity in plasma…

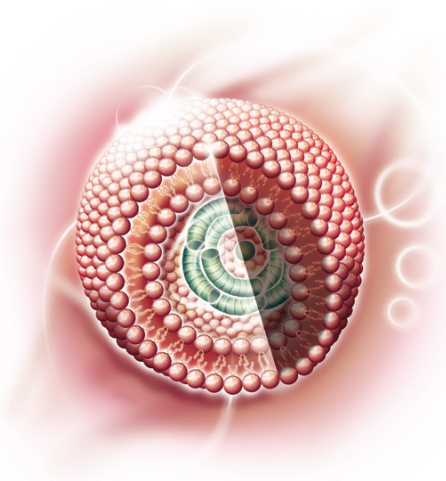
Impact in S&E

Non clinical studies

PK, PD, Tox

Clinical studies

Comparative PK, (efficacy), safety (infusion reactions)



Reflection paper on data requirements for iv iron-based nanocolloidal product developed with reference to an innovator medicinal product

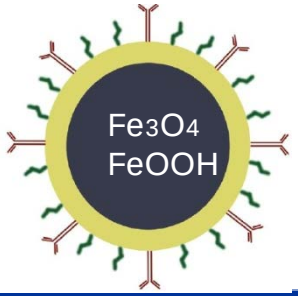
Background

"The inability to fully characterise and define coated iron based particles using quality methods alone together with uncertainties on how quality attributes relate to *in vivo* performance... quality comparability and demonstration of similar plasma concentrations of iron alone, i.e. **conventional bioequivalence studies in humans, would not be sufficient** for the assurance of comparable *in vivo,* fate and effect of these products. Therefore, non-clinical data are required in addition to human clinical PK studies.

Scope

- To assist in the generation of relevant **quality**, **non-clinical** and **clinical** data to support a marketing authorisation for an **intravenous iron-based nano-colloidal product** developed **with reference to** an innovator product.
  - Pharmaceutical data ⇨ Similarity
  - Types of non-clinical (biodistribution) and clinical studies (PK) (S, E)

*PhV/RMP: anaphylactic reactions, long-term safety follow up iron depositiyion



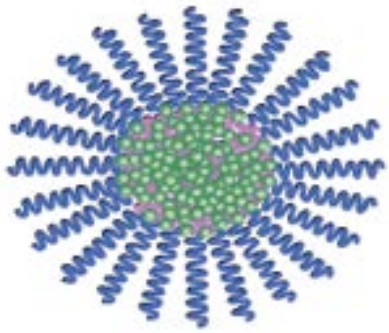
Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

Background

Traditional micelles (solubilisation) ≠ BCM (PK-targeting; release control,…)

Scope

- To assist in the generation of relevant quality, non-clinical and PK clinical comparative data to support a MA for iv **pharmaceutical development**, and **non-clinical** and **early clinical studies** of BCM created to affect PK, stability and distribution of incorporated or conjugated AS in vivo.
- In principle iv administration, but principles might be consider for other routes.
- **Not product specific** ⇨ ***Product specific SA**



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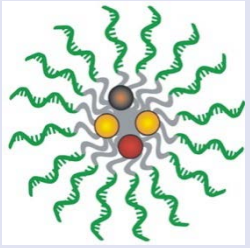


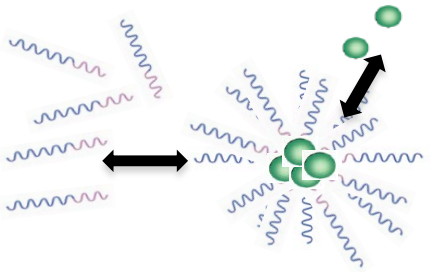
- Quality characterisation
  - Components containing block copolymers: chemistry, impurity profile
  - BCM products:
    - Properties related to the BCM: morpholozy, Z, cac, loading, surface, release, stability
    - Properties related to the manufacturing process: reconstitution, sterility
    - Properties related to the in vivo behaviour: osmolarity, surface, release, degrad.

The methods used must be sensitive enough to ensure batch to batch consistency. This is particularly important to monitor in the case that a block copolymer-active substance conjugate is involved.

*Block copolymer biological activity

*Specifications, stability

- Non-clinical studies (PK, PD, safety, toxicology)
- Considerations for first-in-human studies



Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

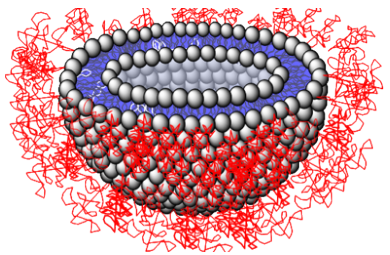
Introduction

"…presence of a coating has the potential to impact on the critical properties of the nanomedicine in terms of safety and efficacy. The physico-chemical nature of the coating, the uniformity of surface coverage, and the coating stability (both in terms of attachment and susceptibility to degradation) will govern the **pharmacokinetics**, the **bio-distribution** of the product and its **intracellular fate**. …**infusion-related reactions**.

In some cases a **coating material may elicit new biological responses**, not observed for either the coating material alone or the unmodified surface alone.

General considerations and product characterisation

- ✓ Characterization of the coating
- ✓ Validation of the coating step (chemistry)
- ✓ Orientation and conformational state of the ligand
- ✓ Stability, premature detaching, degradation…



When developing coated nanomedicines careful consideration should be given to the potential impact of the coating on the efficacy and safety profile of the product

Future expectations

- **Drug delivery**
  - One may expect better targeting and bioavailability of existing medicinal substances by the application of nanotechnology
  - New modes of action

- **Novel applications of nanotechnology may include**
  - nanostructure scaffolds for tissue replacement,
  - nanostructures that allow transport across biological barriers,
  - remote control of nanoprobes,
  - products which may combine and integrate diagnostic and therapeutic properties often in an integrated manner
  - integrated implantable sensory nanoelectronic systems and multifunctional chemical structures for drug delivery

The Innovation Task Force (ITF)

The Innovation Task Force is a **multidisciplinary group** that includes **scientific, regulatory and legal competences**

- Briefing meetings
  - Provides a **forum for early dialogue with applicants** on emerging science and technologies with potential regulatory impact.
  - **Nanotechnology** is one of the ITF areas of interest and a **dedicated group has been established** within it, focusing on nanotechnology scientific and regulatory aspects.

EMA specific initiatives

Scientific Advice and Protocol Assistance

- EU view on scientific issues not covered by or deviating from existing guidance
- Advice on development & agreement of future strategy
- Working party of CHMP

- Voluntary (upon company request)
- Procedure 40 to 70 days
- Face to face meetings for 50% of advice
- Fee-related activity (fee waiver/reduction for orphan products/paediatrics/SMEs)
- Not only product specific, also qualification of biomarkers and other novel methodologies