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EUROPEAN UNION REGULATIONS ON NANOMEDICINE

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Abstract: *Rapidly emerging technologies, such as nanotechnologies, constitute significant challenges to EU regulatory framework due to the uncertainties of development trajectories, product properties and potential risk problems. This article analyses the emerging regulatory activities in relation to nanomedicine, in the context of an increased awareness about particular regulatory questions and problems that have emerged over the last few years, in exploring the particularities of EU medical technology regulatory framework. The main conclusion of this article is that all the deficiencies that could be identified in the EU nanomedicine regulation framework led to the lack of legal certainty, a principle that has high priority in EU medical regulation policy.*

Key words: *nanomedicine, medical technology, EU regulation.*

1. Introduction

Scientific research and discoveries in nanomedicine have provoked enormous enthusiasm ranging from the rational to bizarre [11], due to the highly specific medical intervention at molecular scale for curing disease or repairing damaged tissues. In fact, nanomedicine is designed to address some of the challenges caused by both medical diagnosis and therapy by using nanoscale materials and nanotechnology. Using engineered nanodevices and nanostructures, human biological systems can be monitored, repaired, constructed and controlled at the molecular level. Nobel Prize winner Richard Smalley forecasted that in the not-too-distant future "nanotechnology will have given us specially engineered drugs" that could even make cancer "a thing of the past."

In the last two decades, nanomaterials and nanotechnologies were used or were subject to scientific research in order to be used in the therapeutic area and in diagnosis. For instance, in the therapeutic area, nanoparticles are used to selectively transport drugs to the diseased tissues or cells. Due to the remarkable innovations of the scientists who adopted techniques from computer chip industry to nanoparticules with precise control of size, shape and composition, in the future, such nanoparticles can be used to load a variety of drugs and imaging agents [15] and to deliver them to the selected cells and tissues. Other nanoparticles were designed to be used in photothermal therapy of cancer [9], or in the delivery of siRNA (short double-stranded RNA molecules) to the cell's cytoplasm, triggering thus the degradation of messenger RNA and providing targeted control of gene

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expression that can be useful in many disease states [16]. Nanoparticles have also application in diagnosis, a good example being the use of nanoparticles in the analysis of rare proteins in blood and tissues [13], or the use of gold nanoparticles linked to oligonucleoides as an ultrasensitive assay for detection of mutations in gene [3].

The opportunities revealed by the contemporary nano-research are considered to have a revolutionary impact on medicine, but such optimism is restrained by supported concerns regarding the possible negative impact on the environment and patient's health. As argued before in the literature, the properties that make nanoparticles so promising also make their health and environmental effects extremely difficult to predict [17]. Despite the increasing commercialization and exposure to such products, significant uncertainty exists regarding the potential risks posed by nanomaterials and nanotechnologies [14]. This is actually the main issue to address by regulating nanomedicine, proactive regulation of nanomaterials and nanotechnologies used in medical therapy and diagnosis being required when basic values like human dignity, health, safety, environment, property and privacy are at risk [8]. The main goal in this field is to create the perfect balance between stimulating innovation in nanomedicine and ensuring health protection and environmental safety.

Nanomedicines have been on the European markets for almost two decades, therefore we can state that European Union has discovered the immense potential of nanotechnology and nanomaterials in relation to health. At the same time, we can witness an increased awareness about the particular regulatory problems, due to the balance required between technological benefits and associated risks. The scientific uncertaint in the area of the nanomedicine raised questions about the appropriateness of specific regulation, since, according to the precautionary principle, the scientific uncertainty about technological risks is no reason for inaction if there might be "immense adverse effects", as stated by the European Commission in 2000. The Precautionary Principle is a dynamic tool that can follow developments in a sector and continuously verify that the conditions for the acceptability of a given innovation are fulfilled – thereby enhancing governance.

According to the precautionary principle, the optimal way to minimize the scientific uncertainties is to recognize risk and potential *ex ante*, before the technologies are commercialized on the market. Still, in the particular field of nanomedicine, due to the nature of products and clinical trials of medical technologies, the most valuable patient safety information is obtained from medical vigilance and adverse reporting *ex post* [2]. As a consequence, specific regulatory challenges are constituted by conflicting norms and values that play an important role in the perception and interpretation of phrase used by European Commission, namely "immense adverse effect", as well as in the decisions on balancing the risks and benefits, on gaining public trust and accepting the regulation [7].

This article explores the EU regulatory regime and problems raised in nanomedical regulation as well as the challenges in regard to its implementation. In doing so, our purpose is to offer an overview upon the EU development of the regulatory structure on the approval of nanomedicine, as well as the role played by the European actors and bodies in the regulatory process of nanomedicine. The main aim of the diachronically overview of the EU regulatory process is to help us in identifying the problems that occurred in

this field since the general opinion expressed in literature is that regulatory action within nanomedicine is still in the stage of reflection and preparation [6]. One of the main criticisms raised in this area is regarding the appropriate governance response to the regulatory problems.

2. EU Regulatory Regime of Nanomedicine

There is a wide range of Community legislation related to issues relevant for nanotechnology and nanomaterials, currently in existence or being elaborated. These issues primarily have to do with risk assessment.

Examples of legislation relevant for nanomedicine are the following:

Medicinal products marketed in the European Union are covered by comprehensive EU legislation: Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2003/94/EC, Directive 2003/63/EC. Medicinal products are defined in the EU legislation as any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product (Art. 1.2; 2001/83/EC). All medicinal products marketed in the European Union must obtain an EU product authorisation. Directive 726/2004 lays down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishes a European Medicines Evaluation Agency (EMEA). EMEA's task, according to its mission statement, is "to contribute to the protection and promotion of public and animal health by mobilising scientific resources from throughout the EU to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health care professionals developing efficient and transparent procedures, to allow timely access by users to innovative medicines through a single European marketing authorisation, and in particular through a pharmacovigilance network and the establishment of safe limits for residues in food producing animals".

The European regulatory system for medicinal products offers two routes for authorising medicinal products:

a) A "centralised procedure" with applications made directly to EMEA, leading – if approval is obtained – to the grant of a European marketing authorisation by the Commission. Use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products.
b) A "mutual recognition" procedure, which is applicable to the majority of conventional medicinal products. Applications are made to the Member States selected by the applicant and the procedure operates by mutual recognition of national marketing organisations. Purely national authorisations are still available for medicinal products to be marketed in one Member State.

Both procedures are based on a wide range of requirements laid down in implementing rules and – de facto binding – guidance documents. National clinical trials preceding an EU authorisation must observe the rules laid down in the Declaration of Helsinki, which means, among other things, that they must be assessed by an ethical review committee. Seen in an international context, this EU

regulatory system is unique in providing a network between all national regulatory bodies, coordinated by EMEA.

Medical devices are also covered by EU regulation, but the Directive on medical devices does not make placing on the market subject to a prior marketing authorisation issued by public authorities (Directive 93/42/EEC concerning medical devices and 90/385/EEC relating to active implantable medical devices). A medical device is defined as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software necessary for its proper application intended by the manufacturer to be used for medical purposes for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, … investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means". The Directive does not apply to human blood, blood products, blood cells of human origin, human tissue engineered products, etc

However, depending on risks involved, devices can only be placed on the market if they have been subject to a conformity assessment procedure involving a third party, a so-called Notified Body, designated by a Member State. The Directive deals primarily with risk management. Manufacturers are obliged to carry out an assessment of the risks and to adopt a risk management strategy. This means that they have to adopt measures to eliminate risks, or to reduce risks as far as possible, take the necessary protection measures in relation to risks that cannot be eliminated and, as a last resort, inform users of the residual risks due to any shortcomings of the protection measures adopted and advise any other protective measure regarding risks that cannot be eliminated. The Directive on medical devices includes a risk-benefit analysis.

Cosmetic products are also covered by an EU Directive (Directive 1976/768/EEC). A "cosmetic product" is defined in Article 1 as: "any substance or preparation intended to be placed in contact with the various external parts of the human body or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition". According to Article 2, "a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorised agent or by any other person responsible for placing the product on the Community market".

The Directive lays down requirements in the form of a number of positive and negative lists of ingredients. The basic obligation on a manufacturer is to carry out a risk assessment. The manufacturer must have available an assessment of the safety for human health of the finished product. To that end, the manufacturer must take into consideration the general toxicological profile of the ingredients, their chemical structure and their level of exposure. The risk assessment must take particular account of the specific exposure characteristics of the areas on which the product will be applied or of the

population for which it is intended. There must be *inter alia* a specific assessment for cosmetic products intended for use on children under the age of three and for cosmetic products intended exclusively for use in external intimate hygiene. Still, the Cosmetics Directive does not provide for verification of the manufacturer's risk assessment by a third party before the product is placed on the market. This means that whether the legal requirements are met depends ultimately on assessment by manufacturer.

Chemicals are embraced by one set of rules concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), which introduces changes to the current regulatory system, *inter alia* by placing the burden of risk assessment on manufacturers instead of authorities, widening the scope for registration of chemicals, replacing decentralised implementation by a centralised European system, and replacing a set of rules that have grown over time by a single regulatory system.

Clinical trials for medicinal products are covered by an EU Directive on Clinical Trials, which was amended in 2003 and 2005 (Directive 2001/20/EC, Directive 2003/63/EC). The purpose is to rationalise the procedure involving documentation and administration required for conducting clinical trials, and to ensure that patients are afforded the same protection in all EU Member States. Before clinical trials may commence a number of criteria must be satisfied, including the weighing of predictable risks and drawbacks as regards the therapeutic benefit for each trial subject and society as a whole; respect for the trial subject's right to physical and mental integrity and right to personal privacy; and the obtaining of informed consent.

Data protection is covered by the Directive on the processing of personal data and the protection of privacy in the electronic communications sector (Directive 2002/58/EC, Directive 95/46/EC). Article 8 provides protection regarding health data and establishes exemptions from the provisions laid down in the Directive for data required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy.

The Patent Directive, on protection of biotechnological inventions (Directive 98/44/EC), is designed to ensure effective legally harmonised protection of patents, and in doing so encourage innovation and promote investment in the field of biotechnology, and to establish legal certainty. The inventor secures exclusive rights to control commercial exploitation of his invention for 20 years and, in return, he must disclose a detailed description of his invention, making the new knowledge available to all. This disclosure enables others (researchers etc.) to build on the knowledge gained. The patent may be a product claim or a process claim. The standard criteria for patentability include novelty, inventive step and industrial application. According to Article 3, "biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature". The Directive contains provisions laying down restrictions based on ethical concerns, i.e. order public or morality In addition, diagnostic, therapeutic and surgical methods are traditionally excluded from patenting. This exclusion was intended to maintain the sharing of medical knowledge and know-how for the benefit of patients. It does not concern products or drugs used

for medical purposes. In Europe there is also a traditional academic exemption, mentioned in most national laws, which allows further research without paying a licence to the inventor, if such research is not commercial. The Directive above also states (Article 7) that the EGE "evaluates all ethical aspects of biotechnology".

Other EU legislation. Other European Union legislation of specific importance for risk assessment issues includes Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EC; Regulation (EC) No 1946/2003 on trans-boundary movements of genetically modified organisms; Directive 90/219/EEC on the contained use of genetically modified micro-organisms; and Council Directive 98/81/EC amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms.

Additionally to the above-mentioned regulations, principles of biomedical ethics also require a careful balancing of the benefits of a medical intervention or diagnostic procedure with the risks, not only when placing such products on the market, but also in the research phase. This is especially important in the case of nanomedicine, because not all risks may be known or deducible from existing therapies. It cannot be ruled out that medical interventions based on nanotechnology could have unprecedented biological and adverse effects, which have not been encountered before due to the novelty of these interventions. This is due to the lack of knowledge regarding the behaviour of nanoparticles in the human body, due to the inherent properties of some drug delivery systems to move across biological barriers, if new therapeutic principles are to be established (e.g. gene therapy), and if complex systems which comprise biological, nanotechnological and IT components and/or for which not all relevant parameters of safety and quality can reasonably be tested beforehand (e.g. long-term effects, interference with other components or systems).

At present, possible health and environmental risks of nanoparticles are debated. In the directives which regulate market access for medicinal products and medical devices in the EU, a risk assessment and management is already required in order to obtain market approval. However, it may be challenging to carry out this assessment in practice, because the required knowledge about the behaviour and biological effects of nanoparticles is presently too patchy and assessment schemes are not specifically tailored to assess nanoparticle-specific questions and might require amendment in order to take the specificities of nanotechnologies into account appropriately.

A dedicated nanotoxicological risk assessment might be necessary for novel nanomedicine product which should take into account: the biological fate of nanoparticles including distribution, accumulation and metabolism, medication-specific uptake routes related to the different routes of administration and the types of nanomaterials used, possible side effects, caused by the interaction of nanoparticles with living matter or their transport across biological barriers [4].

The EU has been responding to the challenges of nanotechnology. In 2004 the Commission issued the Communication towards a European strategy for nanotechnology. This identified the potential of nanotechnology but also recognised its risks and the need for the early identification and resolution of safety concerns.

It noted the need for effective research and development support. It stressed the need for effective coordination of national measures through mechanisms such as the

'Open Method of Co-ordination'. It was recognised that there was a need for a "world class infra structure" with "poles of excellence". This document also highlighted the need for recognition of ethical principles in accordance with the EU Charter of Fundamental Rights and Freedoms and other European and international documents.

It also identified the need for effective communication of such information within the scientific community. In addition, the Communication noted the importance of international cooperation. It suggested that there should be an international debate on matters of global concern, including public health, safety, the environment, consumer protection, risk assessment, regulatory approaches, methodology, nomenclature and norms".

The European Technology Platform on Nanomedicine, an industry-led consortium, brought together the key stakeholders in the area to examine the impact of nanotechnology. As part of the Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee, entitled Nanosciences and nanotechnologies: an action plan for Europe 2005–2009, the European Group on Ethics in Science and New Technologies were asked to undertake an ethical review of nanomedicine which would enable the future appropriate ethical review of proposed projects concerning nanoscience and nanotechnology.

The Expert Group highlighted one uncertainty in this area, namely that there was no clear legal definition of nanomedicine. They also identified a major practical problem in attempting to take a holistic approach to the regulation of nanotechnology, namely that there is a diverse range of forms of legal regulation of such technologies. So, for example, at EU level regulation of nanotechnology may arise in the context of the regulation of pharmaceuticals (Regulation CE 726/2004) or medical devices (Directives 93/42/EEC and 90/385/EEC) where other health care law principles are applicable, such as consent, confidentiality and data protection. It was not necessarily always obvious which precise regulatory regime would apply.

3. Regulatory Concerns

Does regulation embrace the relevant areas of nanomedicine, so that no major area is left out? There is extensive regulation on areas where nanomedicine is used in products. Medicinal products and medical devices are subject to strict rules. Cosmetics are also subject to rules requiring *inter alia* risk assessment, but without verification of the manufacturer's risk evaluation. These provisions will probably embrace the products for which nanomedicine is being used. A regulatory framework is in place for research in humans and clinical trials, but informed consent may present a challenge. Informed consent requires the information to be understood. How is it possible to give information about future research possibilities in a rapidly developing research area and to make a realistic risk assessment in view of the many unknowns and the complexities? Patents are possible, but the distinction between products and drugs, on the one hand, and diagnostic, therapeutic and surgical methods, on the other, may be blurred. In view of the knowledge gaps, and the complexity of the matter, concerning the long-term effects of nanomedical diagnostic and therapeutic tools, it may be difficult to provide adequate information concerning a proposed diagnosis, prevention and therapy needed for informed consent. Here the distinction between invasive and non-invasive procedures is very important, since they raise different concerns.

Is the legislation clear and comprehensive, without overlap? The lack of a clear legal definition of nanomedicine, and the fact that current regulation is based on other characteristics where nanomedicine was not part of the considerations on which the wording was based, present a problem, as it may be unclear whether nanomedicine is to be placed within or outside the scope of certain legislation. Some nanomedicinal innovations may fall within several categories of regulation which may apply simultaneously. For example, nanomedical products may combine different mechanisms of action, be they mechanical, chemical, pharmacological or immunological. There may therefore be a risk not only of uncertainty as to which regulation(s) are applicable, but also of there being a plethora of regulatory provisions that are of relevance. Both situations are problematic from a legal point of view. Most important is the fact that it is not in the present legal situation always obvious which directives etc. apply and how they should be interpreted. Clarity would enable scientists, producers of nanomedicine etc. to make sure they operate on safe ground, and European society would feel more secure knowing which safeguards are required and applied. Uncertainty and overlap may result in a situation where the manufacturer may have to apply different systems or can choose between different systems with different procedures and different risk evaluations and assessments.

Does regulation secure adequate protective measures, including evaluation of health-related risks? Risk assessment is included in virtually all product legislation relevant to nanomedicine. There is an obligation on the producer to carry out, although to different degrees, a risk assessment and to adopt risk-management measures for the risks covered by individual directives and regulations. As a general rule these risks are defined broadly. This is the case for medical devices, cosmetic products, chemicals, etc. In the case of medical devices the risk assessment and risk management approach is supplemented by a risk/benefit analysis; clearly identified risks that have been reduced as far as possible can be accepted, provided the benefits outweigh the possible adverse effects. Finally, as part of their post-market obligations, manufacturers have to set up a risk management scheme in relation to aspects not covered by the marketing authorisation. Wide experience has been built up in the sector regarding new risks. EMEA has created the Innovation Task Force (ITF) to ensure EMEA-wide coordination of scientific and regulatory competence in the field of emerging technologies, including nanotechnologies, and to provide a forum for early dialogue with applicants on regulatory, scientific or other issues that may arise from the development.

Is the implementation of existing regulations adequate? Even if regulation includes provisions on risk assessment, this only provides adequate protection if the implementation includes sufficient scientific expertise and the risk actually can be assessed and managed. Specific efforts are needed to develop measures for implementing existing regulations that would respond to the implications of nanomedicine.

Is the present patent system adequate to deal with problems regarding knowledge protection and information dissemination in nanomedicine? The aim of the patent system is to encourage innovation by striking a balance between knowledge protection and information dissemination. There is, however, a risk of excessively broad patents being granted and the risk that the research exemption

and the exemption for diagnostic and therapeutic purposes can be challenged. These factors make the present patent system less well adapted to deal adequately with, on the one hand, knowledge protection and, on the other, information dissemination in the area of nanomedicine, especially if combined with a liberal policy of granting patents. The balance between disclosure and inventors' rights is skewed.

Conclusions

Nanotechnology is within our grasp. It is better to plan now than to suffer the consequences of poor planning later. Nanotechnology will already have enough ethical and legal obstacles to overcome. For instance, nanodevices may become available that will enable constant monitoring of a person's health, opening the door for potential abuse and a discussion of how this will affect privacy rights. Nanodevices that allow gene alteration, say of hair and eye colour, and neurobiochips that stimulate brain function, possibly giving the human machine-like qualities, will no doubt dredge up ethical debates.

Although the FDA appears to be planning to apply the existing regulation scheme to nanomedicine, there are likely to be *sui generis* problems only addressable through the creation of entirely new laws. The bottom line is that nanomedicine will bring miraculous benefits as well as risks. Therefore, we should make efforts now to mitigate foreseeable problems and ensure that nanotechnology will benefit us instead of hampering us.

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