Nanomedicines: EMA experience and perspective

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Agenda

I. EMA and the challenges of nanomedicines

II. Regulatory science contribution to the progress in the field

III. Next steps
Regulators from EU, US, Canada, Japan and Australia started in 2006 a dialogue forum, chaired by EMA, to share experience and understanding.

**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); Mapact (milamoxine) 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 22 April 2009.

**International workshops on nanomedicines**
What are nanomedicines?

In 2011 the EC published a recommendation on the definition of nanomaterials, predisposing size as the critical factor (1-100 nm). The Commission Recommendation of 18 October 2011 on the definition of nanomaterials acknowledges that an upper limit of 100 nm is not scientifically justified across the whole range of nanomaterials. The recommendation 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'.
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": a variety of molecules organised in diverse structures.
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
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](http://ww.abraxane.com/professional/moa.aspx)
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
Scientific challenges

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

Regulatory science for the Evaluation of nanomedicines

**Potential benefits**

Promise of improved:
- Prevention
- Detection
- Treatment of disease
  - Solubility
  - Overcoming biological barriers (BBB)
  - Targeted delivery (EPR, ligands)
  - Bioavailability
  - Controlled release

**Countervailing concerns**

Potential safety risks
- Infusion reactions
- Hypersensitivity reactions
- Oxidative stress
- Altered body distribution
- ...

“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 environmental risk assessment)

*Reflection paper on nanotechnology-based medicinal products for human use*

EuroNanoForum
2015
Regulatory challenges

• ‘Nanosimilars’ - evaluation of “generics” of nanomedicine
  Comparability approach: focus on differences and their potential clinical implications

• **Classification** of borderline and converging technologies
  - Nanomedicinal products may exhibit a complex mechanism of action:
    ▪ combining mechanical, chemical, pharmacological and immunological actions
    ▪ combining diagnostic and therapeutic functions

• **First in line complex nanomedicines** (e.g. conjugated dendrimers)
  ▪ New ways of gathering data
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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Regulatory science approach: pool the best expertise

- **Specialised multidisciplinary expertise:** 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 European Commission, with other EU organisations (e.g. ECHA, EFSA, JRC), networks (QNANO, ETPNano);

- **International cooperation** - Since 2009 EMA chairing an international Regulators expert group (US FDA, Japan MHLW, Health Canada, TGA Australia).

- **Transparent dialogue with stakeholders** (e.g. EMA 1st International Workshop on Nanomedicines 2010).
Regulatory science approach: provide orientation to innovators
Regulatory science approach: develop appropriate and accessible regulatory platforms, tools, incentives

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

- **CHMP Scientific Advice** and **Novel methods qualification** (eg Biomarker):
  industry, consortia, SME, academia
  scientificadvice@ema.europa.eu

- **EMA SME office**
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Next Steps

✓ Further develop fit-for-purpose regulatory science experts in the context of the newly established EU Network Training Centre (EU NTC)

✓ Maintain high level collaboration with the EC and other EU institutions and organisations

✓ Foster global convergence under the umbrella of International Pharmaceutical Regulatory Forum

✓ Promote dialogue and the use of the Methods qualification/scientific Advice to translate PoCs in to know-how and products for Health and Growth.
Thank you for your attention!

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Acknowledgements:
Prof Marisa Papaluca, MD, EMA Senior Scientific Advisor
Mr Falk Ehmann, MD, PhD, EMA Science and Innovation Officer
Mr Ruben Pita, EMA Procedure Manager

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=WC0b01ac0580baed9

  - EMA guidance for companies requesting SA or PA

  - Qualification of novel methodologies for drug developments
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)
- Not only product specific, also qualification of biomarkers and other novel methodologies