Nanomedicines: think big!

On 29 June 2006, the European Medicines Agency (EMEA) published a Reflection Paper "*on nanotechnology-based medicinal products for Human Use*"[1]. Although it is rather peculiar that the scope of this Reflection Paper is limited to products for human use – nanomedicines could prove to be just as useful in the field of veterinary medicinal products – the EMEA clearly wanted to show the pharmaceutical industry that it has both the experience and the willingness to handle applications for regulatory approval based on this rapidly evolving field of technology, say Kristof Roox and Benito Boone.

...introduction

In simple language, nanotechnology is the science of building devices on a microscopical scale from single atoms and molecules. Nanomedicines [2] are defined by the EMEA as the application of nanotechnology to assist in the making of a medical diagnosis or in treating or preventing diseases. They are in fact tiny medicines – or carrier devices for medicines – that can help tackle life-threatening and debilitating diseases. Numerous applications in the medical field are conceivable.

Nanotechnology is an important new science with a tremendous economic potential. By 2015, nanotechnology-based materials, products and services – including nanomedicines – are expected to form global markets worth hundreds of billion of euros each year. The European Commission has recognised and stressed the importance for the EU to maintain and further consolidate its competitive advantage in the field of nanosciences in general, as part of the EU's "Lisbon Strategy", focusing, among others, on the subfield of nanomedicines [3].

There are, however, potential legal obstacles in the field of nanomedicines. These can mainly be found in the patent policy for nanomedicines on the one hand, and problems to obtain regulatory approval for nanotech-based medicinal products on the other hand. While the first issue, which falls out of the scope of this article, seems to be the main cause of concern for the European Commission [4], the regulatory issues are of major importance as well. Many novel applications of nanotechnology will span the regulatory boundaries between medicinal products and medical devices. Since both medical devices and medicinal products are subject to entirely different regulatory and monitoring regimes – the latter being more expensive, time-consuming and more strictly regulated – it should be clear from the start which of these two regulatory pathways will have to be followed.

...medical devices

In the EU, medical devices are regulated by two Directives: Council Directive 93/42/EEC on medical devices; and Council Directive 90/385/EEC on active implantable medical devices.

Article 1(2)a of the aforementioned Directives provides the definition of a "medical device", and article 1(2)c of Directive 90/385 of an "active implantable medical device". A certain number of products have explicitly been excluded from the scope of both Directives, such as human tissues, cosmetics, human blood and plasma, etc. Nanotech-based products are, however, not expressly excluded.

Articles 1(3) and 1(4) of the Directives aim at distinguishing medical devices from medicinal products: as a general rule a product is regulated either by Directive 93/42 – Directive 90/385 if the concerned product is an active implantable medical device – or by Directive 2001/83/EC on the Community code relating to medicinal products for human use. In principle, the procedures under both Directives do not apply cumulatively[5]. The method by which the principal intended action is achieved, is crucial in the definition of a medical device[6].

In order to decide whether a product is considered a medical device or a medicinal product, the following points should be considered, according to the demarcation guidelines issued by the European Commission: 1) the intended purpose of the product taking into account the way the product is presented; and 2) the method by which the principal intended action is achieved.

In the case of a medical device, the principal intended action is typically fulfilled by physical means – including mechanical action, physical barrier, replacement of, or support to, organs or body functions. Where a device is intended to administer a medicinal product, that device is to be governed by Directive 93/42. If, however, such a device is placed on the market in such a way that the device and the medicinal product form *a single integral product* which is intended exclusively for use in the given combination and *which is not reusable*, that single product shall be considered a medicinal product (Article 1(3) of Directive 93/42). If a medical device contains a medicinal substance that acts on the body in a manner ancillary to the device, it will be regulated as a medical device. However, where such substances act in a manner that is *more than ancillary*, the product will be governed as a medicinal product rather than a medical device (article 1(4) of Directive 93/42/EEC).

The aforementioned demarcation guidelines specifically apply these provisions to "drug delivery systems". A device that is intended to deliver or carry a medicinal product is itself regulated as a medical device. The medicinal product that the device is intended to administer must, of course, be approved according to the normal procedures for medicinal products. But if the device is inseparable from the substance, it will be considered a medicinal product in its entirety.

...medicinal products

The definition of a "medicinal product" is provided for by article 1(2) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. A recent amendment, however, added a clarification that *in cases of doubt*, where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and within the definition of a product covered by other Community legislation, the provisions of Directive 2001/83/E shall nonetheless apply.

According to the 7th recital of Directive 2004/27/EC, this new addition does not mean that more products will be categorised as medicinal products than was the case in the past. It was merely intended to take into account both the emergence of new therapies and the growing number of so-called "borderline" products between the medicinal product sector and other sectors, so as to avoid any doubt as to the applicable legislation when a product, whilst *fully* falling within the definition of a medicinal product, may also fall within the definition of other regulated products. Where a product clearly falls under the definition of other product categories, in particular food, food supplements, *medical devices*, biocides or cosmetics, Directive 2001/83/EC does not apply.

If nanomedicines were to be considered as medicinal products, the question would arise as to which procedure would have to be followed to obtain marketing approval. Nanomedicines would not as such fall under the mandatory scope of article 3(1) of Regulation 726/2004/EC forcing applicants to obtain a centralised marketing authorisation. Article 3(2)b, however, provides applicants the option to apply for a centralised Community marketing authorisation, instead of applying for different marketing authorisations in various Member States, if "*the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical*

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innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level". In reality, the EMEA will at this point be the only competent authority having at its disposal the required expertise for assessing nanotech applications. The EMEA's Reflection Paper, which clearly states that it has already granted a number of nanotech-based medicines, is probably also aimed at convincing applicants to make use of the optional scope instead of trying to obtain "decentralised" marketing authorisations.

...nanomedicines

Although the popular denomination "nanomedicines" could lead to a different conclusion, it seems as if nanomedicines do not always qualify as medicinal products. As mentioned above, the primary action of a medicinal product is generally achieved by pharmacological, immunological means or by metabolism (article 1(2)b of Directive 2001/83/EC), whilst the primary intended action of a medical device is more of a physical nature[7].

In its Reflection Paper, the EMEA already acknowledged that the majority of current commercial applications of nanotechnology to medicine was, and is, geared towards drug delivery to enable new modes of action, as well as the better targeting and bioavailability of existing medicinal substances. Nanomedicines, however, may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological and immunological properties and combining diagnostic and therapeutic functions. It will all boil down to determining what the *primary intended* action is.

The American Food and Drug Administration (FDA) regulates nanomedicines as "Combination Products" for which the regulatory pathway has been established by statute[8]. In such cases, the FDA will determine the primary mode of action of the product. This decision will determine the regulatory framework for the product, i.e. a drug, medical device or biological product. The product application will from then onward be managed by the appropriate FDA healthcare Center in consultation with the other Centers. In some cases, neither the FDA nor the applicant can determine the most important therapeutic action at the time a request is submitted. A combination product may also have two independent modes of action, neither of which is subordinate to the other. Depending upon the type of combination product, approval, clearance or licensure may be obtained through submission of a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product. For most combination products, a single marketing application is sufficient for the product's approval, clearance or licensure.

Since the European Directives do not define the term "combination product", applicants for nanomedicines will often have a hard time determining which regulatory pathway they will have to follow, since the complex methods of action can be combined in one single product. As a result, applicants for nanomedicines will have to assess, in close cooperation with the EMEA or competent authorities of Member States, on a case-by-case basis which regulatory regime will govern their product.

...conclusion

It goes without saying that the current ambiguity and legal uncertainty with regard to nanomedicines are not beneficial for competitiveness at all. Without a clear regulatory framework aimed at nanotech-based medicines, both patients and applicants lose valuable time. In this respect, reference can be made to the recently adopted Council Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. According to the initial proposal of the European Commission, "*the lack of a comprehensive, clear and uniform regulatory framework creates legal uncertainties and leads to a fragmentation of the tissue engineering market: similar products are regulated differently in the various Member States, different safety requirements may apply and patients can be denied access to products which are readily available in other countries. This situation needs to be addressed as tissue engineering is an innovative and fast-moving biotechnology sector, which promises to offer a variety of new treatment opportunities for European patients.*" This goes *mutatis mutandis* for nanotechnology-based medicinal products.

Although it has to be acknowledged that creating a comprehensive legal framework for a diverse and rapidly emerging field of technology such as nanomedicines is not the easiest of tasks, the European Commission should try to come up with a legislative proposal sooner rather than later. Even though the European Parliament's Industry, Research and Energy Committee (ITRE) agreed a draft position on nanotechnology at a meeting on 20 June 2006, such initiatives will not result directly in a new Directive. The European Commission intends to work with other bodies, during the four years covered by the action plan, to identify safety issues and develop adaptations to relevant existing legislation[9]. The uncertainty for potential applicants will therefore remain for some time.

Since in many countries, the regulation of nanotech is far from clear, the first country that manages to provide a clear and sufficient regular pathway for nanomedicines, will undoubtedly gain a competitive advantage over the others. As Nobel prize winner Zhores Alfyorov has already pointed out, the absence of a clear regulatory framework in his native country Russia could mean nanotech completely fails over there [10]. Given the enormous potential of nanomedicines, the European Commission should ensure that this will not be the case in the EU. ❊

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[1] http://www.emea.europa.eu/pdfs/human/genetherapy/7976906en.pdf.

[2] The term "nano" (ancient Greek for "dwarf") refers to all molecules and devices/technologies in the size range 1 to a 1000 nanometres (a nanometre is a billionth of a metre or 0.000 000 001 of a metre).

[3] http://ec.europa.eu/research/industrial__technologies/pdf/nano__medicine__vision__paper__en.pdf

[4] In its action plan, the Commission lists a number of proposals with regard to the patenting of nanotechnology, such as the establishment of a nanotechnology Patent Monitoring System e.g. by the European Patent Office (EPO), as well as the harmonisation of practices in the processing of N&N patent applications between patent offices such as the EPO, United States Patent and Trademark Office (USPTO) and Japan Patent Office (JPO), and an agreement as soon as possible on the adoption of the Community patent, noting that the patenting of nanotech inventions in Europe develops slowly compared to other world regions

[5] Guidelines relating to the demarcation between Directive 90/385/EEC on active implantable medical devices, Directive 93/42/EEC on medical devices and Directive 65/65/EEC relating to medicinal products and related Directives, MEDDEV 2.1/3, Rev. 2, July 2001

[6] Jens Schletter, Manfred Ruediger; Sybille Esser , "Regulatory Requirements for Stem Cell-based Therapies", *RAJ Pharma*, Vol. 14, April 2003

[7] "which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be assisted in its function by such means" (article 1(2)a of Directive 93/42)

[8] http://www.fda.gov/nanotechnology/regulation.html

[9] Worldwide Update", *RAJ Pharma*, July 2006, p. 462

[10] *Nanotechwire*, 3 April 2005, http://nanotechwire.com/news.asp?nid=1781&ntid=%20&pg=49

