Nanomedicines: regulatory challenges and risks ahead

**Brian Kelly** reports from the first international scientific workshop dedicated to nanomedicines.

There are a number of fundamental regulatory and scientific issues that must be addressed before nanomedicines can become everyday medical products.

This was the message that emerged from the first international scientific workshop dedicated to nanomedicines – hosted by the European Medicines Agency in London on 2-3 September – where 200 or so delegates from around the world convened to share regulatory experiences and prepare for the evaluation of future nanomedicines.

Clarification is still needed on nanomedicine classification, characterisation and safety, according to the workshop participants, who had gathered from 27 countries including Australia, Canada, India, Japan, the US and EU member states. Clarification is also required on the extent to which the quality, non-clinical and clinical data generated to support marketing authorisation applications must account for the special properties of nanomedicines that contribute to their activity – i.e. their small size and high ratio of surface area to volume.

**Nanotechnology and medicines**

Nanotechnologies have a wide, and still only partially exploited, potential in the development of medicines. They provide scope for engineered nanosystems that could lead to a spectrum of useful functions such as refined drug delivery, advanced combined diagnostics/therapeutic functions, matrices and support structures for regenerative medicines. The main types of nanomedicine products discussed at the EMA workshop were as follows:

- medicines and medical devices: most current commercial applications are geared towards drug delivery to enable new modes of action and better targeting and bioavailability of existing medicinal substances. Nanoparticles such as liposomes, dendrimers, gold nanoshells, quantum dots and fullerenes potentially have a number of advantages over classical drug delivery methods. These include the potential to alter significantly the absorption, distribution and duration of medicines in the body, as well as to allow for targeted delivery of drugs to disease sites;
- tissue engineering and implants: nanotechnology can play a pivotal role in the development of cost-effective therapies for in situ tissue regeneration. Key areas of interest are intelligent biomaterials, bioactive signalling molecules and cells, including stem cells. The biomaterials are designed to respond to the changes in the immediate environment, stimulating regenerative events at the molecular level. Regenerative events at the molecular and cellular levels are key to the fabrication and repair of cells. Nanotechnology could also be used to develop efficient targeting systems for stem cell therapies; and
- nanodiagnostics: nanotechnology can provide tools with better sensitivity, specificity and reliability in diagnostics. It offers the possibility to take different measurements in parallel or to integrate several analytical steps from sample preparation to detection into a single miniaturised device, such as a lab-on-a-chip. Other nanodiagnostics applications include biomolecular sensors and molecular imaging, which aim to create highly sensitive and reliable detection agents that can also deliver and monitor therapy. Super paramagnetic particles seem to offer much promise in this regard.

The EMA has so far reviewed around 18 marketing authorisation applications for nanomedicines. These include liposomal formulations, nanoparticles and polymers/conjugates used as anti-infectives, anti-neoplastic and immuno-modulating agents. The applications were assessed under the existing EU regulatory framework using established principles of benefit-risk analysis, with the scientific flexibility to accept new development models and testing methods in the evaluation of such products. Examples of medicines approved by the European Commission under the centralised procedure are listed in Table 1.

However, emerging therapies such as theranostics and nanosystems used in regenerative medicines give rise to questions on the appropriateness of current regulatory frameworks, the relevance and adequacy of existing requirements and guidelines, and on the availability of adequate expertise to regulators.

**Table 1. Examples of nanomedicines centrally authorised by the European Commission**

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Nanotechnology Purpose</th>
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<tbody>
<tr>
<td>Abraxane (paclitaxel)</td>
<td>Solvent free colloidal suspension of albumin-bound nanoparticles to increase water solubility</td>
</tr>
<tr>
<td>Caelyx (doxorubicin)</td>
<td>Pegylated liposome to increase blood circulation (long acting)</td>
</tr>
<tr>
<td>Emend (aprepitant)</td>
<td>Colloidal dispersion of nanoparticles to increase bioavailability (wet milling method)</td>
</tr>
<tr>
<td>Mepact (mifamurtide)</td>
<td>Liposome encapsulation to facilitate activation of macrophages</td>
</tr>
<tr>
<td>Myocet (doxorubicin)</td>
<td>Liposome encapsulation to reduce cardiac toxicity and to increase tumour tissue distribution</td>
</tr>
<tr>
<td>Rapamune (sirolimus)</td>
<td>Colloidal nanodispersion stabilised with poloxamer to reduce particle size for increased stability and bioavailability</td>
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**Borderline products: call for flexibility**

A key theme at the EMA workshop was the need to understand whether nanomedicines should be classified as a medicine or a medical device. In the EU, for example, novel applications of nanomedicines will likely span the regulatory boundaries between medicinal products and medical devices and this may make their classification challenging.

Generally, the principal intended action of a medical product dictates the regime to which it should be subject. Typically, the device function is fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions) or chemical action. The action of a medicinal product, on the other hand, is generally achieved by pharmacological or immunological or metabolic means.

When products are based on viable cells or tissues, the consensus at the workshop was that the pharmacological, immunological or metabolic action should be considered as the principal mode of action and, in such cases, the products would fall under the medicines rules, most likely as advanced therapy medicinal products (ATMPs).

According to EU Directive 2001/83/EC on human medicines, as amended, and the Medical Devices Directive (93/42/EEC, as amended), the basis for deciding which regulatory regime is applicable to a product that combines a drug and device is the principal mode of action of the combination product. Medical devices may be assisted in their function by pharmacological, immunological or metabolic means, but as soon as these medicinal means are no longer ancillary with respect to the principal mode of action of a product, the product becomes a medicinal product. The claims made for a...
product, in this context, represent an important factor for its classification as a medical device or a medicinal product.

Nanomedicinal products, however, may exhibit a complex mechanism of action that combines mechanical, chemical, pharmacological and immunological properties and that provides both diagnostic and therapeutic functions. This was demonstrated at the workshop by Professor Rutledge Ellis-Behnke of the Massachusetts Institute of Technology in the US, who said that regulators need to consider each step of a product’s mode of action before coming to a conclusion. For example, regenerative nanomedicines may operate at the molecular level and also provide an “environment” that encourages cell growth without necessarily initiating cell growth.

To this end, speakers at the workshop expressed a desire for regulators to be flexible. For example, Jöns Hilborn, professor of polymer chemistry at Uppsala University in Sweden, said that the evolution of stem cell technology does not lend itself to a single concept of product development and regulation. Although laws such as Regulation (EC) 1394/2007 on ATMPs establishes criteria that must be fulfilled before a product can be placed on the market (eg safety, characterisation, purity, potency and clinical efficacy criteria), Prof Hilborn said there must be flexibility in how to fulfil those criteria.

There is no internationally-accepted definition of nanotechnology and nanomaterials

Ambiguity over classification

The workshop also highlighted the fact that there is a lack of an internationally accepted definition of nanotechnology and nanomaterials. This has led to ambiguity over whether a particular technology can in fact be classified as “nano”.

According to Rogério Gaspar, professor of pharmaceutics at the University of Lisbon, in Portugal, and EMA ad-hoc expert on nanomedicines, one of the challenges here is dealing with follow-up nanomedicines that are based on older medicines not previously classified as nanoparticles. Prof Gaspar gave as an example, follow-up iron oxide-based medicines containing colloidal nanoparticulate systems that can be used for imaging, which have been approved under national and/or mutual recognition/decentralised procedures without any clear framework.

Typically, nanomaterials are viewed as structures in the realm of 1 to 100 nanometers. However, it was clear from discussions at the workshop that there is little scientific evidence that the 100nm value is appropriate, rendering the upper limit somewhat arbitrary. Delegates also felt that defining the nanoscale as having a size between approximately 1 and 100nm would not be without problems within a regulatory setting. As such, a more elaborate description is needed to identify unequivocally a nanomaterial or a product containing a nanomaterial.

Several international and national organisations have proposed definitions for the nanoscale and for nanomaterials. In most of the definitions proposed, the size refers to one or more external dimensions or an internal structure within a specified size range. However, solely referring to size as “one or more external dimensions” will not capture aggregates and agglomerates of primary particles or, importantly, more complex multi-component nanomaterials that are widely used in medical and cosmetic applications, as their external dimension is likely to be larger than a specified upper size limit. The inclusion of a reference to “internal structure” with the same specified range as the external dimensions would include materials that consist of aggregates, agglomerates and multi-component assemblies within the scope of the definition. This would also include nanoporous and nanocomposite materials.

The European Commission’s Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) recent consultation on the definition of nanomaterials was discussed at the workshop. According to Dr Philippe Martin, of the commission’s Directorate General for Health and Consumers, the consultation represents a positive step in attempting to harmonise nano definitions.

Specifically, the consultation aims to identify the most appropriate metrics to define materials at nanoscale, taking into account reported size ranges and other relevant characteristics and corresponding metrics, characteristics, physico-chemical properties and thresholds.

In its preliminary opinion, SCENIHR considered that the most important terms that have to be described clearly to avoid misunderstanding and/or misuse are “size” and “nanomaterial”. For the lower limit of the definition of nanomaterials, SCENIHR proposed a size of 1nm. However, it considered that the use of a single upper limit value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. The lower threshold would be the critical threshold for which extensive nano-specific information has to be provided in order to perform case-by-case risk assessment.

Notwithstanding the lack of science behind an upper regulatory limit, Professor Ellis-Behnke referred to a recent US Food and Drug Administration guideline on reporting nanotechnology-related information that does specify upper limits. For example, the FDA guidelines provide the following definitions:

- nanomaterial/nanoscale materials: any materials with at least one dimension smaller than 1,000nm;
- nanoparticles: nano-object with all three external dimensions at the nanoscale that is the size range from approximately 1nm to 100nm; and
- nanotechnology: the understanding and control of matter at dimensions between approximately 1 to 100nm, where unique phenomena enable novel applications.

Other guidelines include the International Organization for Standardization’s technical report on methodology for classifying nanomaterials ISO/TR 13602:2010, Nanotechnologies – Methodology for the classification and categorization of nanomaterials, introduces a classifying system, called “nano-tree”, which can be used for categorising a wide range of nanomaterials (including nano-objects, nanostructures and nano-composites) of various dimensionality of different physical, chemical, magnetic and biological properties.

Characterisation is one of the most difficult challenges for nanomedicine manufacturers

Manufacture

The development, manufacture and characterisation of nanomedicines were discussed by a number of academic and industry representatives at the workshop. Many of the manufacturing challenges applicable to conventional medicines — stability, establishing limits for process impurities and optimising the manufacturing process to produce the selected drug substance particle size distribution within the drug product and so forth — also apply to nanomedicines.

Delegates described a number of manufacturing techniques for nanomedicines currently on the market (see Table 2). However, Simon Holland, director of process understanding & control within GlaxoSmithKline’s Pharmaceutical Development Unit in Ware, UK, believes that characterisation is one of the most difficult challenges for nanomedicine manufacturers.

Dr Holland told the workshop that regulatory agencies are now placing more focus on nanotechnology platforms and are requesting validated predictive characterisation techniques — ie meaningful in vitro/in vivo analytical methodologies. He added that regulatory agencies may be reluctant to issue a manufacturing licence or marketing...
Debate on development

The EMA asked workshop participants to debate on particular issues relating to the development of nanomedicines, in particular the non-clinical aspects of nanomedicine development as follows:

- biodistribution of nanoparticles;
- physico-chemical characteristics and stability, particularly in the blood and in organs;
- cell distribution;
- the immune system effects;
- genotoxicity, if this should always be tested and if so, how, and
- the need for guidance.

It became clear from discussions on these topics that there is no one-size-fits-all approach to these issues. Presenters such as Ruth Duncan, professor emerita at Cardiff University, in the UK, and member of the EMA’s ad-hoc expert group on nanomedicines, advocated a case-by-case approach to determining the appropriate pre-clinical tests that should be conducted, as well as risk assessment in general. Therefore, general pre-clinical guidelines for nanomedicines do not seem to be the most appropriate way forward at this time, although the door was left open for nanomedicine-specific product guidelines.

Other speakers said that existing guidelines could be adapted to meet nanomedicine-specific issues. For example, Jacques Descotes, professor and head of the poison center and pharmacovigilance at Lyon University hospital in France, suggested an immunotoxicology approach based on existing guidelines for conventional medicines, such as ICH S8: Immunotoxicity Studies for Human Pharmaceuticals. Prof Descotes advocated, however, conducting at least one systemic immune function assay (eg a T-dependent antibody response assay, or TDAR) even though this is not a specific requirement in the existing guidelines.

Some assays for genotoxicity may not be appropriate for nanomedicines

Daan Crommelin, professor of pharmacetics at Utrecht University in the Netherlands, made the point that guidelines could be developed based on the learning derived from evaluating existing nanomedicines, such as liposomes and doxorubicin. Prof Crommelin referred in particular to draft FDA guidance in this regard. For liposome-based products, for instance, the FDA draft guidance recommends that manufacturers conduct two studies – a clinical trial and an in vitro study – to demonstrate bioequivalence.

Further, it became clear that some assays for genotoxicity may not be appropriate for nanomedicines. For example, Dr Wim de Jong, a toxicological pathologist at the National Institute for Public Health and the Environment at Bilthoven, the Netherlands, suggested that some bacteria-based genotoxicity assays may not be appropriate as the nanomaterial may be able to penetrate the bacteria.

Safety under the spotlight

The key underlying theme of the workshop was the safety of nanomedicines. Many aspects of the interaction of nanoparticles and biological systems and the effects, if any, at the subcellular level, particularly for inhaled nanoparticles remain unknown. There is a need for more information on the response of living organisms to the presence of nanoparticles of varying size, shape, chemical composition and surface characteristics to understand and categorise the toxicity of nanoparticles. Key factors in the interaction with living structures most likely include nanoparticle dose, the ability of nanoparticles to spread within the body, as well as their solubility.

For example, some nanoparticles dissolve easily and their effects on living organisms are the same as the effects of the chemical they are made of. However, other nanoparticles do not degrade or dissolve readily. Instead, they may accumulate in biological systems and persist for a long time, which makes such nanoparticles of particular concern as they could potentially build up within the lysosomes of cells and cause lysosomal storage disease.

Kenneth Dawson, professor of physical chemistry at University College Dublin, in Ireland, and a member of the EMA’s ad-hoc working party on nanomedicines, indicated that some nanoparticles adsorb proteins when they interact with biological systems, a process known as “protein corona”. Prof Dawson said that protein corona are not static and that proteins may leave nanoparticles. However, the biological implications of this are not yet fully understood and could depend, for instance, on the nanomaterial, the size, the environment (eg blood plasma versus cerebrospinal fluid) and possibly other unknown factors. For that reason, Prof Dawson believes it is crucial to better characterise the nanomaterial (see characterisation above), particularly with respect to the surface of the nanoparticle. In addition, Peter Dobson, academic director of Oxford University’s Begbroke Science Park in the UK, said that nanoparticles of less than 20nm have surface defects that give those nanoparticles “interesting properties” that are poorly understood. Prof Dobson gave the example of zinc oxide, which he said was normally non-magnetic but when produced in sizes of less than 20nm appears to have magnetic properties.

Therefore, any regulatory approvals of nanomedicines are likely to be accompanied with a risk management plan. The relevant EU legislation on risk management is Article 8(3) (ia) of Directive 2001/83/EC, as amended, which states that the marketing authorisation application shall be accompanied “by a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce”.

### Table 2. Examples of processes used to manufacture nanotechnologies

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<thead>
<tr>
<th>Manufacturing Technique</th>
<th>Nanosystem</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media milling</td>
<td>NanoCrystals</td>
<td>Elan</td>
</tr>
<tr>
<td>High pressure homogenisation</td>
<td>NanoEdge</td>
<td>Baxter</td>
</tr>
<tr>
<td>Precipitation</td>
<td>High Gravity Controlled Precipitation</td>
<td>NanoMaterials Technology Pte</td>
</tr>
<tr>
<td>Cryomilling</td>
<td>NanoQUAD</td>
<td>Nanotherapeutics Inc</td>
</tr>
<tr>
<td>Emulsions</td>
<td>BioAqueous</td>
<td>Dow Pharma</td>
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</table>
Article 9(4)(c) of Regulation 726/2004 requires details of conditions and restrictions on the supply or use of the medicinal product attached to the EMA’s positive opinion. There are also EU guidelines on pharmacovigilance, e.g. Volume 9A of the commission’s notice to applicants, guidelines on pharmacovigilance planning, risk management systems and risk management templates (e.g. the EU Risk Management Plan).

Annalis Rubino, of the EMA’s risk management division, told delegates that the risk management framework could be adapted to include references to “other toxicities”, including nano-specific toxicities. Specific risks identified that do not fit into existing sections of the EU-RMP could be discussed in a new section under “Additional EU Requirements”, as is the case for EU-RMPs for advanced therapy medicinal products. Dr Rubino also suggested that the EMA follow the approach adopted by the FDA and produce product-specific safety specifications for nanomedicines.

Conclusion
The assessment of existing nanomedicines has provided valuable experience in examining certain aspects of emerging nanomedicines. Scientific challenges arise from the limitations of current testing methods and the reliability of novel ones, because of the “nanosize” and the unique behaviour of such nanosystems in biological structures. Further scientific research is needed to provide a sound scientific basis for an adequate evaluation of the quality, safety and efficacy of emerging nanomedicines. This should be supported by a continued dialogue between scientists and regulators. Until then, regulators are required to continue using a case-by-case approach when evaluating nanomedicines.

References
4. EU a step closer to defining nanomaterials, RAJ Pharma online, 14 July 2010
8. ISO offers mechanism for classifying nanomaterials, RAJ Pharma online, 23 August 2010 (and also this issue)

Brian Kelly is a regulatory lawyer in the life sciences practice at Covington & Burling LLP, in London, UK. He is also an honorary lecturer in nanotechnology regulation at University College London.

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