EMA perspective on the development of Nanomedicines

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Nanotechnology: definition

“Research and technology development at the atomic, molecular or macromolecular scale leading to the controlled creation and use of structures, devices and systems with a length scale of approximately 1 – 100 nanometers (nm).” (Source: National Nanotech Initiative)
EC definition of Nanomaterial

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

- 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.
Purpose of nanomedicines

Address 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
EMA experience with nanomedicines

- Some 20 Marketing Authorisation Applications
  Mainly anti-infectives, anti-neoplastic & immuno-modulating agents. Various types of nanomedicines systems.

- Over 50 Scientific advice and Protocol assistance

- Orphan Designations

- Innovation Task Force

- SME office
Nanomedicines reviewed by EMA

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 Osteosarcoma)*
  Mifamurtide in multilamellar liposomes.
  Formulation facilitates targeting macrophages and RES

- **Myocet** *(metastatic breast cancer)*
  Doxorubicin in self assembling **lamellar liposomes**.
  Formulation reduces cardiac toxicity and favours distribution to RES
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: www.abraxane.com/professional/moa.aspx
Future applications

- Multifunctional platforms (e.g. polymeric/multifunctional molecular systems)

- Products which combine and integrate diagnostic and therapeutic properties

- Integrated implantable sensory nano-electronic drug systems

- Remote-control nano-probes
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Scientific challenges

- Innovative and evolving scientific field
- EMA to align with state of the art knowledge and evolve methods to evaluate:
  - Characterisation and stability of nanosystems
  - Functionalities of the nanosystems, bio-interface and reactivity of the final product including coating and “excipients”
  - Biomarkers for nanofunctionalities?
  - Bio-distribution and Bio-persistence of nanomaterials and degradation products for long-term safety
  - Dose selection/schedule
  - Unique aspects of associated treatment procedures (e.g. impact of energy sources within and outside the clinical setting, re-administration)
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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EMA approach to nanomedicines

Ensure consistency and collaboration across EU, establishing a platform pooling appropriate expertise for the evaluation of both the scientific and the regulatory aspects.

- Reinforce scientific advice at an early stage
- Complement benefit/risk model
- Evaluate need for additional guidance
EMA framework for nanomedicines

- Evaluation of any nanomedicine based on established principles of **benefit/risk analysis**, rather than solely on the basis of the technology per se (including Risk Management Plans and Environmental Risk Assessment)

- **Specialised multidisciplinary** expertise required: mixed academia and regulators experts group created in 2009 and reinforced in 2011, pooling quality, safety and kinetics expertise to support evaluation and formulate guidelines

- Close **EU cooperation** with other scientific committees (e.g. SCENIHR, EFSA), networks (QNANO, ETPNano) and with European Commission

- **International cooperation**: EMA chairing an international Regulators expert group (US FDA, Japan MHLW, Health Canada, TGA Australia)

- **Transparent dialogue with stakeholders** (e.g. Int’l EMA Nanomedicines Conference in 2010)
Need for additional guidance?

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

Specific guidance on quality, toxicology and clinical development and monitoring aspects is required in this area, since focused and identified sub-technologies are emerging and scientific experience is being gained.
CHMP nanomedicines drafting group – reflection papers

In 2011 the CHMP commissioned the **multidisciplinary drafting group** to develop a series of **four reflection papers** on current scientific and regulatory thinking for nanomedicines.

These documents cover the development both of **new nanomedicines**, and of **nanosimilars** (since the first generation of nanomedicines, including liposomal formulations, iron-based preparations and nanocrystal-based medicines, have started to come off patent).
## CHMP nanopharmaceuticals multidisciplinary drafting group

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<tr>
<th>Topic</th>
<th>Documents</th>
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<tr>
<td>Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product</td>
<td>Draft reflection paper</td>
<td>EMA/CHMP/SWP/620098/2012</td>
<td>Release for consultation Sep 2013</td>
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<td>Deadline for comments 26 Feb 2014</td>
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<td>Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicines products</td>
<td>Reflection paper</td>
<td>EMA/225027/2013</td>
<td>August 2013</td>
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<td>Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product</td>
<td>Draft reflection paper</td>
<td>CHMP/80603/2009/Rev. 02</td>
<td>February 2013</td>
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<tr>
<td>Non-clinical studies for generic nanoparticle iron medicinal product applications</td>
<td>Reflection paper</td>
<td>EMA/CHMP/SWP/100094/2011</td>
<td>March 2011</td>
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Reflection paper on intravenous iron-based nano-colloidal products

Reflection paper on nanoparticles coating

Reflection paper on intravenous liposomal products

Joint EMA/MHLW reflection paper on block copolymer micelles

EMA perspective on the development of Nanomedicines
Reflection paper on data requirements for intravenous liposomal products

- 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 also 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
Reflection paper on data requirements for intravenous iron-based nano-colloidal products

✓ To assist in the generation of relevant **quality, non-clinical** and **clinical** comparative data to support a marketing authorisation of a **nano-sized colloidal** intravenous iron-based preparation developed as a treatment **for iron deficiency anaemia with reference to** a nano-sized colloidal innovator product.

✓ Principles also valid:

  - **to support changes** to the manufacture and control of **existing** iron based nano-sized colloidal products;
  - **for iron preparations being developed for other indications**, including diagnostics.
Joint EMA/MHLW reflection paper on block copolymer micelle medicinal products

- Information for the **pharmaceutical development**, and **non-clinical** and **early clinical studies** of block copolymer micelle medicinal products created to affect pharmacokinetics, stability and distribution of incorporated or conjugated active substances *in vivo*.

- In principle iv administration, but principles might be considered for other routes.

- Not product specific.
Reflection paper on surface coating

✓ General issues to consider during the development of nanomedicines that include a covalent or non-covalent coating, e.g. the effect of the coating on the product stability or on the product pharmacokinetics and bio-distribution (e.g. polymer-coated liposomes);

✓ Consideration of quality, non-clinical and clinical data which will play an important role in the definition of the critical product characteristics of a coated nanomedicine.

✓ 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.
Next-generation nanomedicines and nanosimilars: EU regulators’ initiatives relating to the development and evaluation of nanomedicines

Over the last three decades many first-generation nanomedicines have successfully entered routine clinical use and it is now important for medicines regulatory agencies to consider the mechanisms needed to ensure safe introduction of ‘follow-on’ nanomedicine products, ‘nanosimilars’. Moreover, drug regulators need to ensure that ‘next’-generation nanomedicines enter clinical development and consequently the market in a safe and timely way for the benefit of public health. Here we review recent European Medicines Agency activities that relate to the effective development and evaluation of nanomedicine products while keeping patient and consumer safety at the forefront.

KEYWORDS: block copolymer micelle, coating, colloidal iron-based nanomedicine, drug development, liposomal formulation, nanomedicine, nanosimilar, next-generation nanomedicine, regulatory science

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EMA training on nanomedicines

International webinar training sessions on nanomedicines:

- Block Co-Polymer Micelles (Prof. Kataoka, Japan and Prof. Ruth Duncan, UK) in 2011 and 2012

Further international sessions planned on:

- liposomal formulations
- iron-oxide nano particles
- nanomedicines coating
EMA support to nanomedicines developers

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

- Innovation Task Force (ITF)
  - Briefing meetings with EMA Committees, FDA, MHLW

- CHMP Scientific Advice and novel methods qualification (e.g. biomarkers)
  - Option of Parallel Scientific Advice with FDA

- EMA SME office
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.
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)
- Product specific or qualification of biomarkers and other novel methodologies
- Parallel scientific advice with FDA
EMA SME Office

- Launched in 2005 to support small and medium sized enterprises
- Regulatory and administrative assistance
- Quarterly newsletter
- SME User Guide
- Briefing meetings
- Workshops and training sessions
- Fee reductions
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Conclusions (I)

• Nanotechnology is an emerging science with opportunities for medicines in the fields of drug delivery, diagnostics, theranostics and regenerative medicine.

• Existing EU regulatory framework accommodates nanomedicines, and adapts to address new challenges.

• The accumulation of experience allows to assess the need for the development of guidance specific to nanomedicines.

• Applicants are encouraged to contact the EMA from early stages of development through the Scientific Advice procedure or through informal briefing meetings with the ITF.
Conclusions (II)

- Particular regulatory challenges are presented by the evaluation of ‘nanosimilars’, and by advances in nanoscience giving rise to a new generation of complex, hybrid structures.
- It is expected that nanotechnology will yield innovative products contributing to a more proactive paradigm for the diagnosis and therapy of diseases.
- The focus of the EMA is to facilitate the development of such products.
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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

- Qualification of novel methodologies for drug developments

- Scientific guidelines
EMA support to nanomedicines

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

- **CHMP Scientific Advice** and **Novel methods qualification (e.g. Biomarker)**
  
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