NANOMEDICINE IN EUROPE: REGULATING UNDER UNCERTAINTY

A Thesis for Master Program in Law and Technology
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List of Abbreviations

AIDS – Acquired Immunodeficiency Syndrome

BBB – Blood-Brain Barrier

CE - Conformité Européenne

CLP – Classification, Labelling and Packaging of Substances

EC – European Community

ECHA – European Chemicals Agency

EMA – European Medicines Agency

EMRC – European Medical Research Councils

ENISA – European Network and Information Security Agency

ESF – European Science Foundation

ETP- European Technology Platform

EU – European Union

FDA – Food and Drug Administration

GMO – Genetically Modified Organism

HIV – Human Immunodeficiency Virus

IRGC – International Risk Governance Council

ISO – International Organization for Standardization

IULCID - International Uniform Chemical Information Database

IVDD – In Vitro Diagnostic Medical Devices Directive

MDD – Medical Devices Directive

MEDDEV- Guidelines on Medical Devices

MIR - Magnetic Resonance Imaging

NDDS – Nanoparticle Drug Delivery Systems

nm- nanometer

OECD – Organization for Economic Co-operation and Development

PIP- Poly Implant Prothese

QDs – Quantum Dots

REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals

RIVM – Rijksinstituut voor Volksgezonndheid en Milieu (Dutch National Institute for Public Health and the Environment)

RS & RAE – Royal Society and Royal Academy of Engineering

SCENIHR – Scientific Committee on Emerging and Newly Identified Health Risks

SPION – Superpatamagnetic Iron Oxide Nanoparticles

U.S – United States

UDI – Unique Device Identification

UNESCO – United Nations Educational, Scientific and Cultural Organization

UV – Ultraviolet Illumination

Abstract

Nanomedicine is a revolutionizing field that can benefit both diagnosis and treatment and contribute to a better quality of life. Despite the expected huge benefits, the potential risks on human health are significant as well. This thesis aims to defense a perspective that in case of nascent technologies, where the data are still emerging and scientific uncertainty prevails, risk governance should sustain the process of scientific knowledge by developing guidelines, codes of conduct and public information and provide a minimum level of safety acceptable to protect human health. Although nanomedicine is at an early stage of development some cautious measures should be taken that will provide regulatory mechanisms able to respond to the challenges posed by nanomedicine, establish a minimum level of safety but will also allow the further promotion of scientific knowledge. This multidisciplinary approach can contribute in adopting regulatory choices and tools that will help manage the risks, protect human health and promote scientific knowledge.

Acknowledgements

I would like to express my deepest gratitude to Dr. Federica Lucivero, my study advisor who has always been so patient and willing in assisting me in the elaboration of this thesis. Her comments and suggestions were a valuable contribution to find my way and understand this fascinating topic. I would like also to express my gratitude to Pr. Keens Stuurman, for his significant contribution to the thesis during critical time.

Introduction

Nanotechnology as explained by Bowman and Hodge is not only a field of innovation but a "*heterogeneous family of technologies and applications enabling the exploitation of properties of elements at the atomic level*"[1]. A wide range of products that consumers use on a daily basis, covering different needs such as food, cosmetics, pharmaceuticals, machines, energy storage and other areas as well, incorporate nanotechnology. Indeed according to Nobel Laureate Richard Smalley "*The impact of nanotechnology on the health, wealth and lives of the people will be at least equivalent of the combined influences of microelectronics, medical imaging computer-aided engineering and man made polymers*"[2].

Amongst the most promising fields of application of nanotechnology is medicine. The application of nanoparticles for medical use can benefit areas such as drug development, drug delivery, diagnosis and new ways of treating illness and disease. What makes the application of nanotechnology to medicine unique is the fact that materials at the nanoscale have different properties with regard to size, chemical reactivity, mobility, solubility, magnetic and optical properties[3].

These new properties of nanomedicine applications, despite making them innovative and able to overcome limitations found in traditional medicine, can also pose risks to human health. Whereas the potential benefits can be enormous, scientists have voiced concerns about the possible adverse effects. As this new technology is still in its early stages of development and risks are still emerging, there is no consensus on the potential hazards.

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[1] Bowman, Diana M. and Graeme A. Hodge, 'A Big Regulatory Toolbox for a Small Technology" (2008) 2 Nanoetchic, 193, p.195 <http://link.springer.com/article/10.1007%2Fs11569-008-0038-7> accessed 26 February 2013

[2] Quoted in Munir Abu Bakar, Siti Hajar and Mohd Yasin, ' News and Views Nanotechnology in Healthcare: Are existing Laws Adequate?" (2007) 14 European Journal of Health Law 261, 265 <http://heinonline.org/HOL/Page?handle=hein.journals/eurjhlb14&div=30&g_sent=1&collection=journals> accessed 26 February 2013

[3] The Royal Society & The Royal Academy of Engineering, 'Nanoscience and nanotechnologies□: opportunities and uncertainties', 2004, 1., vii <http://www.raeng.org.uk/news/publications/list/reports/nanoscience_nanotechnologies.pdf>, accessed 26 February 2013

Despite the fact that we are not fully aware of the risks that nanomedicine applications introduce, their commercialization has already taken place.

Despite the fact that their commercialization has already taken place, so far at a European level, specific regulatory provisions that explicitly address nanomedicine haven't been enacted. Of course this does not mean that this area is unregulated. At the current stage where no specific rules exist for nanomedicine, it is expected that the European regulatory regime applicable to medicinal products and devices, will be applicable to nanomedicine as well. But the complex character of nanomedicine applications, the data that still emerge and their specific characteristics raise several regulatory questions.

Under this state of uncertainty and the limited knowledge about the potential risks that surround nanomedicine, only a hypothetical assessment of risks and benefits is possible at this stage. Experts and regulators have developed frameworks to assess the hazards and benefits and estimate the acceptable level of risk compared with the forthcoming benefits. In order to identify risks and benefits, evaluate activities and control risks, different risk management tools have been developed so far and one of them is risk benefit analysis. Risk benefit analysis is the comparison of the risks of a situation to its forthcoming benefits.

In Europe the current regulatory regime applicable to medicinal products and devices, requires a benefit-risk balance in order for market authorization to be granted and further maintained. So it follows that nanomedicine will have to undergo a risk benefit analysis before qualifying for market authorization. Although risk benefit analysis takes into consideration in order to reach a decision both benefits and risks, the scientific uncertainty that surrounds nanomedicine cannot provide the information needed for the identification of risks.

The novelty of nanotechnologies challenges the applicability of risk management tools like risk benefit analysis to cope with the risks that they introduce. Any attempt either to directly apply the existing regulation to this novel technology or introduce new regulatory measures has become a challenging task. The challenges to current regulation and risk management tools call for a critical reflection in order to explore possible solutions.

Although the potential benefits might be enormous, the fact that it is a burgeoning technology results in that at this stage the benefits and risks can only be assessed hypothetically. The lack of knowledge in combination with no consolidate regulation in the field makes it difficult to expect adequate regulatory responses.

Awareness about the regulatory issues that nanomedicine applications pose has emerged the last few years. At present many scholars, competent authorities and bodies like the Scientific Committee on Newly and Emerging Health Risks, the European Group on Ethics in Sciences and New Technologies are trying to address those challenges. Some of them have identified the challenges that nanomedicine applications pose to the current regime and the assessment tools and questioned its adequacy to cope with those challenges, while others have concluded the appropriateness of the regime to address those issues.

This Master Thesis has been motivated by these challenges that nanomedicine applications pose, the difficulty of identifying the risks and the different approaches that have been followed so far to address the issue. After studying the existing literature and trying to understand those challenges, this master thesis will attempt by exploring different strategies, to provide a possible response on how regulation could respond at the early stages of this nascent technology by ensuring at the same time the further development of scientific knowledge and the safety of human health.

Research Question:

Nanomedicine due to their novel character and the risks that still emerge pose challenges to the current regulatory regime. So the question that follows from the above and is the aim of this Master Thesis is:

How do nanomedicine applications challenge the applicability of the European Regulatory Regime to manage the risks that this new technological field introduces and what could be an appropriate regulatory response in managing the risks and ensuring a minimum level of safety, at the early stages of this novel technology?

This thesis will try to raise awareness of the challenges that nanomedicine applications pose from a regulatory perspective. Although nanomedicine is still in its infancy, some cautious measures should be taken that will protect human health but also allow the further development of scientific knowledge. It will defend a perspective of risk governance that sustains the scientific knowledge process by developing guidelines, codes of conduct, public information and providing the minimum safety standards acceptable to protect human health.

The difficulty and complexity of this topic of discussion and the research question lead to multiple sub-questions that need to be answered, to be able to give a complete answer to the research question.

- What is nanotechnology?
- What is nanomedicine?
- What are the potential risks that nanomedicine introduce?
- Is the European medical regulatory regime applicable to nanomedine?
- How nanomedicine applications challenge the current regime?
- Can risk benefit analysis as a risk management tool to address the risks that nanomedicine applications introduce?
- Is Precaution an alternative approach to novel science?
- The role and scope of guidelines, codes of conduct and communication tools towards ensuring a minimum level of safety of human health.

In order to provide a complete answer to the research question the first sub-question that has to be answered is what is nanomedicine. Understanding this field of technology is of extreme relevance of this analysis. Define nanomedicine and try to understand the characteristics of nanomedicine applications, will allow us to understand which are the potential risks that they introduce.

The description of two nanomedicine applications intends to illustrate their benefits and their potential risks and will allow us to address the second sub-question where we will try to answer if the current European regulatory regime is applicable to nanomedicine. By describing the existing legal framework that applies to medicinal products and medical devices we will give the possibility to argue if this legislation is

applicable to nanomedicine and how the specific characteristics of nanomedicine challenge the current regulatory regime. The analysis of the current regulatory regime will attempt to highlight how nanomedicine challenge the concepts of this regime. In addition, as the chemical industry is the main producer of nanomaterials, relevant to our analysis will be the examination of REACH regulation that covers all chemical substances.

A third sub-question on how and to which extent nanomaterials can be covered by REACH has to be analyzed as well. After analyzing the current regulatory regime and showing its limits if we directly apply it to nanomedicine, we will investigate some tools that have been introduced in order to govern emerging sciences whose risks are still unknown. So our fourth sub-question will examine if risk benefit analysis as a risk management tool can address the risks that nanomedicine introduce. As medicinal products and medical devices before grant market authorization have to undergo a risk benefit analysis, it is crucial to analyze if at the current stage of knowledge about the risks and benefits of nanomedicine applications, they can be managed by this tool. After analyzing the risk benefit analysis as a tool to manage the risks that nanomedicine pose, the Precautionary Principle will be examined if it can be an answer to uncertain science, which is our fifth sub-question.

Having identified the limits of the current regime and the deficiencies of risk management tools to manage the risks that nanomedicine pose our sixth sub-question will focus on the role and scope of guidelines, codes of conduct and communication tools in the context of nanomedicine. It will be examined how they could supplement the current regime to overcome some limitations and ensure a minimum level of safety at the early stages of this technology. The final sections of this thesis will include some recommendations on how to manage risks in novel science and conclusive remarks.

Methodology

This research will be traditional/doctrinal research, based on legislation, law books, journal articles. In order to answer the research question we divided it in five (5) Chapters.

In the first Chapter the first sub-question will be answered. In order to answer the first sub-question, it is important first to define what is nanotechnology and subsequently what is nanomedicine. In our effort to define nanomedicine we will show that at present there is no commonly accepted definition that delineates the area. Then the characteristics and properties of nanomedicine will be discussed. The description of two novel applications, optical imaging and targeted drug delivery systems, will allow us to illustrate some advances obtained by the use of nanotechnlogies in medicine but also highlight the potential adverse effects on human health.

Identifying the risks that come along with this technology will lead us to Chapter two, where we will answer the second and third sub-questions. As there is no legal framework designed for nanomedicine, in order to answer the second sub-question, we will examine if the existing medical regulatory regime can be applicable to nanomedicine as well. By analyzing the existing regulatory framework we will try to show how the characteristics of nanomedicine applications make its applicability a difficult task. As an example borderline products will be examined that combine characteristics both from medicine and devices (drug delivery systems) and challenge the applicability of the regime. Besides products that combine characteristics from both medicine and devices, we will show how the novel character of nanomedicine challenges the boundaries between in vitro diagnostic medical devices and medical devices. Relevant to our analysis is also to discuss another legal issue that they create which originates from the classification of medical devices according to the risk that they incorporate. To understand better the challenges that nanomedicine pose 'AcryMed's Silvagard Antimicrobial Surface Treatment' will be examined as an example. In addition, as the chemical industry is the biggest manufacturer of nanomaterials, in order to answer the third sub-question the REACH regulation has to be examined, whether it can successfully address the regulatory issues that nanomaterials and introduce.

After analyzing the current regime and showing its limits if we directly apply to nanomedicine, our third Chapter will investigate some tools that have been introduced to manage risks in novel sciences. In order to answer the fourth sub-question, risk benefit analysis as a tool to manage the risks that nanomedicine introduce will be examined. Taking into consideration that every medicinal product and device before qualify for market authorization has to undergo a risk benefit analysis, it is important to examine if at the current

state of knowledge about the risks and benefits of nanomedicine, risk benefit analysis can manage the risks that they pose. After analyzing risk benefit analysis and showing its limitations to address the risks that nanomedicine introduce, the Precautionary Principle will be examined if it could be an answer to uncertain science. This will answer our fifth sub-question.

Having identified the limits of the current regime and the limits of risk benefit analysis as a tool to address the risks that nanomedicine introduce, Chapter four will examine the role and scope of guidelines, codes of conduct and communication tools in the context of nanomedicine. In order to find an adequate regulatory response that will be able to manage the risks that nanomedicine introduce and ensure a minimum level of safety, this Chapter will focus on the need of developing or implementing guidelines to clarify how the legal requirements of the existing system should apply to nanomedicine. Also codes of conducts will contribute towards the establishment of principles that will be followed by the scientists in the field and public information will help the public to make informed choices, so this technology will follow a safe path of development. Finally Chapter 5 will include recommendations and conclusive considerations according to the findings of the previous chapters.

Chapter 1: Defining Nanomedicine

Introduction

The advent of the 21st century is about to bring great changes to the medical sector. Nanomedicine is expected to contribute significantly to this direction as it carries great hopes for the cure of life threatening diseases and is foreseen to change health care. Nanomedicine can bring significant improvements in sectors such as diagnostic and imaging techniques, implants, sensors, biomarkers, nano-biopsy, drug development and drug delivery systems, passive and active targeting, stem cells and biomaterials. Possible scientific advances can be achieved in the area of cancer treatment, tissue engineering and regenerative medicine.

Nanomedicine relies on the progress of nanoparticles research and application in order to achieve its goals and bring significant improvements in the above mentioned sectors. As the mode of action of all pharmaceutical products can occur at nanoscale, first it is important to define nanotechnology before we further examine how nanomedicine is defined and how the application of nanoparticles in medicine confers them unique characteristics. Nanomedicine promises huge benefits in the medical sector. The description of two areas of application, optical imaging and targeted drug delivery systems will allow us to demonstrate the potential benefits by the use of nanotechnologies in medicine but will also allow us to highlight the potential adverse effects on human health.

1.1 Ambiguities in defining Nanotechnologies

In 2004 the Royal Society and Royal Academy of Engineering in a document entitled 'Nanoscience and nanotechnologies – opportunities and uncertainties', made a distinction between 'nanoscience' and 'nanotechnologies'. According to this distinction nanoscience is defined as *"the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale"*, whereas nanotechnologies were defined as *"design, characterization, production and*

application of structures, devices and systems by controlling shape and size at nanometer scale"[4]. This distinction is useful as nanoscience is encompassed with understanding the phenomena at a nanoscale and their influence on the properties of materials, whereas nanotechnologies act as 'platform' technologies, trying to exploit these phenomena in industry[5].

On the one hand, one of the most cited definitions of Nanotechnology is the one applied by the U.S National Nanotechnology Initiative which defines it as follows: "*Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. (…) At this level the physical, chemical and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules or bulk matter*"[6]. While nanotechnology is defined both by the Royal Society and Royal Academy of Engineering and the U.S National Nanotechnology Initiative, we can see that the definitions are not the same. The definition provided by the Royal Society and Royal Academy of Engineering does not mention anything about size, whereas the definition from the U.S National Nanotechnology Initiative provides a size framework in which nanomaterials can range.

Applications in the field of medicine are very promising. Nanomedicine as a term includes products, properties and processes at a nanoscale. Finding a definition for Nanomedicine is not an easy task in the sense that it is of a hybrid nature, combining a variety of fields of science such as chemistry, biology, mathematics and engineering. Yet there is no common definition of Nanomedicine. According to the European Science Foundation (ESF) Nanomedicine :

"*is the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. It was perceived as embracing*

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[4] ibid 5

[5] Robert Falkner and Nico Jaspers, 'Regulating Nanotechnologies: Risk, Uncertainty and the Global Governance Gap', (2012) 121 Global Environmental Politics, 30, 9 <http://personal.lse.ac.uk/falkner/_private/2012_Falkner_Jaspers_RegulatingNanotechnologies.pdf> accessed 1 March 2013

[6] National Science and Technology Council, Committee on Technology, Subcommittee on Nanoscale Science, Engineering and Technology, 'The National Nanotechnology Initiative Strategic Plan 2007', 1, 5 < http://www.nano.gov/sites/default/files/pub_resource/nni_strategic_plan_2007.pdf?q=NNI_Strategic_Plan_2007.pdf> accessed 1 March 2013

five main sub-disciplines which in many ways are overlapping and underpinned by the following common technical issues:

- *Nanomaterials and Devices*
- *Analytical Tools*
- *Nanoimaging*
- *Novel Therapeutics and Drug Delivery Systems*
- *Clinical, Safety and Toxicological Issues"*[7].

The definition used by the European Technology Platform on Nanomedicine defines it as: "*Nanomedicine is the application of Nanotechnology to health. It exploits the improved and often novel physical, chemical and biological properties of materials at the nanometric scale. Nanomedicine has potential impact on the prevention, early and reliable diagnosis and treatment of diseases."*[8]

Although there are similarities between the two definitions, there is no common accepted definition for nanomedicine. The lack of a clear legal definition combined with the fact of its broad applicability, makes the identification and the novelty assessment of nanomedicine quite a difficult task. The European Group Of Ethics in its 'Opinion on the ethical Aspects of Nanomedicine' identified this difficulty. More specifically, with regard to the lack of a clear legal definition it mentions that the characteristics of the current regime do not take into consideration the characteristics of nanomedicine. When the existing legislation was established, nanomedicine hadn't been introduced in the medicine arena. So it may be unclear whether they will fall inside or outside the scope of legislation [9].

Nanomedicine is not a designated field because a combination of characteristics may apply simultaneously to nanomedical innovations. At that stage they may combine different characteristics of action such as mechanical, chemical, pharmacological or immunological or

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[7] (EMRC), European Medical Research Councils, 'Nanomedicine' 2005, 1., 11 <http://www.esf.org/fileadmin/Public_documents/Publications/Nanomedicine.pdf > accessed 1 March 2013.

[8] European Technology Platform on Nanomedicine 'Nanotechnology for HealthVision Paper and Basis for a Strategic Research Agenda for Nanomedicine', 2005, 1, 6 <ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/nanomedicine_visionpaper.pdf> accessed 1 March 2013

[9] The European Group on Ethics in Science and New Technologies, 'Opinion on the Ethical Aspects of Nanomedicine' 2007, Opinion N° 21, 33 <http://ec.europa.eu/bepa/european-group-ethics/docs/publications/opinion_21_nano_en.pdf> accessed 1 March 2013

even convergence with drugs, devices or a combination of both. The fact that the final medicinal product can result from a combination of components makes its identification and legal assessment challenging. Considering that medicinal products, devices and treatments combine elements of different disciplines of science, the boundaries between them are blurred and they do not follow the traditional classification either of drugs or medical devices.

The determination of whether a product is either a device or a medicine should take into account a variety of factors. Apart from definitions which are of great importance in order to determine in which category (drug or device) a nanomedicine might fit, we should also take into consideration the claim of the product, the main aim of its production as well as the effect it has on the human body.[10] The fact that nanomedicine combines elements from different scientific fields calls for an accurate understanding of the complex processes, as different scientific areas are involved.

Market research that has been conducted and analysts, predict a great boost in the market of pharmaceutical applications. According to recent research the 'nanomedicine market reached $63,8 billion in 2010 and $72, 8 billion in 2011. It is expected to grow to $130,9 billion by 2016 at a compound annual growth rate (CAGR) of 12,5% between years 2011 and 2016'[11].

[10] Joel D'Silva and Geert van Galster, 'News and Views, Taking Temperature – A Review of European Union Regulation of Nanomedicine' (2009) 16 European Journal of Health Law 249, 258 <http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1285099> accessed 2 March 2013

[11] 'New Market Research Report on Nanomedicine in Medical Applications' < http://www.etp-nanomedicine.eu/public/news-events/news-archive-1/new-market-research-report-nanotechnology-in-medical-applications-the-global-market> published by BCC Research accessed 3 March 2013

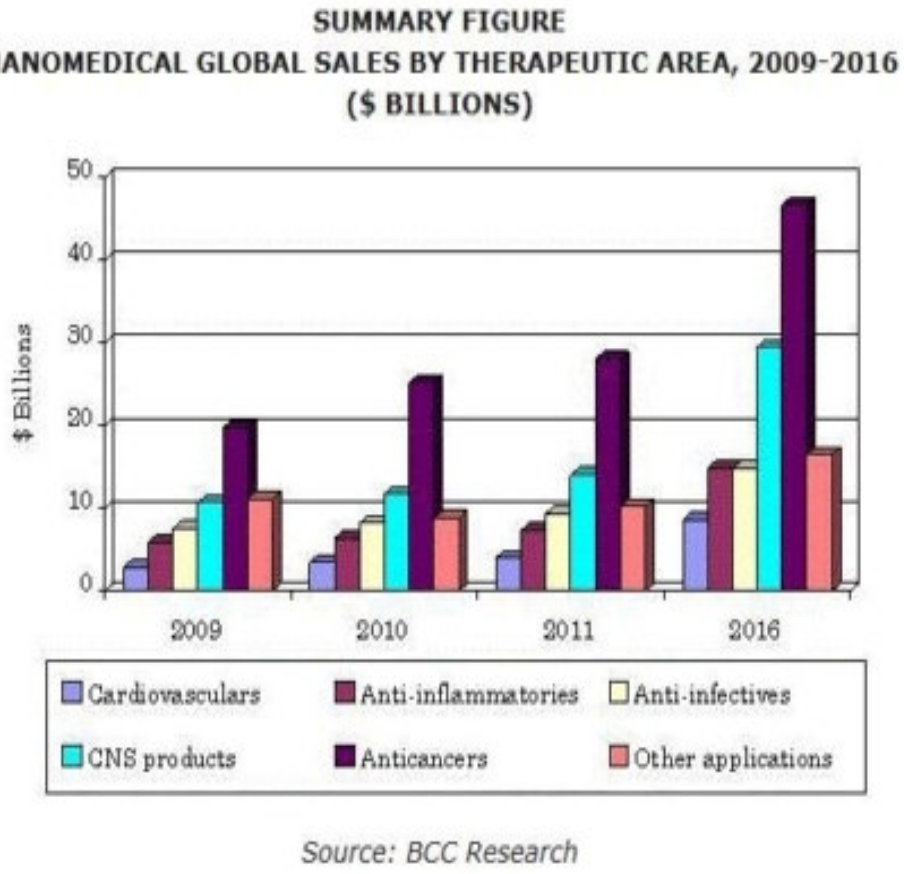

Figure 1. New Market Research Report on Nanomedicine in Medical Applications

As the nanomedicine sector grows at a high rate and the commercialization of those products has already started and is expected to grow further in the next years, it follows that more people will use those kinds of products or will be affected by them. So it is of great importance to understand the mechanisms that come along with them and how they operate, in order to be able to answer whether they fit in the existing regulatory regime or specific regulations are needed.

1.2 Characteristics of Nanotechnology

Nanomedicine relies on the progress of nanoparticles research and application in order to achieve its goals. What makes nanomedicine unique and enables them to offer huge benefits in the medical sector is the use of nanoparticles both in medicine and devices. So it is

important to examine the specific characteristics of nanoparticles in order understand their usefulness in medicine and also the potential risks that they might introduce.

The existence of nanoparticles is not new. Nanoparticles existed in nature a long time ago, a fact that scientists are already aware of[12]. Nanoparticles can originate from natural sources, can be unintentionally released into the environment through a variety of procedures as for example cooking or can be engineered[13]. The properties of nanoparticles make nanomedicine unique, acting in a different way when compared to macroscopic medicine. The nano–characteristics makes them innovative, able to overcome some limitations found in traditional therapeutic and diagnostic agents[14]. Although the small size of nanoparticles makes them unique and have significant usefulness in medicine, it can also pose dangers for human health and the environment. According to some researches "*the smaller the particles are the more reactive and toxic their effects are*"[15].

What makes nanoparticles unique is that since they are operating at a nanoscale their physical characteristics can be exploited in different ways compared to those observed at a microscale. The prevailing characteristics of nanoparticles are their ultra small size, high reactivity, absence of solubility and ultimately their large surface area to mass ratio. Nanoparticles are extremely small in size measuring less than 100 nanometers, often compared to human hair, possessing only a thousandth of its diameter.

Whereas the potential benefits of nanomedicine are immense as more and more products are being marketed, experts and regulators have voiced concerns about their safety. In the field of nanomedicine, much uncertainty exists about the health risks that nanoparticles pose along the path from production to use and disposal[16]. In particular two aspects of nanoparticles raise safety concerns relating to uncertain toxicity effects -(i) their large surface

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[12] O. Renn and M. C. Roco, 'Nanotechnology and the Need for Risk Governance' (2006) 8 Journal of Nanoparticle Research 153,169 <http://link.springer.com/10.1007/s11051-006-9092-7> accessed 3 March 2013

[13] Volker Wagner, Ba□rbel Hu□sing, Sibylle Gaisser, Anne-Katrin Bock 'Nanomedicine: Drivers for development and possible impacts' 2008 JRC Scientific and Technical Reports European Commission, 62 <http://ftp.jrc.es/EURdoc/JRC46744.pdf> accessed 3 March 2013

[14] A. El-Ansary and S. Al-Daihan, 'On the Toxicity of Therapeutically Used Nanoparticles: An Overview' (2009) Journal of Toxicology,1,< http://www.hindawi.com/journals/jt/2009/754810/> accessed 4 March 2013

[15] ibid 3

[16] Wim H De Jong and Paul JA Borm, 'Drug Delivery and Nanoparticles: Applications and Hazards' (2008) 3 International Journal of Nanomedicine, 133, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527668/pdf/ijn-0302-133.pdf > accessed 4 March 3013

area that results in increasing reactivity and (ii) potential, due to their ultra small size, to penetrate the skin and get into the blood and cells[17]. Some experiments that were carried out in laboratories showed that "[...] *the inhalation of certain insoluble ultrafine nanotubes, may cause pulmonary inflammation, tissue damage and lung tumors* [...]"[18].

In an effort to understand not only the risks that the exposure to nanoparticles may pose to the brain, skin, immune system and lungs, but also the benefits for better diagnosis and treatment of the disease, the following sections will introduce studies in two application areas; optical imaging and targeted drug delivery systems. For the scope of this thesis we chose to describe those two areas because the use of nanoparticles in optical imaging and drug delivery systems is considered significant as it aims at earlier detect and better treating of disease. The description of those two applications areas will not be exhaustive but instead is intended to highlight some advances obtained by the use of nanotechnology in medicine. In addition drug delivery systems will be used in the following Chapter as an example to highlight the difficulties of regulating them.

1.2.1 Optical Imaging

The increased progress of knowledge of molecular processes can now be used to develop diagnostic methods for imaging diseases at the molecular level. In vivo imaging at a molecular level uses already known technologies such as optical and nuclear imaging, magnetic resonance imaging and ultrasound to detect diseases[19]. Nanotechnology can contribute significantly to providing improvements in advanced imaging of the human body using magnetic resonance imaging (MIR) or fluorescence microscopy. The most promising nanotechnology originated contrast agents are quantum dots (QDs)[20].

Quantum dots are fluorescent semiconductor nanocrystals coated with inorganic materials that can be used for novel diagnostic purposes. They range form 2 to 10nm in

[17] Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa, 'Emerging Nanopharmaceuticals' Nanomedicine: NBM 2008:4:273-282 <http://research.che.tamu.edu/groups/seminario/nanotechnology/Papers%20related%20to%20Presentations/U6_Emerging%20nanopharmaceuticals.pdf> accessed 4 March 2013

[18] Robert Falkner and Nico Jaspers (n 5) 11

[19] JRC Scientific and Technical Reports (n 13) 24

[20] ibid 24

diameter and can be synthesized via colloidal synthesis or electrochemistry[21]. The small size of these nanoparticles makes quantum effects come into play. These types of nanoparticles are able to absorb white light and re-emit it within nanoseconds under ultraviolet illumination (UV), and the wavelength (or color) depends on their size[22]. For example, -2nm QDs will emit green light, whereas -5nm will emit red light. The use of QDs can confer significant advantages to the area of imaging of cells, lymph nodes and tumors. Except for that, QDs can provide enough surface area to attach therapeutic agents for simultaneous drug delivery, in vivo imaging as well as tissue engineering. Cao et al. first demonstrated imaging and in vivo cancer targeting in a study on living animals, whereas later Bagalkot et al used QDs -apatmer- doxorubicin (Dox) for targeted cancer therapy, imaging and sensing[23].

Not only QDs but also superpatamagnetic iron oxide nanoparticles (SPION) are an interesting category as well, because of their property to provide the most change signal per unit[24]. They can be easily detected by light and electron microscopy and manipulated. Studies that have been conducted by Weissleder et al. showed that cancer metastasis from prostate to lymph node was detected. The outcome of these studies was positive showing that SPION nanoparticles can accurately detect metastases and the imaging protocols are adopted by many MRI centers[25]. As a result of those scientific experiments, cancer of that kind is possible to be detected at an early stage, giving the patient the opportunity to choose between surgical intervention or radiation and chemotherapy, which are the usually applicable therapies in cancer treatment.

1.2.2 Targeted Drug Delivery Systems

One of the most promising areas of application of nanotechnology in medicine is in drug delivery systems. Nanoparticle drug delivery systems (NDDS) are a sub-category of

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21 Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa (n 17) 277

22 RS&RAE (n 3) 10 & Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa (n 17) 277-278

23 Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa (n 17) 277 -278

24 Yiyao Liu, Hirokazu Liyoshi and Michihiro Nakamura, 'Nanomedicine for drug delivery and imaging: A promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles' (2007) 120 International Journal of Cancer, 2527., 2535 <http://onlinelibrary.wiley.com/store/10.1002/ijc.22709/asset/22709_ftp.pdf?v=1&t=hhxc7kce&s=c3682ab3dfb1e001d645b8a3dab582066641b2cc> accessed 5 March 2013

25 ibid

advanced drug delivery systems functioning at nanoscale usually less than 200 nm[26]. In this category of NDDs liposomes, nanosuspentions, dendrimers, polymeric nanoparticles, carbon nanoparticles, inorganic nanotubes and fullerenes are included. According to experts and studies that have been conducted, they can prove of extreme usefulness in increasing the efficacy of drugs already in use and reduce the side effects that patients may face[27].

Studies on nanoparticle based drugs and delivery systems evidenced that they can contribute successfully to the treatment of several types of cancer such as ovarian, lung and skin cancer[28]. Nanoparticles provide the ability to target in specific therapy, carrying and delivering the drug to treat cancerous cells without affecting the healthy cells[29]. One example that illustrates this unique characteristic that helps the treatment of cancer, is the use of Paclitaxel. Paclitaxel is an anti-cancer agent, used since 2005 in the form of Abraxane loaded with a natural polymel, albumin. This form of paclitaxel eliminated the side effects associated with the use of Cremophor EL, another drug for cancer, but also improved the transfer of the drug through the bloodstream and allowed higher drug dosing as well[30].

Nanoparticle based drug delivery systems can also be applied for treatment of neurodegenerative disease, HIV, ocular and respiratory diseases. One of the biggest challenges for drug delivery systems is the natural blood-brain barrier (BBB), which blocks drug transport. The BBB is designed to protect the brain from foreign substances and the compounds that are inserted into the body for therapeutic reasons cannot be recognized. The patient because of this natural barrier should receive higher doses of the drug, which increases the possibility of experiencing adverse effects. Conversely an alternative approach that has been examined by scientists in recent years is the use of a variety of nanoparticle based drugs ranging from polymer particles to liposomes[31].

Besides these two fields, another area that is being explored is the use of nanoparticle-based drugs in treating HIV. The main problem that scientists have to overcome is the poor

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26 JRC Scientific and Technical Reports (n 13) 19

27 ibid 20

28 Shashi K. Muthy, 'Nanoparticles in modern medicine, state of the art and future challenges' (2007) 2 International Journal of Nanomedicine 129, 134 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2673971/pdf/ijn-2-129.pdf> accessed 6 March 2013

29 Wim H. De Jong and Paul JA Borm (n 16) 135

30 Shashi K. Muthy (n 28) 134

31 ibid 135

water solubility of delivery agents. A scientific team (De Jaeghere et colleagues), managed to synthesize nano-based delivery agents that could overcome that problem. Experiments in dogs indicated that using nanoparticles as anti-viral agents against HIV results in more efficient treatment[32].

In treating ocular diseases the shift to nanoparticle-based drug delivery systems occurred because of the need to extend drugs' residence on the ocular mucous layer. Following the usual way of treatment and applying eye drops results in repeated application of drops and often the treatment requires more time in order to be effective because of the movement of mucus during application and the subsequent loss of the applicable medicine. Finally, in treating respiratory diseases the use of nanobased drug delivery approaches is not so extensive, although according to the existing literature, studies have been carried out that show encouraging results for the treatment of allergic asthma and other genetic or inflammatory diseases[33].

1.3 Potential Risks in Nanomedicine

Whereas the potential benefits from the use of nanotechnologies might be great, we should acknowledge the fact that these technologies might have negative effects on humans and the environment. Researchers have voiced concerns about the possible adverse effects that engineered nanoparticles can pose to the human body and the environment and more specifically about toxicity. Until now only few studies have been published on the effects of inhaling free manufactured nanoparticles and we have to rely on previous knowledge from results of studies of exposure to other small particles as for example in urban air and mineral dusts[34].

Humans have always been exposed to some types of nanoparticles that already exist in nature and can be released through a variety of procedures such as cooking, mining, atmospheric photochemistry, forest fires, volcano eruptions etc[35]. Wim De Jong et al. observed that the main characteristics that make engineered nanoparticles of significant

[32] ibid 136
[33] ibid 136-137
[34] RS & RAE (n 3) ix
[35] ibid 35

importance and application to the medical sector, are their large surface to mass ratio, their quantum properties and their ability to absorb and carry other compounds[36]. At the same time the same characteristics can result in increased toxicity.

Due to their small size, nanoparticles interact with the human body and according to studies, small size may lead to an increasing number of them in the body and their small size combined with the large surface area they have, may increase toxicity. Moreover some classes of nanoparticles may be responsible for inflammatory pulmonary effects in the lungs eg. Quantum Dots or polymeric nanoparticles. Each category of nanoparticles interacts in a different way with the human body, depending on several factors.

Notwithstanding the fact that each class of nanoparticles may cause different adverse effects, the routes through which they can be inserted in the human body and interact with it, are the following: i) nanoparticles can be inserted into the body through inhalation, ingestion the nervous system, dermal exposure and the venous system ii) absorption takes place when nanostructures interact with biological components (e.g, cells, proteins) iii) distribution occurs when they spread through different organs iv) their structure might be unchanged, they can be metabolized or modified v) they enter the cells of the organ and can reside there for unknown period of time until they are inserted into other organs or excreted from the body[37].

More specifically, and as far as toxicity is concerned, some studies that have been conducted concluded the possibility of toxic effects. Scientists as Shedova et al. concluded the possibility of cancer occurrence and dermatological disorders associated with an excess in iron. The same team in another study concluded that exposure to single–walled carbon nanotubes may lead to pulmonary toxicity due to oxidative stress. Other studies carried out by Lam et al. observed the possibility of cytotoxicity occurrence in lesioned skin, fibroblasts and keratinocytes after exposure to crystalline silver nanoparticles[38].

Studies have shown that i) the small size of nanoparticles gives them mobility and they can translocate from many organs including the brain without being controllable ii) their

[36] Wim H. De Jong and Paul JA Borm (n 16) 133
[37] A.El-Ansary and S.Al-Daihan (n 14) 1
[38] Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa (n 17) 280

small size makes the removal from the body less efficient iii) small size relates to bigger toxicity per unit compared to larger particles and iv) small size is responsible for quicker penetration of biological structures and their spread in the environment can affect animals and plants[39].

Regarding QDs, as already mentioned they are nanocrystals which have a core made of inorganic element and coated with organic materials such as polyethylene glycol to enhance biocompatibility[40]. Some in vitro studies have shown that quantum dots can be toxic under some conditions. The studies have shown that long term exposure to ultra violet light and the loss of the protective coating which they have, can result in cytotoxicity and cell death[41]. Moreover Wim De Jong et al. recorded that the "*absorption, distribution, metabolism and excretion of quantum dots and therefore toxicity, depend on multiple factors, derived from both inherent physicochemical properties and environmental conditions*"[42]. As far as drug delivery systems are concerned, enhancing cancer therapy by directly targeting tumors and delivery of drugs to the brain is what scientists investigate. The majority of the scientific papers referring to nanoformulations used in drug delivery focus their attention on the reduction of toxicity of the drug, whereas the possible toxicity of the carrier is not considered at the same level[43].

Although the use of nanoparticles offers unique opportunities for advanced diagnosis and therapies, we should also consider the damage to healthy tissue and cell death likely. Despite the fact that more and more in vitro and in vivo experiments take place in order to gain better knowledge of how nanoparticles interact with the human body and the environment, there is still a lack of data. Given the fact that small amounts of engineered nanoparticles are produced, knowledge of the environmental, health and safety impact is analogous. The fact that nanoparticles are already in use in combination with the limited knowledge about their potential adverse effects has attracted the attention of institutional bodies and scholars who voice concerns about those adverse effects and call for regulatory action to be taken.

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[39] Cristina Buzea, Ivan I. Pacheco, Kevin Robbie, 'Nanomaterials and nanoparticles: Sources and toxicity', (2007) 2 Biointephases MR17

[40] A.El-Ansary and S.Al-Daihan (n 14) 2

[41] Wille E. Bawaski, Elena Chidlowsky, Dhruba J. Bharali, Shaker A. Mousa (n 17) 278

[42] Wim. H. De Jong and Paul JA Borm (n 16) 139

[43] ibid

This knowledge gap is mentioned by some scientific reports not only within the European Union context but also worldwide. The Report prepared by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on behalf of the Commission[44] and the White Paper Nanotechnology Risk Governance published in 2006 by the International Risk Governance Council[45] although following different approaches, both stress the lack of data on possible risks associated with nanomedicine with regard to human health and the environment. Another initiative from the Dutch Government and more specifically, the Dutch Health Council report on the health significance of nanotechnology (2006) mentions that "[...] *there is still a lack of understanding about the possible dangers of new, synthetic nanoparticles* [...]"[46].

Moreover, the UNESCO Report on 'The Ethics and Politics of Nanotechnology' mentions the issue of safe and responsible use of nanotechnology and states that the concerns that have been raised so far, are about the hazardousness of nanoparticles and the exposure to risk for humans and for the environment[47].

All the above indicate that the preset level of scientific knowledge around nanotechnology and manufactured nanoparticles leaves some questions unanswered; for example how nanoparticles affect the human body? After exposure to nanoparticles for how long do they reside in the body before excretion? What are the effects on cells and tissue?

Addressing these questions is important in order to understand which are the criteria to measure the hazards posed by nanoparticles and how we can promote the safe use of nanomedicine in the absence of toxicological data. In order to estimate the potential risks that these manufactured nanoparticles can pose to human health and the environment we should

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44 (SCENIHR) Scientific Committee on Emerging and Newly Identified Health Risks, 'Risk Assessment of Product of Nanotechnologies' 2009, 3 (drafted on behalf of Commission in order to provide scientific advice when Commission prepares policy and proposals, relating to consumer safety, public health and the environment) < http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf> accessed 8 March 2013

45 (IRGC) International Risk Governance Council, 'White Paper on Nanotechnology Risk Governance' 2006 <http://irgc.org/wp-content/uploads/2012/04/IRGC_white_paper_2_PDF_final_version-2.pdf> accessed 8 March 2013

46 The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) 37

47 (UNESCO) United Nations Educational, Scientific and Cultural Organization, 'The Ethics and Politics of Nanotechnology'2006,14< http://unesdoc.unesco.org/images/0014/001459/145951e.pdf > accessed 9 March 2013

be able to answer these questions. For the time being, the lack of scientific data to address the aforementioned questions paves the way for more toxicological studies with the aim of better understanding the peculiarities of these nanoparticles and if they pose new risks to human health.

1.4 Conclusive considerations

So far we saw that the application of nanotechnologies in medicine can bring great benefits to the field. The use of nanoparticles can benefit areas such as diagnostic imaging techniques, drug delivery, drug development and treatment of disease. Although nanotechnologies create new opportunities for medicine we should also take into consideration that they generate new risks. The use of QDs and targeted drug delivery systems as examples has shown how the use of nanoparticles can revolutionize the area.

Nevertheless as nanomedicine is still in its early stages of development and the data about their adverse affects are still emerging, there is no consensus about the potential hazards. Despite the fact that some studies have shown potential toxicity, only few of them have been published so far. Of course this paves the way for more toxicological studies. In this state of uncertainty coupled with vague definitions of what nanotechnology and nanomedicine are, it is has become a challenging task for regulators to control both the use and commercialization of nanomedicine applications. How regulators are challenged to address those issues will be examined in the next chapter where the existing regulation under which nanomedicine is expected to fall will be examined. The following chapter will attempt to provide insights into how the current regime in the absence of more specific regulation is applied, how it is challenged by the specific characteristics of nanomedicine and whether there are regulatory problems and gaps.

Chapter 2: Legal Considerations on the Existing Regulatory regime of Nanomedicine in Europe

Introduction

To date on the both sides of the Atlantic, there is no country that has a complete overview of enlisted laws referring to nanomedicine[48]. Of course this does not mean that nanomedicine goes unregulated. In Europe the existing legislations and regulatory systems on medicine and medical devices incorporate some provisions that refer to nanoparticles. Nanotechnologies challenge regulators' expertise to keep up with new technologies and question the suitability of the existing regulatory systems to incorporate them. They challenge regulators to balance technological benefits against possible risks that these technologies incorporate. What is important in this analysis, is how adequate are the existing laws are in dealing with the challenges associated with nanotechnologies. The analysis of medicinal products and medical devices regulation is essential in order to understand the challenges that these technologies put on society. This chapter will examine the current legal system on medicinal products and medical devices in Europe and whether or not nanoparticles can fall under the classifications provided by existing regulations. Moreover it will try to illuminate whether nanoparticles are considered 'new' or already existing substances, compared to medicinal products and medical devices that are in the market now. Is the Regulation for the Registration, Evaluation, Authorization and Restriction of Chemical Substances (REACH)[49] applicable or is there a need for the creation of a new regime? Thereof the understanding of the novelty of nanomedicine applications presupposes the perception of the characteristics and functions of nanoproducts.

[48] Nanomedicine is the application of nanotechnologies in treating or diagnosing dieseases. The term Nanomedicine in the text is used to refer to medicinal products and medical devices made from new or existing substances which are applied at nano-scale.

[49] The term REACH refers to the Regulation No 1907/2006 'Registration, Evaluation, Authorization and Restriction of Chemical' which is the European Community Regulation on chemicals and their safe use.

2.1 The Current Legal Regime for Nanomedicine in Europe

Understanding the current regulatory regime applicable to nanomedicine is important in order to determine its limitations and to discuss which could be the more sufficient regulatory approach. A variety of approaches have been used in order to identify the limitations of the current regulatory system. Some tried to evaluate the applicability of the current legal regime to nanomaterials as a whole without looking into sectors or specific technologies, as the European Commission did (CEC 2008). In its communication to the European Parliament with regard to nanomaterials, their possible risks and the applicability of the current regime to address those questions, the European Community evaluated the system as a whole, without making a distinction between different scientific fields where that nanometarials can be used as for example, food, medical, chemical sector etc[50].

Others as Chaundry et al. followed a sector-by-sector approach (Chaundry et al. 2006). In their research project, they tried to identify regulatory gaps of current legislation to incorporate nanomaterials, by examining each sector separately[51], while others looked at specific commercialized products and their life-cycle (Franco et al. 2007)[52]. More specifically Franco et al. examined three commercially available applications containing fullerenes and carbon nanotubes and by examining them on a life-cycle basis, tried to identify the applicable regulatory regime, identify the gaps and suggest proper solutions. For the scope of this thesis, the existing literature will be reviewed in order to evaluate the applicability of the existing regulatory regime to nanomaterials.

The diversity of opinions about whether nanotechnology applications that touch upon different sectors should be regulated as a whole or following a sector-by-sector approach raises the first regulatory issue. At this stage what is important to realize is that

[50] Commission of European Communities (CEC 2008), 'Communication from the Commission to European Parliament, the Council and the European Economical and Social Committee, Regulatory Aspects of Nanomaterials' COM(2008)366 final < http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0366:FIN:en:PDF> accessed 15 March 2013

[51] Chaundry et al, Science and Research Projects 'A regulatory gaps study for the products and applications of nanotechnologies – CB01075' 2006<http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=13855 > accessed 15 arch 2013

[52] Franko et al., 'Limits and prospects of the "incremental approach" and the European legislation to the management of risks related to nanomaterials', Regulatory Toxicology Pharmacology (2007) 48,171-183 < http://www.innovationsgesellschaft.ch/images/fremde_publikationen/Incremental%20Regulatory%20Approach%20-%20Reg%20%20Tox%20%20and%20Pharmacol%20.pdf> accessed 16 March 2013

nanotechnology is an enabling technology that can be applicable to various different sectors. Therefore, proposals to regulate the technology as a whole will create problems, as each sector will adjust the technology to its own specific needs as applications differ in kind and have divergent characteristics. Regulatory policy should be able to address challenges that each sector poses.

The current regulatory system within Europe was not designed having nanomedicine in mind. As a consequence, one of the biggest challenges that regulators face nowadays is to adjust nanomedicine to the current regime. The existing legal background is established on European Union legislation, legislation of other international instruments and national legislation[53]. The general regulation is supported by a series of guidelines for the assessment, approval and control of the medicinal products within European Union.

The regulatory framework in the European Union under which the nanomedicine may fall is complex and multilevel. To be more specific, for Medicinal Products Regulation 726/2004 on Authorization and Supervision of Medicinal Products for Human and Venitary Use and Directive 2001/83/EC on Medicinal Products for Human Use are applicable. For Medical Devices the normative framework consists of Directive 93/42/EEC concerning Medical Devices, Directive 90/385/EEC for Active Implantable Medical Devices and finally Directive 98/79/EC concerning In Vitro Medical Devices.

Apart from those Directives and Regulations, there are a variety of Guidelines and Principles, as Directive 2001/20/EC for Good Clinical Practice – Clinical Trials of Medicinal Products, Directive 2003/94/EC for Good Manufacturing Practice For Medicinal Products and Directive 2005/28/EC for Good Clinical Practice-investigational Medicinal Products. In order to complete the regulatory puzzle, attention should be paid to the fact that medicinal products for Advanced Therapy[54], Paediatric Use[55] and Orphan[56] are subject to different rules. Finally, other provisions are applicable to GMOs[57], Human Blood and Plasma[58] as well

53 The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) 23

54 Council Regulation (EC) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004

55 Council Regulation (EC) 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

56 Council Regulation (EC) 141/2000 on orphan medicinal products

57 Specific Provisions under Directive 2001/83/EC on medicinal products for human use

as Human Tissue and Cells[59]. Our analysis will focus on the medicinal products and medical devices regime.

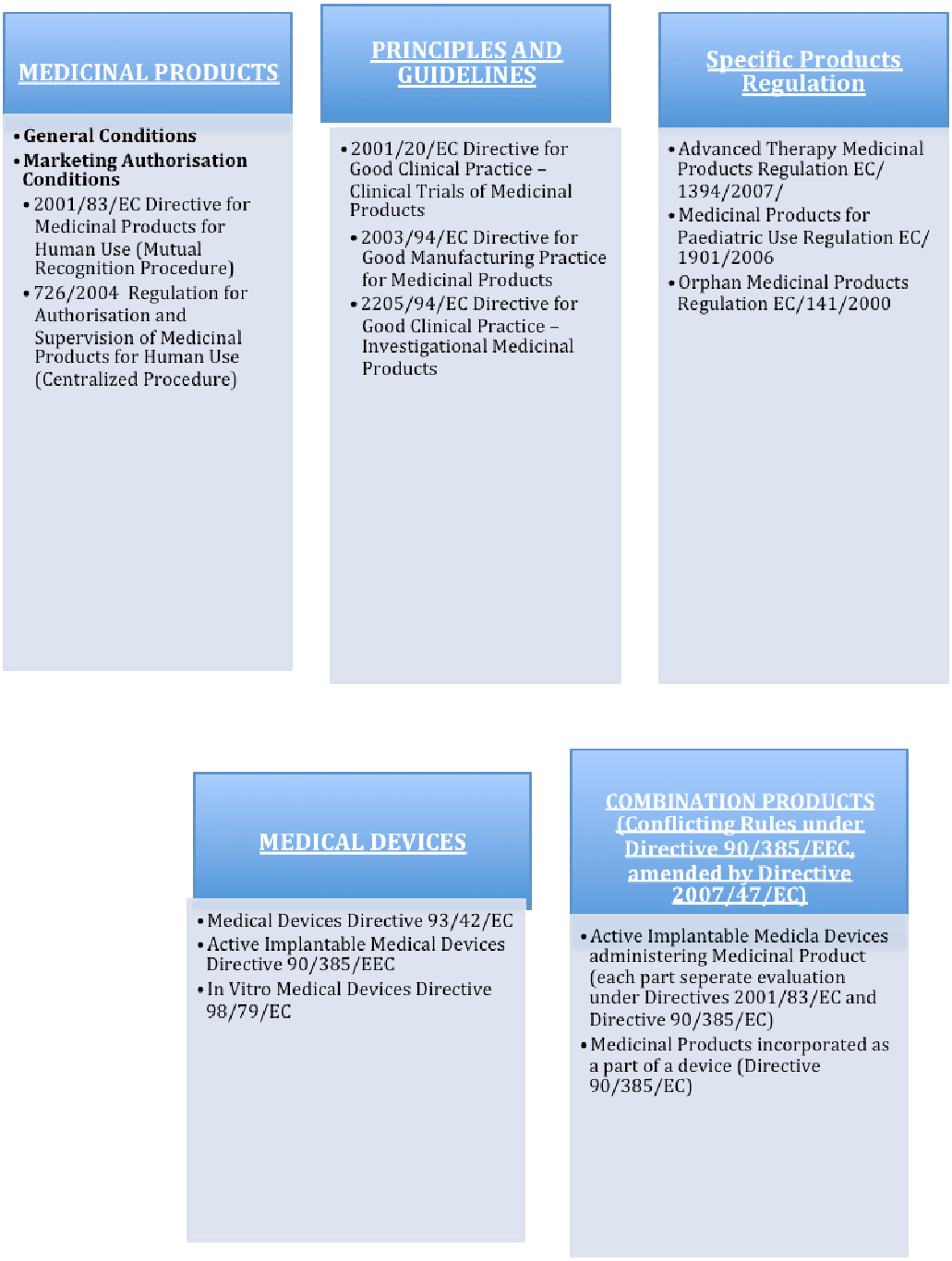

Figure 2. Overview of the European Regulatory Regime for Medicinal Products and Medical Devices

[58] Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

[59] Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells

Medicinal products for Human Use are defined in Directive 2001/83/EC and are covered by extensive EU legislation. According to Art.1 (2) of the Directive a medicinal product is defined as:

"*Any substance or combination of substances presented as having properties 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"*[60].

Before entering the market, medicinal products should go through and obtain market authorization. Regulation (EC) No 2309/93 updated by Regulation (EC) No 726/2004, established the European Medicine Evaluation Agency (EMEA) whose main task is according to its mission statement,

"to contribute to the protection and the promotion of public and animal health by mobilizing 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 Authorization and in particular through a pharmacovigilance network and the establishment of safe limits for residues in food producing animals"[61]

and to set down the Community procedure for authorization and supervision of medicinal products.

In order to enter market, medicinal products should first be authorized as it is stated clearly in Article 3 of the Regulation. Authorization can follow two 'routes'. The first route is considered to be a centralized procedure where the applications are directly submitted to the European Medicine Evaluation Agency. If the application is approved, this leads to the grant of a European market authorization by the Commission. Regulation 726/2004 enlarged the

[60] Council Directive 2001/83/EC on the Community code relating to medicinal products for human use, art. 1(2)
[61] The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) 25

scope of the previous Regulation 2309/93 concerning the centralized procedure. The centralized procedure according to the Annex of the Regulation is mandatory for:

"*medicinal products manufactured using biotechnological process, for orphan medicinal products and for human products containing a new active substance which was not authorized in the Community before 20 May 2004 (where the Regulation (EC) No 726/2004 entered into force) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder and diabetes".*

In addition to the above this procedure is compulsory for *"veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth of treated animals or to increase yields from treated animals".* The centralized procedure is optional for innovative medicinal products. The other 'route' is the mutual recognition procedure, where applications are made to those Member States upon applicants' selection. According to this procedure, mutual recognition takes place by national marketing organizations. This route is followed for the majority of medicinal products[62]. Next to those two 'routes' a third route was introduced with the legislative review in 2004. It is the decentralized procedure, which is applicable in cases where an authorization does not yet exist in any Member State and applications for market authorization are submitted simultaneously to several Member States with only one being responsible for granting the license which is further extended to other national Member States[63].

As far as medical devices are concerned the procedure, which has to be followed, is not the same. Specifically, Directive 93/42/EEC[64] is relevant to nanomedicine applications where in the first article medical devices are defined as:

"*any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: (a)*

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62 ibid 25 & Council Regulation (EC) 726/2004 laying down Community procedures for the authorization And supervision of medicinal products for human and venitary use and establishing a European Medicines agency

63 'Authorization Procedures for Medicinal Products' available at< http://ec.europa.eu/health/authorisation-procedures_en.htm>

64 Council Directive 93/42/EEC concerning medical devices

diagnosis, prevention, monitoring, treatment or alleviation of disease,(b) diagnosis, monitoring, treatment, alleviation or of compensation for an injury or handicap,(c) investigation, replacement or modification of the anatomy or of a physiological process,(d) 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."

In the case of medical devices, they can be placed on the market only if they have undergone a risk assessment involving a third party, which is called a Notified Body, designated by a Member State[65]. If the device complies with those criteria then it can be marked CE (Conformité Européenne). The manufacturers of the device apart from conducting risk assessment, must also demonstrate the effectiveness of the device, establish mechanisms for post market control and furthermore comply with the requirements set in Annex I of the Directive that have to do with the design, use and safety of the devices[66]. Compliance with the requirements of Annex I is presumed with respect to the relevant national standards adopted pursuant to the harmonized standards published in the Official Journal of the European Union[67].

A careful examination of the above Directives leads us to argue that medicinal products and medical devices are subject to different rules and their placement on the market follows separate routes. However, the advances in technology and the advent of nanomedicine, challenges these categories and distinctions on which the existing regulation is based.

2.2 How nanomedicine challenge the current regulatory regime.

Nanomedicine can be very novel systems. They can converge with medicinal products or medical devices or they can be a combination of both. The complexity of those systems makes it difficult to distinguish under which category they will fall and which regulation will be applicable. In the following sections we will examine three cases in order

65 The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) 26
66 Joel D' Silva and Geert van Calster (n 10) 253 & Council Directive 93/42/EEC (n 65) art. 3
67 Council Directive 93/42/EEC (n 65) art. 5

to show how the existing regulatory system is challenged by nanomedicine. First in order to show how the boundaries between medicinal products and medical devices are challenged, we will examine 'borderline products'. More specifically, a drug delivery system namely 'BioSilicon' will be used as an example to show how in cases where a system combines characteristics both of medicine and device it is not clear which regulation will be applicable. Next we will examine how nanomedicine challenge the boundaries between in vitro diagnostic medical devices and medical devices. The third concept that we will analyze is that the complexity of nanomedicine cause classification difficulties in case of medical devices. To better explain this issue 'AcryMed's Silvagard Antimicrobial Surface Treatment' will be used as an example.

2.2.1 Regulating Borderline Products

Nanoproducts usually converge towards medical devices or medicinal products. According to the existing literature, these products frequently referred to as 'borderline products', combine characteristics both from medical devices and medicinal products[68].

An example of this aspect is provided by drug delivery systems. In fact, drug delivery systems like 'BioSilicon' involve pharmaceutical substances and combine characteristics both of devices and medicine. More specifically, BioSilicon which is currently used in the development of treatment of solid tumors, is "*a nanostructured form of elemental silicon that is engineered to create a 'honeycomb' structure of pores. This structure allows silicon to biodegrade while also allowing the retention of various drugs and vaccines within the honeycomb matrix*"[69].

Drug Delivery systems like BioSilicon, which involve pharmaceutical substances, refer to European Regulation on medicinal products which is articulated by Directive 2001/83/EC as amended by Directive 2004/27/EC. According to Art. 1 of the Directive a medicinal product is:

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[68] Joel D' Silva and Geert van Calster (n 10) 257-258

[69] ibid 259 & <http://www.psivida.com/products-bracysil.html> accessed 25 March 2013

"*Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis*."

However, those novel applications seem to create a problem as they go beyond the regulations of both medicinal products and medical devices[70]. If the device and the drug are combined in such a way as to form a product, Art. 1(3) of Directive 93/42/EEC as amended by Directive 2007/47/EC states that:

"*Where an active implantable medical device is intended to administer a substance defined as a medicinal product within the meaning of Article 1 of Directive 2001/83/EC, that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product*".

If medical devices are developed in order to administer a medicinal product they will be governed by the relevant medical devices directives (93/42/EEC and 90/385/EEC), where the medicinal product has to fulfill the requirements laid down in directive 2001/83/EC. In case the medical device and the medicinal product form a single integral unit, then it will fall under directive for medicinal products but the device part has to conform with the safety and standard settings that are laid down in directive for medical devices.

Accordingly, the regulatory model established for drug delivery systems shows that when a medical device and a drug form part of a product not divisible in its components, the entire system is regulated by Directive 2001/83/EC. Whereas, if the system is separable in its two components then it is subject to Directive 93/42/EEC.

So provisions from both directives can apply simultaneously to regulate a combined product. In practical terms, nanomedicine, which primarily have a mechanical action and where the pharmacological action follows, are regulated under the medical devices regime. As DorBeck and Chowdhury mention, the key feature in order to determine under which

[70] Giorgia Guerra, 'European Regulatory Issues in Nanomedicine' (2008) 2 Nanoethics, 87, 91 < http://link.springer.com/article/10.1007/s11569-008-0031-1> accessed 25 March 2013

directive a product may fall so far is its primary mode of action[71]. This is mentioned in Article 1.5(c) of the Directive[72]. But borderline products can combine elements, which combine multiple modes of action neither of which can be identified as being the primary or the secondary[73]. So nanomedicine that combine both characteristics can pose a classification problem. But using the primary mode of action as a key to applying the regulatory regime has been characterized as a too simplistic approach[74]. According to the applicable regime, as already mentioned, their approval to enter the market is granted by a Notified Body on the basis of assessment and conformity with the settled requirements. In case it is not clear under which regime they might fall, there is uncertainty about which authorization procedure should be followed.

According to Barbel R. Dorbeck-Jung and Nupur Chowdhury "[…] *Respondents from companies reported that there is much uncertainty about the applicable regulatory regime in the case of combined products. Companies tend to contact the competent bodies when borderline products raise questions of regime applicability"*[75].

Considering nanotechnology drug delivery systems, the criterion for primary mode of action is challenging to find, as the mechanisms they incorporate are complex. The novelty of those systems is likely to cause blurring of boundaries between regulatory systems.

2.2.2 In Vitro Medical Devices and Medical Devices blurring boundaries

Besides the blurring boundaries between medical devices and medicinal products caused by nanomedicine, these new technologies challenge also other conceptual distinctions

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71 Bärbel R. DorBeck-Jung and Nupur Chowdhury, 'Is European Medical Products Regulation Equipped to Cope with the Challenges of Nanomedicine?' (2011) Law & Policy, 276, 283 <http://doi.wiley.com/10.1111/j.1467-9930.2011.00339.x> accessed 26 March 2013

72 Article 1.5(c) of the MDD was amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market, 2007 OJ (L 247), 21

73 Nupur Chowdhury, 'Regulation of nanomedicines in the EU: distilling lessons from the paediatric and advanced therapy medicinal products approaches' (2010) 5 Nanomedicine (London, England), 135,136 < http://www.nanoarchive.org/9224/1/regulation-nanomed_article.pdf> accessed 1 April 2013

74 Nanomed Round Table Extended Report, 'A report on the nanomedicine environment',25-27 < http://www.philosophie.tu-darmstadt.de/media/institut_fuer_philosophie/diesunddas/nordmann/nanomed.pdf> accessed 2 April 2013

75 Barbel R. Dorbeck-Jung and Nupur Chowdhury (n 71) 290

that are the core of the current regulatory system. Namely, the borderline between the In Vitro Diagnostic Medical Devices Directive and Medical Devices Directive should be considered as well.

According to Article 1 (2) b IVDD : " '*in vitro diagnostic medical device' means any medical device which is reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:*

- *concerning a physiological or pathological state, or*
- *concerning a congenital abnormality, or*
- *to determine the safety and compatibility with potential recipients, or*
- *to monitor therapeutic measures."*

From the above definition follows that in order for a product to be considered an in vitro medical device, it must also fall under the definition of medical device[76]. The determination whether a product falls under which of the two Directives is of great importance, as they are mutually exclusive[77]. The fact that they are mutually exclusive means that a product cannot be a medical device under Directives 98/79/EEC and 93/42/EEC at the same time. A product that qualifies as a medical device shall fall under one of the two directives. Article 1(5)a of the Medical Device Directive, clearly states that "*this directive is not applicable to in vitro diagnostic devices*". Essential characteristic for a product to fall under the regime of medical device or in vitro medical device is the intended purpose of the manufacturer[78]. In addition Article 1(2)b further states that specimen receptacles are considered in vitro diagnostic medical devices: " '*Specimen receptacles' are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary*

[76] Manual on Borderline and Classification in the Community Regulatory Framework For Medical Devices Version 1.14 (03-2013) < http://ec.europa.eu/health/medical-devices/files/wg_minutes_member_lists/borderline_manual_ol_en.pdf> accessed 2 April 2013

[77] European Commission-Directorate General for Health and Consumers, 'Guidelines on Medical Devices: IVD Medical Device Borderline and Classification Issues. A Guide for Manufacturers and Notified Bodies', MEDDEV 2.14/revision 2 (2012), 4 < http://ec.europa.eu/health/medical-devices/files/meddev/2_14_1_rev2_ol_en.pdf > assessed 8 April 2013

[78] ibid 6

containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination".

Tubes intended primarily to collect or store samples for analysis or transportation devices are some devices that qualify under this category[79]. If specimen receptacles are used during the analytical process they are considered as general laboratory equipment and according to the Directive (98/79/EC) cannot be classified as an 'accessory' to an in vitro medical device that is defined in Article 1(2) c[80]. Further the same paragraph of the Article clarifies that an invasive sampling device and specimen receptacles that are applied to the human body fall under the category of Medical Devices and not under In Vitro Diagnostic Medical Devices[81]. If a device combines both characteristics from specimen receptacles and also has analytical functions then the classification is not always obvious. Nevertheless, the application of nanotechnology to medical devices makes this distinction highly difficult. The treatment of a device as in vitro has been based so far on its definition and primary application.

At present, where more and more advanced devices are being manufactured using different material and coatings, the distinction has become even more vague. The difficulty in distinction has further consequences as well. On the basis of classification, different assessment procedures are required to be followed by manufactures before a device qualifies to enter the market, as pre market and post market requirements vary, depending on each category. Moreover, if it is not apparent under which regulatory regime a device qualifies it will be difficult to distinguish which standards it will have to conform to. Also deciding which notified body is going to be competent to assess and authorize the device would be an additional challenge.

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79 Grant Castle and Robin Blaney, 'European Union Regulation of In Vitro Diagnostic Medical Devices' (2010) 227, 233
<http://www.cov.com/files/Publication/5529cdda-e7c3-4ac8-b613-7e945a92ce44/Presentation/PublicationAttachment/9f2d9b63-f46d-4103-bf27-8d603abaeaf8/European%20Union%20Regulation%20of%20In%20Vitro%20Diagnostic%20Medical%20Devices.pdf> accessed 9 April 2013

80 'accessory means an article which, whilst not being an in vitro diagnostic medical device, is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose' article 1(2)c Dir. 98/79/EC

81 Directive 98/79/EC on in vitro diagnostic medical devices Article 1(2) c

2.2.3 Classification difficulties

Another legal issue related to nanomedicine originates from the classification of the medicinal devices made by the European system. Medical devices are classified under Directive 93/42/ECC into four classes. The classification of each category is according to the level of risk that it incorporates. More specifically, there are Class I, Class II which is sub-divided into Class II (a) and Class II (b) and Class III, corresponding to Annex IX of the Directive. According to the classification that has been made, Class I is for all non-invasive devices with low potential risk, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body except for those devices intended to channel or store blood. Class II (a) includes non-invasive moderate potential risk devices, which come into contact with injured skin, principally intended to manage the micro-environment of a wound. Class II (b) relates to high potential risk invasive surgical devices intended for transient use as they are intended to supply energy in the form of ionizing radiation. Finally Class III relates to critical potential risk implantable devices and long-term surgically invasive devices intended either to control, diagnose, monitor or correct a defect, through direct contact, of the heart or the central nervous system. According to the Directive 93/42/EEC, different safety standards and risk assessment procedures are posed to each Class of medical devices, depending on the inherent level of risk that characterizes them[82].

Specifically, under the general rule of low risk that characterizes Class I, the production of devices that qualify under this category can be carried out relying solely on manufacturers' responsibility. Devices that fall under Class II (a) require the intervention during the production stage of an official body designated by the Member State. Class II (b) and Class III, which are characterized by high potential risk, call for inspection of an official body during the design and manufacture procedure. From the classification that has been made to medical devices we can deduce that the criteria that have been used to classify medical devices are the degree of invasiveness to the human body, the duration of invasiveness and the way the human body is affected. The way the classification is done seems to establish a system where the higher the degree of invasiveness and effect on the human body, the higher the risk, so higher safety standards should be adopted.

[82] Giorgia Guerra (n 70) 90

One of the problems that nanomedical devices carry with them is their complexity. Apart from complexity the main challenge that nanotechnologies incorporate, is the difficulty of estimating quantitatively and qualitatively the class of risk; that makes it neither easy nor practical to classify or examine them under this regulatory system that is based on different risk levels. Features such as multifunctionality, variability and the unknown health risks of upcoming nanomedical products, make it unclear whether the quality, efficacy and safety standards on which this normative system is tailored are adequate to balance the evaluation of nanomedicine. Evaluation of potential health risks is of core importance for classifying a nanomedical product. But identification of potential risks due to the novel character of this technology is still at an early stage.

Another aspect of nanomedicine that is often neglected is the potential environmental impact they might have after their release into the environment. Laboratory studies that have been conducted for conventional medicine have shown ecotoxicological effects after their release into the environment[83] (Fent et al. 2006). The same effects can be assumed for nanomedicine although to our knowledge there is yet no official study presenting such results. In the European Union the Directive 2004/27/EEC which amended Directive 2001/83/EC, introduced an obligation to evaluate potential environmental impact. According to the above Directive, applicants are expected to evaluate the potential environmental risks of medicinal products and limit them with specific arrangements. But Recital 18 of the same Directive however, states that environmental impact in not to be considered as a criterion for refusal of marketing authorization. Therefore potential environmental impact is not a criterion for approval or rejection of an application[84].

Moreover within the European Union the 2001/95/EC general product safety directive was adopted. The product safety directive functions in a 'horizontal' way, meaning that it is applicable to all products placed on the market or made available to consumers, aiming at

[83] Karl Fent, Anna A. Weston, Daniel Caminada, 'Ecotoxicology of human pharmaceuticals' (2006) 76 Aquatic Toxicology 122-159 <http://www.biol.uw.edu.pl/pl/files/docs/st_dokt/SD_SCB_Ecotoxicology_of_human_pharmaceuticals.pdf> accessed 9 April 2013

[84] European Medicines Agency, 'Guideline on the Environmental Risk Assessment of Medicinal products for Human Use' (2006) <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf> accessed 9 April 2013

improving the functioning of the internal market and ensuring that manufacturers produce safe medical devices, which are in accordance with the requirements posed by regulation. So it is applicable to medical devices incorporating nanomaterials as well.

2.3 AcryMed's Silvagard Antimicrobial Surface Treatment

For a better understanding of the challenges that nanomedicine poses, how the boundaries are blurred and the difficulty of classification, an example will be used to review the existing standards.

The nanoparticle technology that will be examined is the AcryMed's Silvagard Antimicrobial Surface Treatment [85]. AcryMed's new silver nanoparticle technology, SilvaGard, claims to offer an effective, low-cost method that produces antimicrobial effectiveness by applying a surface of ionic silver to a medical device. Those medical devices can be implantable, indwelling or percutaneous. The medical devices that incorporate this technology are able to provide effective treatment that can last from days to weeks or even months, depending upon the application requirements. SilvaGard is potentially an ambitious nano-application that can be used to prevent hospital–related infections[86]. AcryMed being a company established in Portland Oregon, had to receive approval for its products from the FDA. The initial clearance was given in 2005 to I-Flow Corporation, a subsidiary of AcryMed, for marketing the ON-Q SilverSoaker Catheter covered with SilvaGard[87]. I-Flow was certified under ISO 13485 (13485:2003) and also received the mark CE, meaning that the company's products could be exported to countries of the European Community[88].

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[85] Bruce L. Gibbins, 'SilvaGard – Technology Summary' (2005) AcryMed <http://www.acrymed.com/pdf/SilvaGard%20Technical%20Summary.pdf> accessed 10 April 2013

[86] ibid

[87] FDA- 510(K) Premarket Notification Decision Summary – I-Flow Corporation - ON-Q SilverSoaker Catheter <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHFOIAElectronicReadingRoom/UCM252436.pdf > accessed at 10 April 2013

[88] Annual Report (10-K SEC Filing) filed by I-Flow Corporation on 3/3/2006 <http://sec.edgar-online.com/i-flow-corp-de/10-k-annual-report/2006/03/03/Section2.aspx> accessed 10 April 2013 and Joel D'Silva and Geert van Calster (n 10) 265-267

The size of SilvaGard nanoparticles is about 10nm[89]. At this small size according to the characteristics that have already been described in the previous chapter, their surface area is large comparative to their volume. This may results in increased reactivity and toxicity. Different studies have been conducted to reveal possible side effects of silver nanoparticles. One of them that was conducted on rats by Ji JH et al. showed that the accumulation of silver in tissues is dose-dependent without significant health effects[90], while another study by Braydich-Stolle et al. showed that under certain conditions, silver nanoparticles that are used as antimicrobial agents in bone cement or other implantable devices could be toxic for bone-lining cells and other tissues[91]. Recently another study by Trop et al. examining the use of silver-coated wound dressing Acticoat, concluded that toxic effect in burn patients is possible so more studies are required[92].

Technology like SilvaGard can have a wide scope of application, as it can be applicable to a wide range of medical devices. In Europe, medical devices are subject to Medical Devices Directive, where their classification is based on the level of risk they incorporate. According to the risk they may carry, different assessment procedures take place before they can be qualified for entering the market. Manufacturers have to carry out risk assessments, demonstrate effectiveness of the device and comply with the requirements set out in Annex I of the aforementioned directive. Having a medical device to meet all these requirements and go through the established procedures before it qualifies for market authorization, makes the system seem stringent as it covers a variety of criteria.

However, in the example we examined this does not seem to be the case. SilvaGard technology qualifies for use in a wide range of applications. It can be used in devices that can be classified as low risk or in devices that come in direct contact with the human body as in the case of SilvaGard coated catheters. Therefore a technology as such can blur the

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89 Bruce L. Gibbins (n 85) 4

90 Ji JH, JH Jung, Kim SS et al., 'Twenty-Eight –Day Inhalation Toxicity Study of Silver Nanoparticles in Sprague-Dawley Rats' (2007) 10 Inhalation Toxicology, 857. <http://www.ncbi.nlm.nih.gov/pubmed/17687717> & P.V Asharani et al 'Toxicity of silver nanoparticles in zebrafish models' (2008) 19 Nanotechnology 255102 <http://xa.yimg.com/kq/groups/15186538/89669430/name/Tox_Ag_Asharani2008.pdf> accessed 11 April 2013

91 Laura Braydich-Stolle et al, 'In vitro cytotoxicity of nanoparticles in mammalian germline stem cells.' (2005) 88 Toxicological Sciences: an official journal of the Society of Toxicology, 412, < http://toxsci.oxfordjournals.org/content/88/2/412.full.pdf+html> accessed 11 April 2013

92 M. Trop et al , 'Silver –Coated Dressing Acticoat Caused Raised Liver Enzymes and Argyria-like Symptoms in Burn Patients' (2006) 60 Journal of Trauma-Injury Infection & Critical care, 648 <http://www.ncbi.nlm.nih.gov/pubmed/16531870> accessed 12 April 2013

boundaries between the mode of action on the human body and its intended purpose, making the risk evaluation problematic. To further explain this case, although it's applicability on a medical device can be classified as being a low risk one, when coming into contact with human body and interacting with it, it can be more hazardous and pose new risks. So although it should be subject to stricter examination and other procedures before it qualifies for market authorization, in fact it won't happen because of its classification as a low risk.

Moreover it is likely that the distinction between medical devices and medicinal products will be challenging as well. Hence, a possible revaluation of existing standards and regulations is necessary, as the compatibility and testing standards were not designed to be able to assess nanoparticles.

Ultimately, to determine the adequacy of the existing regulatory system to address those questions, different approaches have been taken so far. In its opinion to the European Commission, the European Group of Ethics in Science and New Technologies[93] concluded that the areas where nanomedicine can be used are covered by extensive regulation and at this point there is no need for new nano-specific regulation. Instead, the focal point should be the correct implementation and compliance with law. About the risk assessment it is of the opinion that no nano-product enters the market without appropriate risk assessment but the existing methods should be adapted to nanomedicine or revised where required[94]. Another opinion from the European Commission in its 'Communication on regulatory aspects of nanomaterials' states that the current legislative framework in Europe "*covers in principle the potential health, safety and environmental risks and this can be enhanced by simply improving the implementation of current legislation through review*"[95]. Of the same opinion is the European Technology Platform on Nanomedicine in its vision paper.

In addition the second Regulatory Review on Nanomaterials that was published in October 2012 similarly concluded that "*Important Challenges relate primarily to establishing*

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[93] The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) & SCENIHR Report (n 44)

[94] The European Group on Ethics in Science and New Technologies Opinion N° 21 (n 9) & (SCENIHR) Scientific Committee on Emerging and Newly Identified Health Risks, 'The appropriateness of existing regulatory methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies' 2006 < http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf> accessed 12 April 2013

[95] COM (2008) 366 final (n 50) 11

validated methods and instrumentation for detection, characterization and analysis, completing information on hazards of nanomaterials *and developing methods to assess exposure to nanomaterials"* [96]. Nevertheless the current situation has led some commentators as Guerra to support the view that a new regulatory response would be appropriate for nanomedicine.

2.4 Nanoparticles compared within REACH regulation. 'New substances' or already existing ones?

So far we saw how the novel and complex character of nanomedicine applications poses challenges to the applicability of the existing regulatory regime that covers medicinal products and medical devices. As the main manufacturer of nanoparticles that are being used in the medical sector is the chemical industry and nanomedicine relies on the progress of nanoparticles research and application in order to achieve its goals, relevant to our analysis should be considered the examination of REACH. By examining REACH regulation and how it approaches nanoparticles we will attempt to see if it can successfully address the issues that they raise.

The Regulation EC No 1907/2006 concerning 'Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and establishing European Chemicals Agency (ECHA)'[97] came into effect on 1 June 2007. In addition certain provisions relating to the classification and labeling of substances, which initially were dealt with by REACH, now are dealt with by a separate Regulation (EC) No 1278/2008 on Classification, Labeling and Packaging (CLP)[98]. Taking into consideration the fact that many provisions included in REACH are connected to classification, REACH and CLP are interlinked.

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[96] Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee – Second Regulatory Review on Nanomaterials, COM (2012) 572, 11 < http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0572:FIN:en:PDF> accessed 7 June 2013

[97] Council Regulation (EC) 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and omission of Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

[98] Council Regulation (EC) 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (CLP), amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

The overarching aim of REACH is to "*ensure a high level of protection of human health and the environment including the promotion of alternative methods of assessment of hazards of substances, as well as the free circulation of substances on the internal market while enacting competitiveness and innovation"* as stated in Article 1(1).

Although within REACH there is no explicit reference to nanosubstances, it is applicable to all chemicals, including nanosubstances and it will play an important role in addressing nanotechnology issues related with environmental, health and safety risks. How and to what extent nanotechnology is covered by REACH has to be analyzed. Examining whether or not REACH can sufficiently address the issue of nanomaterials can be used as a starting point in order to either adjust current legislation to fit nanomaterials or develop new regulatory tools.

One of the main challenges that nanometerials pose and has already been mentioned in the preceding chapter is that nanoparticles can be found in already existing chemicals, actually being the result of their manipulation at a molecular level. The chemicals most frequently mentioned as being manipulated at a nano level are:

- Carbon : carbon nanotubes and fuellerenes
- Silver
- Zinc oxide
- Titanium dioxide
- Gold
- Silicon dioxide
- Cerium oxide
- Aluminum oxide

Although nanoproducts are derived from the same chemicals that already exist in nature, their manipulation at the nano-level confers on them different characteristics and that are applicable in a wide range of sectors. Both REACH in Article 3(1) and CLP in Article 2(7) use the same definition for what they consider as a substance:

"*substance: means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition".*

They do not mention anything about the size, shape or physical state of the substances. Therefore it is considered that they include all substances, physical states and structures in any particle size even if the substance is in nanoscale. In European legislation so far no definition has been developed that could possibly cover nanomaterials. Because both Regulations account on the 'substance concept' a definition would be useful in order for them to consistently apply to nanomaterials[99].

REACH provides a different approach to risk assessment of chemical substances included in products. The principle 'no data, no market' which applies to the commercialization of chemicals, reflects its aim that it "*is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment*"[100]. REACH explicitly states that it is based on the Precautionary Principle. All substances manufactured in volume of one ton or more per year are required to be registered under REACH. Manufacturers or importers of chemicals substances are obliged to submit to the European Chemical Agency a technical dossier with relevant data on properties and uses, toxicity, eco-toxicity, classification and labeling. The classification and labeling of substances should follow the rules that are stated in CLP Regulation. It is worth noting that Article 9(5) of CLP states that:

"*When evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used"*[101].

[99] Annali dell' Istituto Superiore di Sanita, 'The New European Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation): basic features' (2011) 123, 148 <http://www.iss.it/binary/hclp/cont/ANNALI_2_2011_sezione_1.pdf > assessed at 22 May 2013

[100] REACH (n 97) Art 1(3)

[101] CLP (n 98) Article 9

From the above Article in combination with Articles 5(1), 6(1) and 8(6) of CLP it follows that the hazard identification should be based on available information that is related to the properties of the substance or mixture before being placed on the market. In addition, in case the quantity of the manufactured or imported substances outreaches in quantity 10 tons or more per year, the registrant is obliged to provide a chemical safety report along with the technical dossier. Moreover under registrants' responsibility the register dossier has to be updated, whenever the composition, use, knowledge of risks or classification and labelling of a substance change[102]. According to the European Commission the meaning of this is that:

"*when an existing chemical substance, already placed on the market as bulk substance, is introduced on the market in a nanomaterial form (nanoform), the registration dossier will have to be updated to include specific properties of the nanoform of that substance"*[103].

As already mentioned, what a substance is, is defined according to Article 3(1) of REACH and Article 5(1) of CLP. Whether nanomaterials will be considered by current legislation different or the equivalent to the bulk material is of great importance, because according to the answer we will give to that question, the requirements that manufacturers must meet before placing nanometarials on the market will be affected. But Article 3(1) does not mention any specific requirement of properties, size or shape that substances should have and although there is no explicit reference to nanomaterials, it applies to all substances, covering nanomaterials as well. While the substance definition covers nanomaterials and under REACH substances are identified according to their chemical composition, nanomaterials require a more careful observation because besides their composition, there are other criteria that give them uniqueness. The Technical Guidance Document for Identification and naming of substances under REACH and CLP, version 1.2 2012, stated that:

"*the current development in nano-technology and insights in related hazard effects may cause the need for additional information on size of the substances in the future. The*

[102] REACH (n 97) Article 22
[103] COM (2008) 366 final (n 50) 4

current state of development is not mature enough to include guidance on the identification of substances in the nanoform in this guidance document"[104].

The SCHENIHR report identified that the limited knowledge on the distinctive character of nanomaterials and their use in nanotechnology applications in terms of substance identification and hazard profile makes the establishment of standardized and consistent criteria in order to evaluate their potential toxicological effects a challenging task[105].

Therefore, additional information about nanomaterials is necessary in order to conduct an analysis between them and the bulk materials. Guidelines can help for an evaluation to take place. But the need for further work on reviewing the existing or adopting new guidance documents, has been acknowledged in the CASG Nano report of December 2008 where it is stated that:

" […] *further work is needed to provide guidance for substances at nanoscale. In particular, the question needs to be clarified in which cases a nanomaterial is to be considered as a separate substance and in which cases it should be considered as a particular form of a bulk substance. As part of the preparations for such guidance, the Commission services are currently preparing a separate document in co-operation with the REACH Competent Authorities and its subgroup on nanomaterials"*[106].

Making clear whether there is a distinction or not, is closely connected with the requirement of registration, as REACH does not clarify if nanoforms equivalent to bulk materials have to be registered. The quantitative criterion that has to be taken into consideration for registering conventional chemicals seems to be unproblematic, whereas for producers of nanoscale substances, it seems to leave the question open, as it is not clear whether they will have to be registered under REACH or not. The fact that the production of

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104 European Chemicals Agency (ECHA), 'Guidance for Identification and naming of substances under REACH and CLP' 2012 version 1.2, 24 <http://echa.europa.eu/documents/10162/13643/substance_id_en.pdf> accessed 11 April 2013

105 (SCENIHR) Scientific Committee on Emerging and Newly Identified Health Risks,'Opinion on the appropriateness of the Risk Assessment Methodology in accordance with the technical guidance documents for new and existing substances for assessing the risks of nanomaterials.' 2007, <http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf> accessed 13 April 2013

106 European Commission, 'Follow-up to the 6th Meeting of the REACH Competent Authorities for the Implementation of the Regulation (EC) 1907/2006 (REACH) Nanomaterials in REACH' 2008, 10 <http://ec.europa.eu/environment/chemicals/reach/pdf/nanomaterials.pdf> accessed 13 April 2013

nanomaterials does not occur in large amounts, will probably exclude them from REACH legislation. In case of no obligation for registration, information about risk assessment, which comes along with it, will not be available too[107]. Whether they can be registered or not will depend on the existence of an equivalent bulk substance as well as how it is to be categorized under REACH[108]. With regard to that, the SCHENIR opinion on 'The appropriateness of the risk assessment methodology in accordance with the Technical Guidance Documents for new and existing substances for assessing the risks of nanomaterials' concluded that the evaluation of health and environmental risks posed by nanoparticles have to be evaluated on a case-by-case basis[109].

A recent development took place in October 2011 when the European Commission put forward a recommendation on the 'Definition of Nanomaterial'[110]. Further clarification on the term was given in a list of nineteen questions published on the website of the European Commission[111]. The Commission considers the definition given in the Recommendation as a reference in determining whether a material should be considered as 'nanomaterial' for legislative and policy purposes in the European Union, which will be reviewed again in December 2014. The initiative of the Commission has been welcomed by a number of actors such as the Dutch National Institute for Public Health and the Environment (RIVM)[112] and the competent German federal Authorities[113] but both recognized problems regarding the feasibility of the definition and the need for further guidance .

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107 Linda Breggin et al, 'Securing the Promise of Nanotechnologies: towards transatlantic regulatory cooperation' 2009, 45 <http://www.chathamhouse.org/sites/default/files/public/Research/Energy,%20Environment%20and%20Development/r0909_nanotechnologies.pdf>, accessed 13 April 2013

108 European Commission (2008) (n 106) 8-10

109 SCENIHR (2007) (n 105) 50-53

110 European Commission, 'Commission Recommendation of 18 October 2011 on the definition of nanomaterials' (2011/696/EU) < http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF> accessed 1 June 2013

111 European Commission, Nanomaterials: 'Questions and Answers on the Commission Recommendation on the definition of Nanomaterial' < http://ec.europa.eu/environment/chemicals/nanotech/questions_answers.htm> accessed 23 May 2013

112 Eric A.J Bleeker et al., 'Interpretation and implications of the European Commission Recommendation on the definition of nanomaterial' 2012, RIVM Letter report <http://www.rivm.nl/en/Library/Scientific/Reports/2012/juni/Interpretation_and_implications_of_the_European_Commission_s_definition_on_nanomaterials> assessed at 23 May 2013

113 German Competent Authorities, 'Nanomaterials and REACH-Background Paper on the Position of German Competent Authorities'< http://www.bfr.bund.de/cm/349/nanomaterials-and-reach.pdf >assessed 23 May 2013

According to the recommended definition which is based on a reference report by the European Commission Joint Research Center[114] and an opinion by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENHIR 2010)[115] nanomaterial is defined as:

"*a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.*"[116]

In order for a material to be considered as nanomaterial it has to fulfill the above proposed criteria. So the key elements that are included in the proposed definition with regard to nanomaterials are the natural, incidental or manufactured nanomaterials, including their aggregates and agglomerates with at least 50% of the number-based sized particle distribution being within the range of 1-100nm. The proposed definition of nanomaterials can have implications with regard to medicinal products and medical devices. The definition includes not only manufactured particles but also incidental and naturally occurring ones. The reasoning behind this choice was addressed in question 6 which is available on European Commissions' website and states that: "*The Recommendation only identifies a nanomaterial on the basis of its particle size* […]".[117]

Size is a decisive factor in order to distinguish nanomaterials from materials that cannot fall under this category. As described in the first chapter the size of the materials is an important element because their potential to cause damage is due to the fact that their small size makes them behave differently from bulk materials and have different properties. The

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114 Göran Lövestam et al., 'Considerations on a Definition of Nanomaterial for Regulatory Purposes' 2010 The European Commission Joint Research Center Report <http://ec.europa.eu/dgs/jrc/downloads/jrc_reference_report_201007_nanomaterials.pdf> accessed 25 May 2013

115 (SCENIHR) Scientific Committee on Emerging and Newly Identified Health Risks, 'Opinion on the scientific basis for the definition of the term "nanomaterial" ' 2010 <http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf> accessed 25 May 2013

116 European Commission Recommendation (18 October 2011) (n 110)

117 European Commission, Nanomaterials (n 111) question 6

proposed threshold under the Recommendation, which is between 1nm-100nm, can be debated because a number of nanomaterials can have dimensions smaller than 1nm as for example fullerenes and single-wall carbon nanotubes[118]. As stated in the RIVM report, the definition of agglomerate is related to the external surface area, which is a measurable unit. As the report further states, in order to proceed further with the assessment, a comparison between the surface area with the agglomerates/aggregates and without them has to take place.[119] However this might prove difficult because this technique has been used so far for powders and not particles incorporated in liquids.

In case the definition becomes part of the current regime some amendments will have to take place. First of all, in order for the recommended definition to be applicable to REACH, REACH has to be amended in order to include it. For the identification of nanomaterials at the European level, consideration has been given to two approaches so far[120]. The approaches are whether size, shape and design of nanomaterial can be used to identify or characterize the nanomaterial, so those properties can function either as 'identifier' or 'characterizer'[121]. The proposed definition pays specific attention to the size, which can be characterized as the key element and the other properties arise due to the size. If a substance occurs both in bulk and at nanoscale it is likely that a different registration will be required and a different dossier will be submitted[122].

Furthermore the adoption of the definition will help to make clear whether some materials can be considered as nanomaterials or not. With regard to the volume of production, due to the fact that nanomaterials are not produced in big quantities the threshold of one ton volume per year will have to be amended to fit the reduced volumes of nanomaterial production[123].

The diversity of characteristics at nanoscale will probably create the need for new testing criteria. Also the International Uniform Chemical Information Database (IUCLID)[124]

118 German Competent Authorities (n 113) 3
119 Eric A.J Bleeker et al. RIVM Letter report (n 112) 16
120 Annali dell' Istituto Superiore di Sanita (n 99) 150
121 ibid
122 Eric A.J Bleeker et al. RIVM Letter report (n 112) 32
123 ibid
124 http://iuclid.eu/index.php?fuseaction=home.project

that is a tool for the collection and evaluation of data in the Frame of the European Risk Assessment Evaluation Program will have to be adapted to fit the registration of nanomaterials.

Although the Second Regulatory Review on Nanomaterials among its conclusions included that "*REACH sets the best possible framework for risk management of nanomaterials […] but more specific requirements for nanomaterials within the framework have proven necessary. The Commission envisages modifications in some of the REACH Annexes and encourages ECHA to further develop guidance for registrations after 2013*"[125], it did not propose any further regulatory action, despite the fact that the accompanying Staff Working Paper acknowledged the failure of REACH to provide considerable information on nanomaterials[126].

REACH provides a good basis for regulation of nanomaterials in EU but as already described, amendments to its provisions will have to take place in order to cover nanomaterials. Nevertheless another option that has been proposed by the Center for International Environmental Law is the development of a stand-alone regulation, 'nano patch' next to REACH, which will determine how the REACH can fit to nanomaterials.

2.4.1 REACH and its approach to medicinal products and medical devices

Apart from the above, REACH legislation also includes some provisions that are related to medicinal products and medical devices. Article 2(5)(a) excludes from the requirement of registration, evaluation and authorization substances used in medicinal products. Contrarily, medical and in vitro diagnostic devices fall under the scope of REACH. Nevertheless Art. 2(6)(c) provides an exception:

"*medical devices which are invasive or used in direct physical contact with the human body in so far as Community measures lay down provisions for the classification and*

[125] COM (2012) 572 (n 96) 11

[126] Commission Staff Working Paper 'Types and uses of nanomaterials, including safety aspects' SWD (2012) 288 final Accompanying the Communication form the Commission to the European Parliament, the Council and the European economic and Social Committee, 26-30 < http://ec.europa.eu/nanotechnology/pdf/second_regulatory_review_on_nanomaterials_-_staff_working_paper_accompanying_com(2012)_572.pdf> accessed 5 June 2013

labeling of dangerous substances and preparations which ensure the same level of information provision and protection as Directive 1999/45/EC".[127]

From the above it starts becoming clear that there are some uncertainties on how European legislation approaches medical devices, which contain nanomaterials. Nowadays, many nanoproducts combine characteristics from both medical devices and medicinal products, often called borderline products and their complexity challenges the European legislation. Taking as an example a borderline product, the part of the medical device would fall under REACH regulation but the part of the substance, which qualifies, as a medicinal product would fall under the exception. In case the medical device contains a dangerous chemical substance according to Art. 2(6)(c), it is excluded from REACH and instead is regulated by Directive 1999/45/EC which will be replaced by CLP Regulation[128]. The classification of a substance as dangerous relies on the degree and the nature of hazards, which are classified into categories of danger by the above mentioned directive. So the identification of hazard and risk is necessary for the classification of danger. But in the case of nanomaterials, the lack of knowledge, the insufficient data and the limited studies that have been conducted to study their characteristics makes classification extremely difficult.

In an effort to help this complex situation and the competent authorities with borderline products, the European Commission provided some guidelines. These guidelines contained in the MEDDEV 2.1/3rev3[129], are given to help manufacturers of borderline products to recognize the category in which their product might stand. Although these guidelines are constantly updated to keep up with the changes in the relevant field, notably they do not mention anything about devices incorporating nanomaterials. Therefore, regulating nanotechnology and its novel applications and products for reasons other than understanding their nature and processes, requires a convergence of regulatory tools that all together will help towards this direction. The implementation of REACH, which will gradually replace a variety of legislation, can be considered as one of the biggest regulatory initiatives within the European Union.

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127 REACH (n 97) Article 2 (6)(c)

128 CLP (n 98)

129 European Commission-Medical Devices: Guidance Document, 'Borderline products, drug-delivery products and medical devices incorporating as integral part, an ancillary medicinal substance or and ancillary human blood derivative' MEDDEV 2.1/3rev3 <http://ec.europa.eu/health/medical-devices/files/meddev/2_1_3_rev_3-12_2009_en.pdf> accessed 13 April 2013

As already described the current regulatory regime of medicinal products does not contain any specific provisions with regard to nanomaterials and careful risk assessment and risk management on a case by case basis is needed before a medicinal product is granted market authorization. In the discussed Recommendation in paragraph 17 it is stated that '*given the special circumstances […] in the pharmaceutical sector […] the definition in this Recommendation should not prejudice the use of the term 'nano' when defining certain pharmaceuticals and medical devices*'[130].

But currently there is not a coherent and commonly acceptable definition on nanomedicine and EMA on its website[131] on the topic of nanotechnology and its use in medicine states that '*nanotechnology is the use of tiny structures –less than 1,000 nanometres across-that are designed to have specific properties*'. In addition in a Reflection paper in 2006 EMA states that the nanometre scale can range between the atomic level at around 0,2 nm (2 Å) up to around 100 nm[132]. So in comparison with the size range of nanomaterials that is proposed under the Recommendation of the Commission there are significant differences. How the definition will be implemented in the current legislation might result is some products despite incorporating nanomaterials, not falling under the scope of definition.

With regard to medical devices, the current regime as described above requires a risk assessment and risk management before granting market authorization but does not contain any specific provisions for nanomaterials. The Recommendation of the Commission on the definition of nanomaterials in paragraph 17 refers to medical devices as well. In September 2012 the European Commission announced the 'Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009'[133]. The new Regulation in

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130 Commission Recommendation (18 October 2011) (n 110) 5

131 European Medicines Agency <http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&mid=WC0b01ac05800baed9> accessed 22 May 2013

132 European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) 'Reflection Paper on nanotechnology-based medicinal products for Human Use' 2006, 3 <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069728.pdf > accessed at 22 May 2013

133 European Commission, 'Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No

the preamble 13 recognizes the "*scientific uncertainty about the risks and benefits of nanomaterials used for medical devices […] and the necessity to adapt the proposed definition based on Recommendation 2011/696*" and nanomaterials are being covered by article 2(15), Rule 19 and Annex VII (6.7).

Although the existing regime have been subject to criticism, the proposed Regulation took place at a time where the concerns about the inadequacy of the existing regulatory framework have been increased in the light of the French breast implant scandal (PIP)[134]. According to the proposal, two Regulations will replace the current Directives. One Regulation will be about Medical devices while the second will be about In Vitro Diagnostic Medical Devices[135].

The new regulatory proposal aims to ensure a high level of safety of medical devices so both patients and practitioners feel confident when use them, assist the internal Market in order to function efficiently and also promote innovation in medical technology[136]. In order to achieve these goals, the proposed amendments where given in the form of Regulations that will be directly applicable to all Member States, unlike Directives, and the same requirements for medical devices will have to apply thorough Europe[137]. According to the proposal, the current system will not be abandoned but some of its characteristics will be adopted by the proposed regime. More specific, medical devices will continue to be divided in four classes and be subject to conformity assessment according to the classification of the level of risk[138]. Also the concept of Notified Bodies remains and they are involved in the conformity assessment procedure.

In order to achieve the above mentioned goals the proposed Regulation broadens the scope of medical devices regime. Products that were not covered by the existing regime will be included to this Regulation. For example, products manufactured utilizing non-viable human tissues and some aesthetic products such as non-corrective contact lenses will be

1223/2009' 2012 < http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0542:FIN:EN:PDF> accessed 26 May 2013

134 ibid 2

135 ibid

136 ibid

137 ibid 15

138 ibid

included in the scope of the Regulation[139]. In addition under the future regime the grant of market authorization as already mentioned above will be maintained. The main amendments according to the proposal will be the following. In order to ensure the traceability of medical devices, manufactures will have to fit a Unique Device Identification (UDI) in medical devices[140] and all the operators will have to identify the device within the supply chain[141]. In case the device is of high risk the manufacturer will have to additional safety and clinical data[142]. In addition the European databank on medical devices will be extended and will contain information on all economic operators on EU market[143].

Furthermore the future regime introduces the 'qualified person' concept that is already used under medicinal products regulation[144]. In addition the Proposal clarifies the provisions for parallel imports of medical devices. The rules regarding notified bodies and the procedures for conformity assessment and CE labeling are modified to empower the position of notified bodies vis-a-vis manufacturers[145]. Also the Medical Device Coordination Group is created[146] which will be involved in the assessment process of notified bodies[147] and conformity assessment of high-risk medical devices[148].

The approach taken in the Proposed Regulation establishes stricter assessment criteria and aims at a high level of safety of medical devices. In addition the provisions referring to nanomaterials aim to establish a high level of safety of devices that include them and classify them in the category of high risk, so stricter assessment criteria will be applicable. Nevertheless the review of the Recommendation will take place in a year from now and it still remains to be seen if and what kind of changes will be introduced and whether or not the

139 ibid 4
140 ibid Article 24 of the Proposed Regulation
141 ibid Article 23 of the Proposed Regulation
142 ibid Article 26 of the Proposed Regulation
143 ibid Article 27 of the Proposed Regulation & Francois-Regis Babinet and Peter Bogaert, 'Innovation vs. Safety: The New Proposed Rules for Medical Devices in the European Union' (2013) <http://www.cov.com/files/Publication/d7e410e3-5be0-40d0-b429-675ec89cbeca/Presentation/PublicationAttachment/2705762b-1429-4690-8b7a-4015b0bc9a15/Innovation_vs_Safety_New_Proposed_Rules_for_Medical_Devices_in_EU.pdf> accessed 6 June 2013
144 Proposed Regulation (n 133) 6 & Article 13
145 ibid 21
146 ibid Article 78 of the Proposed regulation
147 ibid Article 80 of the Proposed Regulation
148 ibid Article 44 of the Proposed Regulation

definition will finally be adopted by other regulatory initiatives as the Proposal for a Regulation of medical devices.

2.5 Conclusive Considerations on Nanomedicine and Regulation

As regards nanoparticles, the following thoughts-conclusion can be derived. Although there is no specific reference to nanoparticles, REACH with the procedures that has been established, allows the gathering and collecting and disseminating of data amongst the competent authorities and scientists about benefits, hazards and toxicity of nanoparticles. This can help to fill the communication gap as a 'database' with all this information that has been created. From a business perspective amongst the benefits can be a better availability of information, improved cooperation along the supply chain as well as reduction in costs from health damage to workers. It is an important legal tool that can help monitor the safety of people and the environment.

Nevertheless, limitations have been identified in the applicability of REACH to nanosubstances. One limitation is that it is still not clear whether a nanomaterial should be considered equivalent to the bulk substance. The second limitation is that the requirement of production substances in tonnage volumes is not compatible with nanoparticles, which are usually produced, in smaller quantities.

The recent initiative from the European Commission although significant for a commonly accepted definition to be established, is not without its problems. If substances fall under REACH it should be examined if the rules, methods and tools for example hazard identification, risk assessment and risk management that are provided under REACH can be used for the assessment of nanomaterials. The fact that at that size their properties are different from those of bulk materials makes it possible to have different toxicological and eco-toxicological effects. Also in order to be consistent with the precautionary principle that underlies REACH, the requirements and the instruments in REACH such as dossier evaluation, substance evaluation, authorization, restriction, safety etc. must be applicable to nanomaterials as well[149].

[149] German Competent Authorities (n 113) 4

With regard to medicinal products and medical devices, in case they contain nanomaterials, the question that arises is if the established method of risk assessment under the current regime is tailored for them as well. The properties of nanometerials differ significantly from those of conventional substances. Still there is a lot of uncertainty about their properties, potential effects and toxicity.

As RIVM comments, "*the inclusion of size distribution without any further specification can have further implications as a material that will contain some particles under 100nm it would be doubtful whether it will comply with the definition or not*"[150]. Moreover further guidance for the measurement techniques as well as the consistent application in the legislation and enforcement of the definition is needed. As RIVM further states, new standardized methods should be developed and new guidance is needed with regard to methods of risk assessment and analysis of results[151].

To sum up, as appears from the discussion in the previous chapter, we identified that nanomedicine have unique characteristics and introduce new risks for human health. In this chapter we tried to answer if the existing regulatory regime is challenged by those characteristics and whether there are regulatory problems and gaps. In order to answer these questions we examined the current regulation existing in the EU supplemented by some examples for a better understanding. The analysis has shown that nanomedicine challenge some core concepts used in this regime. More specifically, nanomedicine challenge the boundaries between medicinal products and medical devices as well as they introduce difficulties in distinction between in vitro diagnostic medical devices and medical devices. In addition classification difficulties arise from the novel and complex character of medical devices and the still unknown health risks. The use of 'Silvagard AcryMed's Antimicrobial Surface Treatment' as an example attempted to reflect some of these challenges.

In order to complete the examination of the regulatory puzzle and by taking into consideration that the use of nanoparticles in medicine is what makes them innovative, relevant to our analysis was the examination of REACH regulation in order to see if this regulation can address the issues that nanoparticles raise. Although REACH provides a good

[150] Eric A.J Bleeker et al. RIVM Letter report (n 112)16
[151] ibid 8-37 (18,19,21,31)

basis for regulating nanomaterials, limitations have been identified. The examination of the proposed definition of nanomaterial and the Proposed Regulation for medical devices that will include it, showed that despite the fact that they are significant steps, they have some deficiencies. They haven't been adopted yet, so it still remains to see if and in what form they will finally be introduced.

All the above indicate that the characteristics of nanoparticles that make nanomedicine novel, challenge the existing regulatory regime if we directly apply it to them. Nanomedicine are innovative and challenge the established concepts of the regime, causing uncertainty about the category which they might fall and the regulatory criteria which will have to be followed. Ultimately the current regime cannot fully address the issues that nanoparticles introduce. The regime should be able to take into consideration that nanomaterials require a more careful observation because besides their chemical composition, there are other criteria that give them uniqueness. Until more data become available the European Union by using REACH and other directives should approach the regulation of medical devices and products that include nanoparticles and the so-called borderline products with diligence, trying to make their classification less blurry.

Chapter 3: How to Manage the Risks in Novel Sciences

Introduction

Science changed the way people perceive the world and became a new tool through which man explores and interacts with nature. This new tool, despite giving people the power to understand nature and make progress in almost every known field, did not do it without raising political, regulatory, ethical and philosophical issues. Along with the discoveries resulting from applied science, inherent in its nature are risks, uncertainties and complexities. Society has to be prepared not only to take advantage of science but also to find ways to manage risks and uncertainties accompanying these technologies.

Over the last decade nanoscience and nanotechnologies have emerged as a new transformative force for industrial society with an emerging range of applications almost in every field, from chemicals to energy, food, pharmaceuticals and others as well[152]. What characterizes nanotechnology is that it presents both unprecedented challenges by its nature, complexity and unpredictability of risk. As nanotechnology emerged from laboratories into industrial manufacture and then into commercialization the potential risks for humans and the environment have become a priority[153]. The constantly emerging risks combined with the limited knowledge led experts and regulators to develop frameworks to assess the hazards and benefits and estimate the acceptable level of risk compared to the forthcoming benefits. A regulatory tool to achieve this measurement of risks, is risk/benefit analysis. A main goal of this regulatory approach is to identify potential risks and benefits, provide methods to control risks, evaluate activities as high or low risk and calculate the acceptability of the risks.

After identifying in the previous chapter limitations in the existing regulatory regime if we directly apply it to nanotechnologies, this chapter will investigate some tools that have

[152] Robert Falkner and Nico Jaspers (n 5) 3

[153] Gary E. Marchant, Douglas J. Sylvester, Kenneth W. Abbott, 'Risk Management Principles for Nanotechnology' (2008) 2 Nanoethics, 43., <http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1020104> accessed 4 June 2013

been introduced to govern emerging science and manage the risks that they introduce. More specifically this chapter analyzes the risk benefit analysis as a tool to manage risks and underlines the reasons why this model seems to be inadequate to take fully into consideration and cope with the risks and benefits in nanomedicine. Then it goes on to further to examine whether the Precautionary Principle as a decision making tool could give a full account of risks associated with nanomedicine and be a reliable answer to uncertain science.

3.1 The classical model of risk benefit analysis and it's applicability to Nanomedicine and novel science.

Making its appearance first in the US and around the 1970s in Europe, risk regulation operating in the context of scientific uncertainty was employed by governments as a regulatory policy because of the uncertainty that at the time characterized industrial activities with possible negative effects for humans and the environment[154].

Employing a kind of policy like this had a twofold purpose. According to Hutter, on the one hand risk regulation tried to control the possible damages caused by economic activities and on the other hand it tried to establish an acceptable level of risk that these beneficial but at the same time potentially harmful activities had[155].

The interest towards risk-based regulation has grown significantly during the last decades. Risk-based regulation as a term seems to cover a wide range of approaches[156]. To state it more specific, the use of the term by some regulatory agencies was thought either to embrace a whole framework of governance or to include some risk based tools[157]. According to the existing literature on risk based regulation it can be defined as "*the application of a systematic framework that prioritizes regulatory activities and deployment of regulators*

[154] Giorgia Guerra (n 70) 94

[155] ibid

[156] Bridget M. Hutter, 'The Attractions of Risk-based regulation: accounting for the emergence of risk ideas in regulation' 2005, Centre of Analysis of Risk Regulation, London School of Economics and Political Sciences, Discussion Paper, 3 <http://webfirstlive.lse.ac.uk/researchAndExpertise/units/CARR/pdf/DPs/Disspaper33.pdf> accessed 5 June 2013

[157] ibid

resources on an evidenced based assessment of risk" [158]. With risk as a concept, its assessment, quantification and management is placed in the design of regulation and its further implementation[159].

Risk based regulation can provide a framework in which the regulators can take measures and relate their enforcement with the objectives they aim for[160]. According to Black and Baldwin although different risk based approaches have been adopted so far by various countries, nevertheless they share some common key elements[161]. The approach to each element may vary across countries and we will refer to them in brief.

Nevertheless, as Black and Baldwin observe, they all share a common starting point which is the focus on the risks and not on the rules.[162] This means that the primary focus of risk based frameworks, is to identify the risks that regulators aim to manage and not to look for compliance with the rules. As they further observe, regulators usually deal with a variety of rules, where each and every rule cannot be enforceable in every regulatory area at the same time[163]. So selections have to be made. In that sense risk based frameworks try to establish priorities so that the decisions taken will be explicit and also provide a clear outline within which decisions can be understood and explained[164].

Despite the fact that the these frameworks can differentiate in terms of complexity, as Black and Baldwin observed, they have a number of central elements[165]. The first element that they recognized is that risk-based regulation requires that the organization sets its objectives that reflect what risks it intends to control. These objectives will be set by the

158 Rober Baldwin and Julia Black, 'Really responsive regulation' 2007 Law, Society and Economy Working Papers, London School of Economics <http://www.lse.ac.uk/collections/law/wps/WPS15-2007BlackandBaldwin.pdf> accessed 5 June 2013

159 Deborah Peterson and Sally Fensling, 'Risk-based regulation: good practice and lessons for the Victorian context' 2011,1., 2 Conference paper presented at the Victorian Competition and Efficiency Commission Regulatory Conference, Melbourne < http://www.vcec.vic.gov.au/CA256EAF001C7B21/WebObj/20110328-Risk-basedregulation-DPIpaperforVCECconference/$File/20110328%20-%20Risk-based%20regulation%20-%20DPI%20paper%20for%20VCEC%20conference.PDF> accessed 5 June 2013

160 Robert Baldwin and Julia Black (n 158) 13

161 Julia Black and Robert Baldwin, 'Really responsive risk-based regulation' (2010) 32 Law and Policy, 181, p. 183 < http://doi.wiley.com/10.1111/j.1467-9930.2010.00318.x> accessed 5 June 2013

162 Robert Baldwin and Julia Black (n 158)13

163 Julia Black and Robert Baldwin R. (n 161)184

164 ibid

165 ibid

governmental policy when establishing the legislation, where the regulator should clearly identify the objectives and the risks that the regulated activity may present[166].

The second element is that the regulator must set his own 'risk appetite' which has to be in line with governmental policy, reflecting what kind of risks he can accept and to what extent. Determining the type and the level of risk tolerance can be a very challenging task for the regulator. Peterson and Fensling recognized that difficulties in setting the 'risk appetite' can arise from the fact that risk tolerance is triggered by factors such as political considerations about risk, available data and public perceptions about risk which might be contradictory[167]. Black and Baldwin further observed that when determining the risk, regulators face political risk, which means that their considerations about the acceptable level of risk will differ in relation to what the public, media and politicians consider to be acceptable[168].

The third element is that an assessment of hazard or adverse effect should take place along with the likelihood of its occurrence. The assessment will identify the likelihood of occurrence of an event and its impact. During risk assessment it is important to identify the risks as well as their nature and their possible consequences.[169] Another factor that will also determine whether and what kind of regulatory action will be taken is who is subject to risk[170]. In addition risk assessments can take the form of qualitative and/or quantitative analysis.

The fourth element or risk-based regulation identified by Black and Baldwin is the assignment of scores or ranks to those who are regulated on the basis of risk assessment. The assessment of risks and the assignment of scores to the subjects of regulation, depends also, as Deborah and Fensling note, on "*acquiring intelligence about their characteristics, the scale and nature of their activities, their capacity and capabilities for self-managing risks, their market orientation and their reputational sensitivity to publicity about their record in handling risk*"[171].

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166 ibid 185
167 Deborah Peterson and Sally Fensling (n 159)12
168 Julia Black & Robert Baldwin (n 161)184
169 ibid
170 Deborah Peterson and Sally Fensling (n 159)14
171 ibid15 <quoted from Black 2010b>

The last element involves the distribution of regulatory resources. This means that according to the risk scores, supervisory, inspection and enforcement resources will be allocated to those who are regulated.[172] In order to achieve its goals, risk-based regulation uses risk-based tools that can have their origins in economy, for example cost-benefit analysis or in science, risk assessment tools[173].

Risk analysis as a regulatory policy has been adopted in environmental and health law. As stated in the paper of the International Risk Governance Council (IRGC) 'An Introduction to the IRGC Risk Governance Framework', risk governance "*deals with the identification, assessment, management and communication of risks in a broad context. It includes the totality of actors, rules, conventions, process and mechanisms and is concerned with how relevant risk information is collected, analyzed and communicated, and how management decisions are taken. […] Many risks, and in particular those arising from emerging technologies, are accompanied by potential benefits and opportunities*"[174].

In Europe risk analysis is considered a horizontal procedure that includes various steps. The steps are identification of risk, risk assessment, risk management and risk communication which are tidily divided. Both medicinal products and medical devices before market authorization is granted are mandated to undergo a risk assessment. The use of risk benefit analysis as a regulatory tool is not only important for scientists to assist them in measuring the risks and benefits that activities have, but also for regulators because they need the information that will be generated in order to take proper regulatory action.

The first component of a risk analysis is risk assessment. Risk assessment as described by the OECD, intends to "*calculate or estimate the risk to a given organism, system or (sub)population, including the identification of uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as*

172 Julia Black and Robert Baldwin (n 161) 185

173 Bridget M. Hutter (n 156) 3

174 (IRGC) International Risk Governance Council, 'An Introduction to the IRGC Risk Governance Framework', 2005, 1., 4 <http://www.irgc.org/IMG/pdf/An_introduction_to_the_IRGC_Risk_Governance_Framework.pdf > accessed 6 June 2013

well as the characteristics of the specific target system"[175]. In that sense hazard is the inherent property of a substance to cause potential harm, whereas risk is the likelihood of that harm occurring[176].

Risk assessment consists of four steps: hazard identification, hazard characterization, exposure assessment and risk characterization[177]. When in risk assessment the analysis of risks takes place it can be estimated qualitatively or quantitatively[178]. As ENISA states in its website qualitative analysis *"the likelihood of occurrence of potential adverse effects are described in detail, where quantitative analysis assigns numerical values both to the likelihood of occurrence and impact of an event*"[179].

Risk assessment has to identify and characterize the risks in order to establish a safe basis for further decision making, regarding risks. So far, there are no fixed rules about how a risk assessment should be carried out but what is important is to ensure that all relevant risks and hazards are taken into consideration. Some tools that are used to identify risks are checklists, judgments based on experience and records, system analysis, scenario analysis and systems engineering techniques[180]. In addition a tool that contributes to decision making is the "evidence approach"[181]. As Janhel J. et al. mention, this means "*that the process accounts on the totality of data in a holistic manner and facilitates transparency and quantification in decision making*" [182]. A robust risk-assessment is the basis for an effective risk management program. In classical risk assessment, scientific knowledge is measurable and monitored. As they further observe, values and ethics as forms of knowledge are significant factors as well[183].

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175 (OECD) Organisation for Economic Co-operation and Development, 'Descriptions of Selected Key Generic Terms Used in Chemical Hazard/Risk Assessment', 2003,1., 16 <http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2003)15> accessed 6 June 2013

176 ibid 15

177 J Jahnel, T Fleischer, S B Seitz, 'Risk assessment of nanomaterials and nanoproducts –adaption of traditional approaches' (2013) 429 Journal of Physics: Conference Series 012063, 2 <http://iopscience.iop.org/1742-6596/429/1/012063/pdf/1742-6596_429_1_012063.pdf > accessed 6 June 2013

178 (ENISA) European Network and Information Security Agency, 'Risk Assessment' <http://www.enisa.europa.eu/activities/risk-management/current-risk/risk-management-inventory/rm-process/risk-assessment > accessed 6 June 2013

179 ibid

180 ibid

181 J Janhel, T Fleischer and S B Seitz (n 177) 2

182 ibid

183 ibid 3

After risk assessment, risk management takes place where it focuses on communication, mitigation and decision making[184] . According to the OECD, it consists of three steps: risk evaluation, emission and exposure control and risk monitoring[185]. Risk management is the decision making process, which takes into consideration the information deriving from risk assessment, as well as social, political, ethical factors in order to decide and implement appropriate regulatory action[186]. So, while risk assessment is occupied with identifying the risks and prioritizing the measures to control them, risk management includes the monitoring of the identified risks.

Over the time in order to assess not only the risks but also the benefits that new activities carry, different risk management tools have been developed. The three most common traditional models as Marchant et al. refer to are i) acceptable risk ii) risk/benefit analysis and iii) feasibility (or best available technology)[187]. As they all aim at assessing and monitoring the risks and benefits of an activity, we can understand that the risk as a concept plays a dominant role. So questions as what is the meaning of risk and how it is perceived, are important in order to understand how the assessment takes place under those tools.

Risk is a complex concept which in its broad sense, refers both to the probability and the consequent impacts of the occurrence of an invent[188]. In a simpler way as Markus Schmidt refers to it "*Risk is always the risk of something (technical facility, natural hazard), to someone (an individual, a group of people, society or all humankind)".*[189] In that sense risk is not characterized solely by technical elements but also by social, cultural and psychological elements. As Paul Slovic observes: "*It does not exist 'out there,' independent of our minds and cultures, waiting to be measured. Instead, risk is seen as a concept that*

184 Paul Slovic and Elke U. Weber, 'Perception of Risk Posed by Extreme Events' 2002), 1., 2 < http://cursos.campusvirtualsp.org/pluginfile.php/7062/mod_page/content/1/modulo2/content/perception-of-risk-posed-by-extreme-events.pdf> accessed 6 June 2013

185 OECD (n 175)17

186 ibid16

187 Gary E. Marchant, Douglas J. Sylvester, Kenneth W. Abbott (n 153) 44

188 Sigve Oltedal et al., 'Explaining risk perception. An evaluation of cultural theory' 2004, 1., 11 <ftp://131.252.97.79/Transfer/ES_Pubs/ESVal/risk_perception/Cultural_theory.pdf> assessed 26 May 2013

189 Markus Schmidt, 'Investigating risk perception: a small introduction' 2004, Chapter 3 in: Schmidt M. 2004. Loss of agro-biodiversity in Vaviloy centers, with a special focus on the risk of genetically modified organisms (GMOs). PhD Thesis Vienna Austria, 3 <http://www.markusschmidt.eu/pdf/Intro_risk_perception_Schmidt.pdf> accessed 26 May 2013

human beings have invented to help them understand and cope with the dangers and uncertainties of life".[190]

The perception of risk can be affected by elements of subjectivity such as our thoughts, beliefs and culture. Oltedal observes that the what way a person perceives risk may be very different from what is considered to be "objective" risk[191]. 'Objective risk' can be considered a risk that stands independently from a person's understanding and concerns about the origins of the risk[192]. Statistics and probability distributions can be used in order to calculate the so-called 'objective risk'[193]. But a perceived risk reflects the individuals' understanding of a phenomenon. Paul Slovic notices that the term 'risk' "*means different things to different people*"[194]. Depending on how risks and benefits stand in people's perception and how they calculate the benefits from an activity, the further acceptability of the risk can be affected[195]. R.Bell et al. use the approach that "*acceptable risk represents the level of risk that society is prepared to accept without any specific risk management options*"[196].

Decisions concerning benefits and risks are taken by analyzing those concepts, according to a risk benefit analysis. For novel medicinal products and medical devices like nanomedicine, where so far no specific legislation has been put forward, we have to examine if the risk benefit analysis that is being employed in the context of market authorization for both medicinal products and medical devices, is robust enough to cope with the risks and the benefits that come along with them.

Risk benefit analysis is the comparison of the risks of a situation to its related benefits. Risk benefit analysis as Rosemarie et al. refer to it "*is a systematic use of information to identify initiating events, causes and consequences of these initiating events*

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190 Paul Slovic and Elke U. Weber (n 184) 4

191 Sigve Oltedal et al. (n 188) 11

192 ibid

193 ibid

194 Paul Slovic, 'Perception of Risk' (1987) 236 Science, 280, 283 <http://www.uns.ethz.ch/edu/teach/0.pdf> accessed 5 June 2013

195 Roger Brownsword and Morag Goodwin, *Law and the Technologies of the Twenty-First Century* (1st Cambridge University Press 2012), 117-118

196 R. Bell, T. Glade & M. Danscheid, 'Challenges in defining acceptable risk levels' [2006], Department of Geography, University of Bonn, Germany
< http://homepage.univie.ac.at/thomas.glade/Publications/BellEtAl2005a.pdf> accessed 7 June 2013

and express risk and benefit"[197]. At the first step of risk benefit analysis the identification of risks takes place, where risks and benefits involved in an activity are measured both qualitatively and quantitatively. After the identification of risks and benefits in order to take decisions their evaluation takes place[198].

The evaluation of risks and benefits is the "*Establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent, involving the complex process of determining the significance of the identified hazards and the estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent"*[199]. Once risks and benefits have been evaluated, decisions have to be made "*concerning which risks need treatment and which do not*"[200]. So the evaluation of the risks is the determination of their acceptability. While the first step of risk benefit analysis, in order to assess the risks uses scientific facts and methods and it is free from values, the second step, which is the evaluation of the risks and benefits in order to take decisions, is not value-free as it is influenced by normative values, public perception and acceptability of the risk.

The public perception and the acceptability of the risk influence the analysis. Brownsword and Goodwin observe that terms as 'low risk', 'high risk' and safe are used in describing the effect of a technology when we perform an assessment[201]. When trying to connect a term with a certain technology we have to be very careful as so far, there is a distinction between what lay people and experts perceive as a risk further influencing its acceptability. The interplay between risk assessment and the public acceptability of the risks is significant. But there is a difference between how lay people and experts perceive risk. An example used by Brownsword and Goodwin to describe this situation is that nuclear technology in lay people's perception seems of a high risk, whereas among expert-cycles it is perceived as low risk, meaning that high damage potential is combined with low probability

197 Rosemarie D L C Bernade et al., 'The risk-benefit task of research ethics committees: An evaluation of current approaches and the need to incorporate decision studies methods.' (2012) 13 BMC Medical Ethics 6, 4 < http://www.biomedcentral.com/content/pdf/1472-6939-13-6.pdf> accessed 7 June 2013
198 ibid
199 OECD (n 175) 17
200 ENISA (n 178)
201 Roge Brownsword and Morag Goodwin (n 195) 116-117

of occurrence[202]. Whether the risk is considered as low or high, its acceptability depends on how the benefits are estimated.

They further observe that how risks are perceived is reflected in the fact that the lower the evaluation of the risk the higher the possibility to accept it and vice versa[203]. With regard to this, the gap between peoples' and scientists' perception of the risk that surrounds new technologies is supplemented by the factors of what is risk and uncertainty. No commonly accepted definition of the term exists either in science or public perception. Usually the term is associated with undesirable adverse effects that can occur as a result of an activity. It is both a normative and a descriptive concept[204]. As David Garland puts it:

"*Today's accounts of risk are remarkable for their multiplicity and for the variety they give to them. Risk is a calculation. Risk is a commodity. Risk is a capital. Risk is a technique of government. Risk is objective and scientifically knowable. Risk is a subjective and socially constructed. Risk is a problem, a threat, a source of insecurity. Risk is a pleasure, a thrill, a source of profit and freedom. Risk is the means whereby we colonize and control the future. 'Risk society is our late modern world spinning out of control*".[205]

This quote used from David Garland to describe the term risk, reflects the fact that risk as a concept can have various meanings and it is used in various ways across different disciplines. It shows its multidimensional character, its randomness as a term, the fact that is does have a coherent meaning and as a result it can mean different things to different people.

But characterizing risks, trying to evaluate them and finding ways to reduce them is challenging especially in the case of nanomedicine where the risks are still emerging. How can someone be aware of the risks when this technology is still in its infancy? The uncertainty that surrounds nanomedicine, the tendency of the public to formulate premature

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202 ibid 116-117

203 ibid 117-118

204 Bronwen Morgan & Karen Yeung, *An Introduction to Law and Regulation. Text and Materials* (1st Cambridge University Press 2007), 13

205 Linda F. Holge, 'Concepts of Risk in Nanomedicine Research' (2012) 40 The Journal of Law, medicine & ethics: a journal of the American Society of Law, Medicine & Ethics 809, 811 <http://lawvalue.umn.edu/prod/groups/ahc/@pub/@ahc/@consortlv/documents/article/ahc_article_426293.pdf> accessed 7 June 2013

opinions about the risks and the benefits and the existing knowledge gap, make it possible to jeopardize the further development of novel technologies.

Under this perspective it is crucial that risk benefit analysis can take into consideration all these factors and complexities associated with the risks and benefits. However, the separation of scientific data form values and the difficulty to adjust to complex and multi-factored situations, makes it challenging for risk benefit analysis as a regulatory tool to manage scientific uncertainty, knowledge gaps and gathered data.

In nascent technologies as nanomedicine the management of uncertainties is no longer the task for only one scientific field, as this technology includes the convergence of various disciplines and expertise. As mentioned above, the current model of risk benefit analysis holds a distinction between the risk assessment, which relies on scientific data to assess the risks and benefits, and risk evaluation, which in order to determine the acceptability of the risks, relies on perceptions about risks associated to a technology or a product.

As nanomedicine is only at an early stage of development, Marchant et al. consider that the current level of knowledge of risks and benefits is too uncertain, in order to be able to interpret them by using risk benefit analysis[206]. In addition in risk benefit analysis, risks and benefits are estimated both quantitatively and qualitatively. Despite the fact that some studies have shown potential toxicity of novel materials due to their special characteristics such as surface area, solubility etc, it is still not clear whether a specific toxicological estimation is required[207]. Some studies in animals show possible toxicity of nanomaterials, but involve high exposure doses that do not permit human risk assessment[208].

According to them given that the toxicity of nanomaterials can be affected by the set of characteristics they appear to have, the extrapolation of data regarding their toxicity has to be done on a case-by-case basis[209]. However at present accepted test methods have not yet been developed that can produce reliable data that can be used in quantitative assessments of the risk of nanomedicine.[210].

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206 Gary Marchant Douglas J. Sylvester and Kenneth W. Abbott (n 153) 44
207 J Janhel, T Fleischer and S B Seitz (n 177) 3
208 Gary E. Marchant, Douglas J. Sylvester and Kenneth W. Abbott (n 153) 44
209 ibid
210 ibid

Another factor the can further matter is that the development of risk assessment cannot keep up with the rapid development of this technology. Furthermore the scientific uncertainty that surrounds nanomedicine due to the fact that it is still under development, the data that still emerge and the knowledge gap between risks and benefits, make its applicability a challenging task, as risk benefit analysis in the phase of risk assessment relies on scientific data.

In addition this knowledge gap between risks and benefits of this technology and the available data, can also affect the public acceptability of the technology. As already mentioned, in the phase of risk evaluation the public acceptability of the risks is an important factor. But the lack of adequate public awareness about the risks and the benefits of this nascent technology may lead to lower acceptability from the public, which consequently will affect the further development of the technology.

Apart from the fact that the there is lack of data to conduct the risk benefit analysis, the distinction that the classical model holds between scientific data and values is not helpful to overcome the uncertainties that derive from novel technologies. In novel sciences where the research depends on multiple factors and variables, the results have to be based both on qualitative and quantitative risk analysis. So a risk analysis that does not only aim to assess the magnitude of risk but can also take into consideration the types of risks could better comprehend the risks associated with novel technologies.

The mere reliance on scientific data during risk assessment cannot during risk management respond to questions such as: Which factors are likely to produce adverse effects? What is the dose of administration relationship? What is the level under which a substance will likely pose harm to human health? What is the relationship between the different variables present in a research? Questions like these cannot yet be answered during the risk assessment phase. Limitations that may affect the risk benefit analysis as Conrad G. Brunk observes are that "[…] *in the context of risk estimation scientific data do not interpret themselves; to determine what the data indicate concerning the risks of a product, the assessor has no alternative but to employ an interpretive point of view"*[211].

[211] Gornad G. Brunk, Lawrence Haworth and Breda Lee, *Values Assumptions in Risk Assessment: A case study of the Alachlor Controversy,* (1st Wilfried Laurier University Press 1991 Waterloo Canada), 26 <

This of course is to say that science is not important in order to make estimations concerning the available data but in emerging technologies as nanotechnology, the dimensions of not much available data, the constantly changing data and the rapid development of the technology have to be taken into consideration as well. But risk benefit analysis in the phase of risk assessment, relies on existing scientific data and does not take into consideration the case that the risks are still unknown and have to be further investigated. As a result the risk benefit analysis won't be able to give reliable answers about the risks and benefits of a medicinal product or a medical device as the risks cannot be investigated in their full dimensions. In addition if risk assessment does not come up with reliable results about risks and benefits, this will further affect risk evaluation that is the second stage of risk benefit analysis. Risk evaluation grounds its judgments on the assessment of risks. In addition as European Commission notices, the public in modern societies wants to be informed about the risks and benefits of new emerging technologies[212]. The failure of adequate public awareness of risks and benefits of new technologies in combination with the fact that risk evaluation is affected by the perceptions of risk will contribute to the lower acceptability of the technology.

This of course does not mean that risk assessment frameworks are not necessary in estimating the risk and benefits arising from nanotechnology applications[213]. The concept of risk that these technologies introduce is dynamic and should be taken into consideration as a variable of the research and not as an outcome. In order to understand how variables of risk can affect the result of research we have to look at an example. Some carbon nanotube studies by Warheit et al. that were conducted on mice and rat highlighted the relationship

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http://books.google.nl/books?id=QdZ4paHKtdIC&pg=PR2&lpg=PR2&dq=Conrad+G.+Brunk,+Lawrence+Haworth+and+Brenda+Lee+%E2%80%9CValues+Assumptions+in+Risk-Assessment:+a+case+study+in+alachlor+controversy,%E2%80%9D&source=bl&ots=8f4JrUCVo-&sig=how-rbNMyoPqW7E7hsYUScGAbDs&hl=en&sa=X&ei=Ui6UUbbYOaKN0AWVs4HADg&ved=0CGAQ6AEwCA#v=onepage&q=Conrad%20G.%20Brunk%2C%20Lawrence%20Haworth%20and%20Brenda%20Lee%20%E2%80%9CValues%20Assumptions%20in%20Risk-Assessment%3A%20a%20case%20study%20in%20alachlor%20controversy%2C%E2%80%9D&f=false> accessed 7 June 2013

[212] European Commission, 'First Report on the Harmonisation of Risk Assessment Procedures' 2000, 1., 130 <http://www.bfr.bund.de/cm/343/first_report_on_the_harmonisation_of_risk_assessment_procedures.pdf> accessed 7 June 2013

[213] Gary E. Marchant, Douglas J. Sylvester and Kenneth W. Abbott (n 153) 45

between dose exposure and occurrence of harm[214]. Depending on the higher or lower dose administration the harm occurrence varied[215].

The interpretation of this is that the higher dose of a chemical can cause harm, where a lower dose of the same chemical cannot be harmful. In the framework of risk benefit analysis this means that the adverse effects of a product are not uniform and can be affected by measures such as dose. Also the risks should be related to real situations and cannot be perceived risks. In addition in nanomedicine the assessment of risks should not only be an evaluation of the adverse effects of the final product but it should also be an evaluation of the process through which the product was examined since not only the product itself but other factors such as dose/exposure might result in adverse effects.

What has emerged from the above is that : i) the current level o knowledge of risks and benefits in nanomedicine is too uncertain in order to be able to interpret them by using risk benefit analysis ii) the knowledge gap as the data are still emerging will affect both risk assessment and risk evaluation iii) the assessment and management of risks in nanomedicine is not a task of only one scientific field iv) even in the same sub-category of nanoparticles the adverse effects may differ because they are affected by measures such as dose v) the study of risk should be related to real situations and not only perceived risks vi) the assessment and management of risks should include both the adverse effects of the final product as well as the process through which the product was examined vii) the risk that these technologies introduce is not static but rather a dynamic concept.

The classical model of risk benefit analysis, at the current stage of knowledge of risks and benefit in nanomedicine, lacks the scientific information in order to come to reliable conclusions. In addition, it cannot collate how not simply the risk but the levels of risk can affect the occurrence of a harmful event. It fails to capture that the risk that these novel technologies introduce is dynamic and even the same sub-category of nanoparticles may present different levels of risk. Conversely, a risk benefit analysis that takes into consideration both qualitatively and quantitatively all the subsets of risk and also includes variables like dose/exposure could be more responsive. Finally a risk benefit analysis that

[214] D B Warheit et al., 'Comparative Pulmonary Toxicity Assessment on Single-wall-Carbon Nanotubes in Rats.' (2004) 77 Toxicological Sciences: an official journal of the Society of Toxicology,117., <http://toxsci.oxfordjournals.org/content/77/1/117.full.pdf> accessed 7 June 2013

[215] ibid 119

includes also in the assessment normative values that can give reliable answers to questions such as under which level a substance will be harmful or how the risk variables affect the research could give more reliable answers.

3.2 Is Precaution an alternative to Uncertain Science?

The precautionary principle as Fisher et al refer to it, is a principle of public decision making[216] that is used in a variety of disciplines in order to manage scientific uncertainties that come with novel technologies as for example genetically modifies organisms (GMOs), nanotechnology etc. Nanotechnologies create a new kind of risk and hazards that challenge the qualitative and quantitative estimation, as they depend on variables. As these new technologies pose new challenges, the precautionary principle has emerged as an alternative tool to manage risks[217]. A short phrase that can reflect this is that it is 'better safe than sorry'[218]. As nanotechnology is surrounded by uncertainty it can be a very good candidate for the application of the precautionary principle. In order to understand how this principle can function in the context of nanotechnology it is important to understand its origins and its various interpretations.

3.2.1 The origins and various interpretations of the Precautionary Principle

A broad term that can be used to describe the underlying notion of the precautionary principle is that 'prevention is better than cure'[219]. The Precautionary Principle is a decision making tool that is used to manage scientific uncertainties that new technologies can pose. The first elements of precaution have their roots in the US and British environmental law back in 1970s. At the European level, German environmental law was amongst the first legislative initiatives that introduced the principle.[220]

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216 Elizabeth Fisher, Judith Jones and Rene von Schomberg, *Implementing the Precautionary Principle: Perspectives and Prospects* (Edward Elgar, 2006), 3

217 Gary E. Marchant, Douglas J. Sylvester and Kenneth W. Abbott (n 153) 45

218 ibid

219 Sue Mayer and Andy Stirling, 'Finding a Precautionary Approach to Technological Developments – Lessons for the Evaluation of GM Crops' (2002) 15 Journal of Agricultural and Environmental Ethics, 57., 60 < http://link.springer.com/article/10.1023/A%3A1013866125341> assessed 15 May 2013

220 Hans Somsen, *The Regulatory Challenge of Biotechnology Human Genetics, Food and Patents* (1st Edward Elgar UK 2007), 120

The first appearance in the international arena was in the 1970s at the North Sea Ministerial conferences on marine pollution. The Ministerial Declaration of the Second International Conference on the Protection of the North Sea provided an approach towards that principle:

"*in order to protect the North Sea from possibly damaging effects of the most dangerous substances, a precautionary approach is necessary which may require action to control inputs of such substances even before a causal link has been established by absolutely clear scientific evidence*".

After its appearance in documents like the above it started gradually to be included in both national and international documents. The primary foundation of the principle can be considered the Rio Declaration on Environment and Development (1992), where the principle was recognized and incorporated within the text of the Rio Declaration in Principle 15 as:

"*In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*"[221].

Besides the Rio Declaration, it was also incorporated in the Convention on Biological Diversity (CBD 1992) and Convention on Climate Change (Article 3, 1992). Other agreements in which the principle was given "functional effect" are the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (1998), the Stockholm Convention on Persistent Organic Pollutants (2001) and the Cartagena Protocol on Biosafety (2001)[222].

In the European Union the principle is detailed in Article 191(ex art 174) of the Treaty on the Functioning of the European Union. In paragraph 2 of the artile it was noted

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221 Rio Declaration on Environment and Development, Principle 15 <http://www.un.org/cyberschoolbus/peace/earthsummit.htm > accessed 11 May 2013

222 Rosie Cooney, *The Precautionary Principle in Biodiversity Conversation and Natural Resource Management: An issues paper for policy-makers, researchers and practitioners* (1st IUCN, Gland, Switzerland and Cambridge, UK. xi + 55pp 2004), 12

that the environmental policy should "*be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay"*. The Communication of the European Commission on the Precautionary Principle (COM 2000) aimed at establishing a general understanding of the principle and providing guidance on its consistent application[223]. According to the Communication the application of the Precautionary Principle must be coherent and cannot be used to discriminate against a new technology. More specifically the summary states that:

"[…]*where preliminary objective scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community"*[224].

However when scholars refer to the term there is no agreement on its meaning. According to the Swedish Philosopher Per Sandin, nineteen formulations of the Precautionary Principle exist and the differentiations are observed around four variables that he defined as threat, uncertainty, action and command[225]. For example with regard to the threat, this means that the different versions of the precautionary principle differ in the level of threat, which is necessary in order for the principle to be triggered. So some versions may require 'serious threats' in order to apply, where some others may refer to 'possible risks'. As far as action is concerned the different versions of the principle require different action, when there possible threat is detected, action that may vary from banning an activity to take measures to ensure safety.

Despite the lack of a commonly accepted definition there are some key elements of the principle on which the scholars seem to reach a level of agreement: i) the uncertainty cannot be used as a pretext to delay action; ii) the burden of proof might be reversed, from 'recipients' to prove than an agent or technology is harmful to 'proponents', to prove that it is

223 Roger Brownsword and Morag Goodwin (n 195)143

224 European Commission, 'Communication from the Commission on the precautionary principle' (COM2000), p. 3 <http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf >assessed 12 May 2013

225 Per Sandin, 'Dimensions of the Precautionary Principle,' (1999) 5 Human and Ecology Risk Assessment, 889 <quoted form the book Gary E. Marchant and Kenneth L. Moosman, *Arbitrary and capricious:the precautionary principle in the European Union Courts* (1st edn International Policy Press 2005),10>

innocuous; iii) it is important to take into consideration different factors to prevent harm, at an early stage and iv) the decision making process should be transparent and democratic as much as possible[226]. As Neil Manson has suggested all the various versions of the principle specify a condition of 'damage', a condition of 'knowledge' and a condition of 'remedy', each of which can be specified in many different ways[227].

Another factor that can further complicate the application of the principle as Marchant et al. notices, is the fact that it is not clear in which cases the principle does not apply[228]. In addition, to the formulations of the Precautionary Principle, there have been identified three versions of the Principle according to which the principle is characterized as strong, moderate and weak. The version of the Precautionary Principle that was formulated and finalized in the International Conference of Wingspread in 1998 and which is known as the Wingspread Declaration reflects the strong version where it is stated that:

"*When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof*"[229].

As Cass R. Sustein observes, the strong version of the Precautionary Principle, can demonstrate that when an activity can pose a threat or cause harm to human health or to the environment, even if the sources of threat cannot absolutely be established, regulatory measures should be taken to protect human health and the environment. It is up to the actor who supports the activity to prove the non-harmful effect of the activity[230]. A more extreme formulation of the principle could potentially lead to the ban or prohibition of potentially

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226 Marco Martuzzi and Roberto Bertollini, 'The Precautionary Principle, Science and Human Health Protection' (2004) 17 International Journal of occupational Medicine and environmental Health 43, 44 < http://www.imp.lodz.pl/upload/oficyna/artykuly/pdf/full/Mar5-01-04.pdf> accessed 12 May 2013

227 Neil Manson, 'Formulating the Precautionary Principle' (2008) 24 Environmental Ethics 263, <http://home.olemiss.edu/~namanson/Formulating%20the%20PP.pdf> accessed 12 May 2013

228 Gary E. Marchant and Kenneth L. Moosman '*Arbitrary and Carpicious*' (1st edn International Policy Press 2005),12

229 'Wingspread Conference on the Precautionary Principle' (1998) 'The Science and the Environmental Network' < http://www.sehn.org/wing.html> assessed 12 May 2013

230 Cass R. Sustein, 'Beyond the Precautionary Principle' (2003) 149 University of Pennsylvania Law Review 1003,1012-1013 < http://sciencepolicy.colorado.edu/students/envs_5000/sunstein_2003.pdf> accessed 12 May 2013

harmful activities or products[231]. On the other side, the weak version is reflected in the Rio Declaration where the principle 15 states:

"*In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*"[232].

The weak version of the Precautionary Principle can be summarized as follows. In case there is lack of scientific data about the potential occurrence of harm, this cannot be considered as a reason that can justify regulatory inaction. So precautionary measures can be justified even if the connection between the harms and the effects to human health, hold a low possibility of occurrence[233].

At a moderate formulation the presence of an uncertain threat can become the basis for action once it has been established that a threat exists according to Peterson[234]. The moderate formulation of the Precautionary Principle may not be very different form the weak version, because the precautionary measures may reflect a 'wait and see' approach. A 'wait and see' approach means that an issue should be reviewed when improved information become available and the policies which will be adopted should be flexible in order to adjust to the new information[235].

So far the Precautionary Principle has been the subject of a lot of debate not only at a European Union level but also internationally. Marchant and Sylvester underline that the questions that arise do not only consider the nature of the principle and its elements but the level of the potential risk, the scientific evaluation of the potential adverse effects, the level of hazard that should enact precautionary measures, the quantity of data that can be considered enough to demonstrate that a product or an activity is safe to proceed further and the nature of

231 Deborah C. Peterson, 'Precaution: principles and practice in Australian environmental and natural resource management' (2006) 50 Australian Journal of Agricultural and Resource Economics 469, 473 < http://ageconsearch.umn.edu/bitstream/116985/2/j.1467-8489.2006.00372.x.pdf> accessed 12 May 20113

232 Rio Declaration (n 221) Principle 15

233 Cass R. Sustein (n 230) 1011-1012

234 Deborah C. Peterson (n 231) 473

235 ibid 473-474

action that should be taken to satisfy the principle as well[236]. In an emerging field as nanotechnology and especially nanomedicine where, the potential risks and benefits cannot yet be fully demonstrated, we should examine how the precautionary principle can be applied.

3.2.2 The Precautionary Principle in the context of Nanotechnolgy

Nanotechnology as it is still an emerging field is surrounded by a lot of uncertainty. Also it is a very good example that reflects the regulatory challenges when new technologies are discovered. Novel sciences as nanotechnology, trigger regulators because they have to choose how they will approach those new technologies, what actions they should take and what should be prioritized when they take regulatory action towards a field that is characterized by uncertainty. These uncertainties are intensified by the fact that nanotechnology is not a uniform field of science but it is an "umbrella" that includes other fields of sciences[237]. Given its multidisciplinary character and the uncertainties that accompany this technology, these questions have been subject to debate on how to proceed further at the early stages of the technology.

As R. Brownsword notices, decision-makers are troubled by how to proceed further as they have to balance the rights of individuals and industry with the need to take measures to protect human health and the environment[238]. The debate on how to proceed further with nanotechnology has attracted the attention of many scholars, interest groups and governmental agencies, as Marchant and Sylvester highlighted[239].

But so far there has been no coherent interpretation of the precautionary principle and which should be its role in governance so that in broader terms, we can set the debate on nanomedicine around two spectrums. On the one side there are supporters of a more cautious

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[236] Gary E. Marchant and Douglas J. Sylvester, 'Transnational Models for Regulation of Nanotechnology' [2006] The Journal of Law, Medicine & Ethics, 714, 721<http://papers.ssrn.com/sol3/papers.cfm?abstract_id=907161> accessed 7 June 2013 and Roger Brownsword and Morag Goodwin (n 195) 142-146

[237] Douglas K. R. Robinson, Martin Ruivenkamp, Arie Rip, 'Tracking the evolution of new and emerging S&T via statement-linkages: Vision assessment in molecular machines' (2007) 70 Scientometrics, 831, <http://link.springer.com/content/pdf/10.1007%2Fs11192-007-0314-2.pdf> accessed 8 June 2013

[238] Roger Brownsword and Morag Goodwin (n 195) 142

[239] Gary E. Marchant, Douglas J. Sylvester and Kenneth W. Abbott (n 153) 45

approach to new technologies that are surrounded by uncertainty, and on the other hand there are those who perceive the precautionary principle as having a "**technology-freezing effect**"[240].

Scholars as Sir Soren Holms and John Harris referred to the precautionary principle as a "**technology-freezing effect**"[241], where Marchant underlines that the consistent application of the principle might prevent the development of any technology. Moreover Sustein supports that the[242], "*precautionary principle leads to wrong directions, but if it is taken for all that it is worth, it leads to no direction at all*". According to their view, the application of the principle can have negative implications on the development of novel technologies since the regulators can have the power to influence the acceptability of new technologies.

In opposition to these approaches that perceive the adoption of the Precautionary Principle as having a negative impact on new technologies, there are advocates of the principle that argue that the adoption of the principle can prove effective in dealing with the uncertainties that come along with new technologies as nanotechnology. According to Stirling the adoption of the precautionary principle does not mean a ban but instead in case of uncertainty **it can** prove a good way to protect human health and the environment[243]. He continues:

"[…]precaution does not automatically entail bans and phase-outs, but instead it calls for deliberative and comprehensive attention to contending policy or technology pathways. Far from being in tension with science, precaution offers a way to be more measured and rational about uncertainty, ambiguity and ignorance"[244].

In addition Heselhaus, argues that the precautionary principle is an instrument that can be used in order to protect human health and plays and important role in the consumer

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240 Gary E. Marchant and Douglas J. Sylvester (n 236) 721 <quoted by S. Holm and J. Harris, Letter, 'Precautionary Principle Stifles Discovery' (1999) 400 Nature, 398.>

241 ibid

242 Cass R. Sustein (n 230) 1012-1013

243 Andrew Stirling, ' Risk, precaution and science: towards a more constructive policy debate' (2007) 8 European Molecular Biology Organization (EMBO) reports, 309., 312 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1852772/> assessed 28 May 2013

244 ibid 314

protection law[245]. Moreover in Renn's view the precautionary principle can be an answer to uncertainty: "*in my view the main purpose of precaution is to avoid irreversible decisions*"[246] *and "it's a prudent and sound choice in the face of uncertainty"*[247].

Taking into consideration the enormous challenges that nanotechnology generates some scholars argue that neither traditional risk management tools nor the precautionary principle can be used in the context of nanomedicine. More specifically, Marchant et al. in their paper 'Risk Management Principles for Nanotechnology' criticize the application of the precautionary principle in the context of Nanotechnology and find many deficits[248]. According to their view, amongst the problems with the application of the precautionary Principle as a tool to manage uncertainties is the fact that there is not a consistent interpretation of the principle[249]. They continue by saying that:

" […]no version of the precautionary principle answers the critical questions that need to be considered in moving forward with regulatory decisions, such as what level or type of evidence (if any) of harm is sufficient to trigger the principle, what level of risk is acceptable, and how should the benefits of a technology be weighted against its risks[…]"[250].

Nevertheless they recognize that: "*yet simply waiting for these uncertainties to be solved before undertaking risk management efforts would not be prudent, in part because of the growing public concerns about nanotechnology driven by risk-perception heuristics such as effect and availability. A more reflexive, incremental and cooperative risk management approach is required, which not only will help manage emerging risks from nanotechnology applications, but will also create a new risk management model for managing future emerging technologies"*[251].

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245 Sebastian Heselhaus, 'Nanomaterials and the Precautionary Principle in the EU' (2010) 33 Journal of Consumer Policy, 91., < http://link.springer.com/10.1007/s10603-009-9123-8> accessed 6 June 2013

246 Ortwin Renn, 'Precaution and analysis: two sides of the same coin? Introduction to Talking Point on the precautionary principle' (2007) 8 European Molecular Biology Organization (EMBO) reports, 303., < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1852770/pdf/7400950.pdf> accessed 28 May 2013

247 Ortwin Renn and Andrew Stirling, 'The Precautionary Principle: A new paradigm for Risk Management and Participation' [2004] Institut du développement durable et des relations internationals, 3 <http://www.iddri.org/Publications/Collections/Idees-pour-le-debat/id_0403_renn&stirling.pdf > accessed 29 May 2013

248 Gary E. Marchant, Douglas J. Sylvester, Kenneth W. Abbott (n 153) 43-60

249 ibid 46

250 ibid

251 ibid 43

The above shows that there is an ongoing debate around how to regulate nanomedicine and which strategy we should adopt. On the one side, the adoption of a very strict model of regulation in the early stages of the technology with the aim to prevent harm can further impede the development of the technology. On the other side with the uncertainty that surrounds nanomedicine, trying to fit it in the current regime is not without its problems. Nevertheless we should not forget that the way in which regulators seek to manage uncertainties of new technologies could influence their acceptability and vice versa.

In addition some examples that come from the past could illuminate this interplay between the regulatory choices and public acceptance of a technology. An illustrative example is the case of Genetically Modified Organisms (GMOs) that is used as a parallelism by some scholars for the following reasons. As Ronald Sandler has pointed out, the parallelism between GMOs and Nanotechnology is popular because "*the GMO experience is recent and provides familiar framework for scientists and researchers and the media when dealing with nanotechnology; at present there is a knowledge gap regarding nanotechnology as there was with GMOs; nanotechnology poses the same type of political and social challenges as GMOs and finally many people have some of the same concerns about nanotechnology as those expressed about GMOs*"[252].

The appearance of GMOs in Europe raised concerns not only for the public but also for governmental institutions and non-governmental organizations[253]. As Brownsword and Goodwin identified, the concerns that were raised were about the inherent risk that GMOs had with possible negative impact on human health and the environment, the unacceptability of the risk in the sense that the potential benefit will not recoup for the damages and also some moral concerns as well[254]. All these expressed concerns about this new technology resulted in the adoption of the Precautionary principle in the context of regulation of GMOs.

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252 Ronald Sandler and W. D. Kay, 'The GMO-Nanotech (Dis)Analogy?' (2006) 26 Bulletin of Science, Technology & Society, 57., 58 < http://umassk12.net/nano/2008summer/Gibson/GMO.pdf> accessed 7 June 2013

253 Alan Raybould, and Guy M. Poppy, 'Commercializing genetically modified crops under EU regulations: Objectives and barriers' (2012) 3 GM Crops and Food: Biotechnology in Agriculture and the Food Chain 9, < http://www.landesbioscience.com/journals/gmcrops/article/18961/2011GMC0040R.pdf > accessed 27 May 2013 <quoted by Tait J. 'More Faust than Franksestain: the European debate about the precautionary principle and risk regulation for genetically modified crops' 2001 4 Journal Risk Res, 175-89> <http://www.landesbioscience.com/journals/36/article/18961/>

254 Roger Brownsword and Morag Goodwin (n 195) 128

The experience of GMOs allows us to argue that in the early stages of a new technology it is important to take regulatory action, which will not impede innovation but will also secure safety. So far in the field of nanomedicine which is in its early stages, neither a specific regulatory regime exists nor a new risk management model. Until the proposed reformulation of the regulatory regime takes place and how the proposed amendments will be implemented is decided, it is important to provide some guidance through other regulatory tools in order to ensure the safe use of the technology.

Ultimately the view of this thesis advocates Stirling's[255] view that regulation in case of new emerging technologies does not mean a ban but instead it should provide at its early stages, through the use of other regulatory tools guidance for its safe use and its further development.

3.3 Conclusive Considerations

Having identified the limits of the existing regulatory regime if we directly apply it to nanotechnologies, in this chapter we examined some specific tools that have been introduced to govern emerging sciences and technologies whose effects are surrounded by uncertainty and their risks are still emerging. More specific risk benefit analysis and the Precautionary Principle have been examined in order to see if they can successfully manage the risks that these new technologies introduce.

Nanomedicine at the present state of knowledge presents unprecedented challenges by its nature, complexity and unpredictability of the risk and they are at an early stage of development. Risk benefit analysis as a tool to manage risks, is a two-stage procedure that holds a net distinction between scientific data and values. In case of nanomedicine a variety of factors challenge the reliability of risk benefit analysis as a tool to manage risks. More specifically, factors such as the data that still emerge, the knowledge gap between risks and benefits, the fact that the assessment and management of risks is not a task of only one scientific field and the net distinction between scientific data and values that this tool holds, make the applicability of risk benefit analysis in the case of nanomedicine a difficult task.

[255] Andrew Stirling (n 243) 312

Risk benefit analysis fails to capture how the risk that this new technology introduces is dynamic and can be affected by factors such as dose/volume exposure.

The fact that the current model of risk benefit analysis has many deficiencies in managing the risks of nanomedicine applications does not automatically mean that we should adopt measures that will ban the development of this nascent technology. Conversely, what has been argued in this Chapter is that a more robust model of risk benefit analysis that would capture the risk in its all dimensions and variables could give more reliable answers.

The limitations that have been identified in the risk benefit analysis as a tool to assess and manage the risks that these new technologies introduce, lead us to examine the Precautionary Principle if it could be an answer to uncertainty that surrounds nanomedicine. What has emerged is that the Precautionary Principle is not a coherent concept, it has many formulations and it has been subject to a lot of debate. Nevertheless the experiences of the past (GMOs) allowed us to argue that in case of emergent technologies some regulatory action should be taken that will aim to the protection of human health but will not impede the further development of the technology.

It follows that the regulatory choices that will be made in the early stages of any new technology can further impact on its development. Regulation can either be very strict and consequently prohibit its development or provide some guidance through the use of other regulatory tools such as the code, guidelines and communication that can absorb those concerns, inform the public and promote the safe use of the technology.

Therefore in the early stages of nascent technologies where uncertainty prevails, some precautionary measures should be taken that together with the use of other tools will provide guidance and ensure safety without impeding the further development of the technology. Accordingly to this perspective adopting such and approach towards the regulation of this new technology is not in conflict with its further development. To what extent these tools will help towards that direction will be examined in the following section.

Chapter 4: The role and scope of guidelines, codes of conduct and communication tools in the context of Nanomedicine

Introduction

From the analysis that was conducted in the preceding Chapters, what has emerged is that the current European regulatory regime that is applicable to medicinal products and medical devices it is expected to be applied to nanomedicine too. This system in order to estimate risks and benefits that medicinal products and medical devices incorporate, has established a risk benefit analysis through which is trying to measure the risks and benefits and further manage them. But the current state of knowledge about the risks of nanomedicine, the lack of data and their unknown effects make the applicability of risk benefit analysis problematic and generate concerns.

From the examination of the current legislation and the tools that uses to measure and manage risks, has emerged that nanomedicine applications create challenges that require a more responsive action. The current normative system is not adequately equipped to manage all those risks and effectively assess the safety of nanomedicine in the pre-market approval stage.

Regulation in case of nanotechnology is necessary because if we leave it unregulated it is possible that some nanomaterials will cause health risks and probably raise concerns. At the European level some initiatives have recently been put forward in order to address the issue of nanomedicine. Until these initiatives become final a minimum level of safety and controlling of risks should be established. In the absence of a coherent regime and as more nanoproducts are entering the market, legislators, researchers and manufactures should know how to proceed further and what is the relevant regulatory framework when dealing with a the specific product or device. Also the public should be informed about the products and the

devices that will use in order to be able to make informed choices and not raise concerns due to the lack of knowledge.

So, in the absence of regulatory provisions that directly refer to them, some other innovative approaches could be used in order ensure a minimum level of safety and promote the further development of the technology. In this situation and given the obstacles to traditional regulation as was described in the previous chapters, this chapter will examine some other regulatory mechanisms. In this chapter we will highlight the role and scope of guidelines, codes of conducts and communication tools in the context of nanotechnology and how at the current state of knowledge, they can be engaged in order to help the safe development of the technology and protect human health.

4.1 The role and scope of Guidelines in the context of Nanomedicine

The European pharmaceutical legislative framework is supported by guidelines. European Medical Agency defines guidelines within the pharmaceutical legislation as '*A guideline is a Community document with explicit legal basis referred to in the legislative framework as intended to fulfill a legal obligation laid down in the Community pharmaceutical legislation. It provides advice to applicants or marketing authorization holders, competent authorities, and/or other interested parties on the best or most appropriate way to fulfill an obligation laid down in the community pharmaceutical legislation*'[256].

However guidelines are not legally binding but are considered as 'soft-law'[257] and can have quasi-binding character which as EMA observes "*can derive from the legal basis when the guideline intends to specify how to fulfill a legal obligation*"[258]. The uncertainty of the

256 European Medical Agency (EMA), 'Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework' (2009), 4 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf> accessed 30 May 2013

257 " 'Soft-law' usually refers to legal tools working on the basis of voluntary compliance and not supported by legally institutionalized sanctions" Elena Pariotti, 'LAW, UNCERTAINTY AND EMERGING TECHNOLOGIES Towards a Constructive Implementation of the Precautionary Principle in the Case of Nanotechnologies' (2010) 62 Persona y Derrecho 15, 24 <http://dspace.unav.es/dspace/bitstream/10171/27644/1/LAW,%20UNCERTAINTY%20AND%20EMERGING%20TECHNOLOGIES.pdf> accessed 31 May 2013

258 EMA (2009) (n 256) 4

level of risk that surrounds nanomedicine makes it difficult to identify and categorize the risk under the classification system of risk that has been made under the European regulatory framework. In addition novel nanomedicine applications challenge the boundaries between the medicinal products and medical devices. An illustrative example that reflects this challenge as described in the previous Chapters is the targeted drug delivery systems. As the existing legal framework for medicinal products and medical devices is expected to be applied to nanomedicine and more products are being marketed, it is important for legislators, manufactures and producers to know which legislative framework will be applicable in each case.

So far there is neither a separate regulatory regime for nanomedicine nor provisions in the existing regime that cover nanomedicine. Under this perspective, guidelines are needed. Detailed guidelines at the current stage will clarify the legal requirements and criteria and will help to the classification of cases that are considered as borderline products. So far in European level different types of pharmaceutical guidelines exist as regulatory guidelines, scientific guidelines, good manufacturing practice guidelines etc[259]. With regard to borderline products that contain characteristics both from medicinal products and medical devices, the European Commission has provided some guidelines. More specifically, the MEDDEV 2.1/3rev.3[260] aims to clarify the requirements under which a product that combines both characteristics will fall either under the Directive of Medicinal Products or the Directive of Medical Devices.

In addition the recent MEDDEV 2.14/1 revision 2[261] on Medical Devices and In Vitro Diagnostic Medical Devices, aims to clarify the requirements under which a medical device that combines characteristics will fall under the Directive of Medical Devices or the Directive of In Vitro Diagnostic Medical Devices and also provides some guidance on classification issues. But these guidelines do not contain any reference about medicinal products or devices that contain nanomaterials.

Despite the fact that they are not legally binding their contribution as guiding documents that provide further information about borderline issues is valuable. But the

[259] ibid
[260] MEDDEV 2.1/3rev. 3 (n 129)
[261] MEDDEV 2.14/1 revision 2 (n 77)

existing guidelines do not contain any reference about medicinal products and devices that contain nanomaterials. So the development of guidelines that would refer to them could help overcome some difficulties. More specifically, guidelines could contribute in understanding the dynamics of nanomedicine applications. As combined products create an issue on which legislation and further which regulatory authority is competent to regulate these products, guidelines can provide some clarity on those issues. In addition they could be implemented in order to clarify the evaluation criteria on whether a chemical substance in the nanoform should be considered separate or the same with the substance in bulk form. At the current stage of development of nanomedicine and with the lack of legally binding rules that explicitly refer to them, guidelines as a source of information will help solving classification issues and create a climate of certainty on how to deal with the challenges that nanomedicine pose. The adoption of flexible guidelines as a source of information that will provide clarity on challenging nanotechnology applications in combination with a mechanism that could whenever necessary intervene and provide further interpretation on complex issues could be at present a sound regulatory approach.

4.2 The role and scope of Code of Conduct in the context of Nanomedicine

As described by Hodge et al. "*Codes of Conduct are instruments used in order to gather and communicate a set of rules outlining the responsibilities of proper practices for an individual or organization where no mandatory rules are present*"[262]. Codes of Conduct can be used in order to describe an approach towards a new sector of technology, as nanotechnology.

The European Commission in 2008 drafted a recommendation for a Code of Conduct for responsible nanosciences and nanotechnologies research. The code of conduct was the first nano-specific EU legal measure and its aim as it is stated in the Recommendation is to '[…] *to invite all stakeholders to act responsibly and cooperate with each other, in line with the N&N Strategy and Action Plan of the Commission, in order to ensure that N&N research*

[262] Graeme A. Hodge, Diana M. Bowman and Andrew D. Maynard *International Handbook on Regulating Nanotechnologies* (Edward Elgar 2010 UK), 452

is undertaken in the Community in a safe, ethical and effective framework, supporting sustainable economical, social and environmental development"[263].

The EU Code of Conduct was drafted in a period where the lack and insufficiency of scientific data about the potential risks of nanotechnology did not encourage further regulatory action to be taken.[264] The idea behind drafting the code was to promote a responsible research and establish communication between the different actors in Nanotechnology field [265]. According to European Commission the Code of conduct is not legally binding but it is complementary to legislation and provides the actors involved in nanosciences and nanotechnologies research with guidelines and principles in order to adopt a responsible approach towards nanotechnologies and nanosciences research in European Community[266].

The Code of Conduct is comprised by seven principles namely the principle of public well-being, sustainability, precaution, democracy, excellence, innovation and responsibility and addresses not only Member States but also employers, research bodies, researchers, civil society and non governmental organizations involved or interested in Nanosciences and Nanotechnologies research[267]. The Code of Conduct perceives the European Member States as actors that can effectively be involved in the nanotechnology dialogue and bring closer the interested parties in the field of nanotechnology[268].

Some other examples include the 'Responsible NanoCode' which was developed in 2008 by the UK Royal Society, Insight Investment and the Nanotechnology Industries

263 European Commission, 'COMMISSION RECOMMENDATION of 07/02/2008 on a code of conduct for responsible nanosciences and nanotechnologies research', 5 < http://ec.europa.eu/nanotechnology/pdf/nanocode-rec_pe0894c_en.pdf> accessed 31 May 2013

264 Noela Invernizzi, 'EC code of conduct for responsible nanotechnology' (2010) <http://www.thebrokeronline.eu/Blogs/Nano-Rights-and-Peace/EC-code-of-conduct-for-responsible-nanotechnology> accessed 1 June 2013

265 European Commission, *Understanding Public Debate on Nanotechnologies: Options for Framing Public Policy* , (René von Schomberg and Sarah Davies (ed), Publications Office of the European Union 2010), p. 8 <http://ec.europa.eu/research/science-society/document_library/pdf_06/understanding-public-debate-on-nanotechnologies_en.pdf> accessed 1 June 2013

266 European Commission RECOMMENDATION (07/02/2008) (n 263) 5

267 ibid 6

268 European Commission (n 265) 9

Association [269]. The aim of the 'Responsible NanoCode' as stated in its text is to*"[…] establish a consensus of good practice in the research, production, retail and disposal of products using nanotechnologies and to provide guidance on what organizations can do to demonstrate responsible governance of this dynamic area of technology"*[270]. In addition some private industries have developed in the context of their activities codes of conduct as a responsible approach to nanotechnology research. So far in the area of private industry some initiatives have been put forward from some companies to address the nanotechnology field with responsibility.

Examples from private enterprises taking measures towards a responsible approach to nanotechnology is the chemical company BASF, which has developed a 'Nanotechnology code of conduct' with aim to focus on defining principles about responsible engagement in nanotechnology sector[271]. Their "Nanotechnology code of conduct" starts with "*[…] in order to tap into the opportunities offered by technological advances, we want to use new technologies when manufacturing innovative and marketable products. Only with these actual products can we perform a rational assessment of their potential risks compared with their opportunities. This means that only a willingness to identify opportunities and risks in a stepwise approach makes innovations based on new technologies possible […]*." As Kearnes and Rip observe, BASF's intention with this code of conduct is to provide a strategy for "rational risk assessment" and try to place itself accordingly before more strict regulation comes into force[272]. Also the Swiss Retailer's Association published the 'Code of Conduct: Nanotechnologies' [273].

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269 <http://www.nanotechia.org/activities/responsible-nano-code> and <http://nanotechia.org/sites/default/files/20080501_The%20Responsible%20Nano%20Code%20Update%20Annoucement.pdf> accessed 213 June 2013

270 Insight Investment, Royal Society, Center for Process innovation, Nanotechnology Industries Association, "Information on the Responsible NanoCode Initiative" 2008, 3 < http://www.nanoandme.org/downloads/The%20Responsible%20Nano%20Code.pdf> accessed 23 June 2013

271 BASF 'Nanotechnology Code of Conduct' <http://www.basf.com/group/corporate/nanotechnology/en/microsites/nanotechnology/safety/code-of-conduct> accessed 1 June 2013

272 Mathiew Kearnes and Arie Rip, 'The emerging governance landscape of Nanotechnology' (2009) S. *Gammel, A. Lösch and A. Nordmann, Jenseits von Regulierung: Zum politischen Umgang mit der Nanotechnologie. Berlin: Akademische Verlagsgesellschaf,* p. 17 http://www.geography.dur.ac.uk/Projects/Portals/88/Publications/The%20Emerging%20Governance%20Landscape%20of%20Nanotechnology.pdf> accessed 23 June 2013

273 Code of Conduct Nanotechnologies <http://www.innovationsgesellschaft.ch/media/archive2/publikationen/CoC_Nanotechnologies_english.pdf> accessed 1 June 2013

Although Codes of Conduct are not legally binding and have a voluntary character, as Bowman et al. mention "*they have been broadly welcomed by governments, authorities and various other interested groups as suitable tool to bridge the current uncertainties […]*"[274]. Some key elements in favor of these voluntary measures that they have identified are their quick implementation, flexibility and adaptability.

The current state of knowledge about the potential risks of nanotechnology, the lack of data about the toxicity and eco-toxicity of nanomaterials and the potential exposure paths, make the existence of the European Code of Conduct and also codes in the context of the activities of private enterprises significant first steps towards a responsible approach to nanotechnology issue. Establishing and adopting and further promoting voluntary measures as codes of conduct, can help towards a safe development of nanotechnology since its early stages, as they can further promote the dialogue between different stakeholders, establish principles that will have to be followed by all the actors involved in the field and can promote a coherent approach towards the research and development in this field of science.

In the absence of mandatory measures and binding laws regarding nanotechnology, the adoption of a Code of Conduct can be the first step of a common approach towards this technology. The existence of EU Code of Conduct has a twofold purpose. On the one hand it intends to promote the research in the area of nanotechnology in order to take advantage of the potential benefits and on the other hand to protect human health and the environment[275]. A European Code of Conduct can become a tool that can assist scientists to proceed with safety in the context of their research, establish a responsible European approach towards nanotechnology, contribute to the dialogue between various stakeholders and promote a sound -based on the standards set in the code- development of nanotechnology in European level.

[274] Graeme A. Hodge, Diana M. Bowman and Andrew D. Maynard (n 262) 455
[275] Noela Invernizzi (n 264)

4.3 The role and scope of Communication based tools in the context of Nanomedicine

The European Commission in its Communication 2007[276] recognizes that another important factor that contributes to the development of novel technologies, as nanotechnology is the societal acceptance of the technology. More specific it states: "*societal acceptance is a key aspect of the development of nanotechnologies. The Commission has to take into account people's expectations and concerns. […] there should be public consensus on their overall impact. Their expected benefits as well as their potential risks and any required measures, must be fully and accurately presented and public debate must be encouraged, to help people form an independent view […]*"[277].

From this point of view we can understand that the public acceptance of a technology is an important factor for its further development. At the current state of the art where no specific nanotechnology laws exist, the use of communication tools can contribute to the achievement of regulatory policies for further development of nanotechnology.

Communication based techniques rely on their attempt to educate and inform them who will be affected by a certain regulation. Morgan and Yeung mention that in their simplest form and in order to achieve their goals they focus on improving the information available to the public so it can make informed choices that will help the achievement of regulatory policies[278].

Government directed campaigns, information campaigns, guidance and mandatory disclosure could be included in the category of communication tools[279]. So far the Commission has published a variety of informational material aiming to inform public about nanotechnology. Along with these activities a handbook 'Communicating Science, a survival

[276] European Commission, 'COMMUNICATION FROM THE COMMISION TO THE COUNCIL, THE EUROPEAN PARLIAMENT AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009' [2007] < http://www.fp7.org.tr/tubitak_content_files/270/AksiyonPlani/comm_2007_0505_en.pdf> accessed 2 June 2013
[277] ibid 7
[278] Morgan and Yeung (n 204) 97-98
[279] ibid

Kit for Scientists'[280], websites in European level but also in national level have been created in order to inform the public and establish an effective dialogue between the different actors involved in nanotechnology field. Some illustrative examples are the European Commission's platform on Nanotechnology[281] and in Member States level each state has established its own website (Germany, France, Netherlands, UK, Italy)[282].

In addition mandatory disclosure can prove of great significance in the context of nanotechnology. By using mandatory disclosure, the state can oblige the producers to disclose a variety of information concerning a product for which nanotechnology either was used in the production or contains nanomaterials. The information can vary from the composition of the product, to the process of production and its side effects. In that way, on the one side, purchasers can make informed choices based on how attractive and acceptable a product appears to them and decide whether or not they will buy a product for which nanotechnology has been used either during the process of production or the product itself contains nanomaterials[283]. On the other side producers can adjust their products to the purchasers needs. In addition mandatory disclosure is a way to discourage purchasers from injecting fraudulent information to the public[284].

As long as no specific laws are yet established regarding nanotechnology using communication based tools, will help inform the public, it is a way to influence social behavior so the public will not raise concerns for this new technology due to the lack of knowledge and also influence its behavior so that to act in a way that is consistent with regulatory objectives.

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280 European Commission, 'Communicating science "A SCIENTIST'S SURVIVAL KIT" (2006) <http://ec.europa.eu/research/science-society/pdf/communicating-science_en.pdf> accessed 2 June 2013

281 http://ec.europa.eu/nanotechnology/index_en.html and http://cordis.europa.eu/nanotechnology/

282 http://www.nanotruck.de/ (Germany), http://ilarion.free.fr/nanomonde/ (France) , http://www.nanopodium.nl/CieMDN/english/ (Netherlands), http://www.nano.org.uk/ (UK), http://www.nanotechitaly.it/ (Italy)

283 Morgan and Yeung (n 204) 97

284 ibid 97-98

4. 4 Conclusion

The regulatory attempt to respond to the challenges that nanoproducts introduce faces several obstacles. Taking into consideration the existing gaps in scientific knowledge, the data that still emerge and the gradually increasing number of nanomedicine applications, the settlement of this matter is not expected to take place in the short term. In the absence of a regime or provisions in the existing regime that cover nanomedicine applications, this chapter examined some other mechanisms that at the current state of knowledge could supplement the regime and contribute towards the adoption of a safe path of development of this emerging technology. The development and adoption of guidelines that would refer to nanomaterials could provide clarity on complex nanomedicine applications that challenge the boundaries between medicinal products and devices and create a climate of certainty on how to deal with the challenges they introduce, clarify the relevant regulatory framework and the competent authorities. Besides guidelines, the establishment and dissemination of codes of conduct can contribute towards the development of a safe path of this technology as it could assist the involved parties in the field to proceed with responsibility and safety during their research and development of nanomedicine applications. As the societal acceptance of a technology has been recognized as an important factor for its further development, the adoption and further support of communication tools such as the publish of informative material, the creation of information points such as websites where the public can access and get informed as well as the support of mandatory disclosure can contribute towards this direction. All the these measures in the present state can have a constructive role in coping with the uncertainties that nanomedicine introduce, help to build a knowledge base and provide a minimum level of safety for human health.

Recommendations and Conclusive Remarks

Recommendations

The analysis that took place in the previous Chapters showed that nanotechnology is an emerging technology that is still at its early stages. Although it is a very promising technology with potential benefits, the current state of knowledge about the potential risks and hazards is still limited. The limited knowledge about the potential risks and the uncertainty that surrounds this technology, is reflected in the current normative system which does not seem adequate to deal with all the challenges posed by this novel technology. The knowledge gap between the potential benefits and risks paves the way for more toxicological studies in order to understand the novel characteristics of nanomaterials on a wide range of applications that this technology can be used. What has emerged after reviewing the existing literature, is that in cases where scientific uncertainty prevails the improvement of knowledge requires the involvement of different actors that will all together cooperate in order to share their current state of knowledge so a minimum level of safety can be established.

In case of nanotechnology the cooperation between scientists, regulators, legal scholars and the public can prove beneficial as each group can contribute with each own means to promote further the scientific development. The adoption of a multidisciplinary approach that sustains scientific knowledge by developing guidelines, codes of conduct and inform the public, but also protects human health, can open the way for a responsible approach towards nanotechnology. From this point of view nanotechnology offers the chance for a major interplay between science and law, where law will not be in conflict with technology due to the uncertainties that come along with its novel character but instead it will try to create a pathway for its safe development.

This interlink between science and law can have further consequences as well. The fact that nanomedicine applications combine characteristics from different scientific fields and challenge the boundaries between them, require the amendment of the existing normative

system in order to be able to address those challenges. A first step towards that direction, as it has already been proposed, it is the adoption of a common definition on nanomaterial, so it would have the same meaning for each scientific field. Further the current normative system on medicinal products and medical devices considers nanomedicine applications from a broad perspective, trying to fit them in the existing norms without taking into consideration the practical issues that arise, as they challenge the boundaries between medical devices and medicinal products. Amending the current legislation in order to include provisions about nanomaterials in devices and medicinal products would be welcomed as well.

Moreover the concept of risk that novel technologies introduce is dynamic and multidimensional and requires a new model of risk/benefit analysis. A model that takes into consideration both in risk assessment and risk evaluation the different levels of risk that nanomedicine applications can introduce simultaneously, as well as not only concrete scientific data but also social and ethical values, would allow a multidimensional identification of risk.

In case the scientific data are inadequate to provide a basis for taking further regulatory action with regard to identify and classify the risks as well as to come into definitions, some precautionary measures should be taken in order to manage the challenges and prevent the occurrence of adverse effects. The adoption of precautionary measures as was explained in the previous chapters does not mean an automatic ban of this emerging technology but instead, through the development of guidelines, codes of conduct and informing the public, a safe development of the technology.

At this early stage of nanomedicine where the potential benefits and risks are not fully demonstrated and the scientific data are still emerging, the development of a regulatory regime that would explicitly cover nanomedicine would not be either a feasible or an appropriate choice as it could probably impede its further development. In such a scenario, with the data still emerging and scientific knowledge too limited to lead to reliable conclusions about the harms to the human body, precautionary measures should be adopted in order to manage the challenges and prevent the occurrence of harmful events. An approach that aims to develop step-by-step precautionary measures and guidelines, codes of conduct and public information paves the way for sustaining scientific knowledge process under conditions of uncertainty. Regulatory guidelines should be developed that will refer to

nanomedicine applications that incorporate nanomaterials and try to provide clarity on which category they fall under. This approach could be helpful for researchers and legal experts when they are confronted with complex systems and they do not know which legal requirements are applicable. The support and further development of codes of conduct should aim at contributing towards a coherent approach to this field of science. More realistically, the development of a code of conduct that would refer to the nanomedicine field of research and would establish principles that will have to be followed by all actors involved in the field can promote a coherent approach towards the research of nanomedicine applications. Making the public aware of the use of nanoparticles in medicine so that it can be informed about and aware of the potential risks, would allow the public to make informed choices and not raise concerns due to lack of knowledge.

In addition examples as GMOs experience can be used to avoid the pitfalls of the past. The lesson from GMOs experience suggests that regulatory action should promote both scientific knowledge and also provide a level of safety. Despite the limitations of REACH regulation with regard to nanomaterials it can be used as a tool to fill this communication gap. REACH and the procedures that have been established under it, recognizes the importance of gathering, collecting and disseminating information between the different interested parties about the characteristics, risks and potential adverse effects of nanomaterials. In that way REACH can function as a "data center" that will provide with information the researchers, regulators and the public.

Regulatory choices that favor the dissemination of nanomedicine data so all the involved parties to be adequately informed and also promote a multidisciplinary approach that will use different tools to inform the public, absorb potential concerns and establish a minimum level of safety, can facilitate a productive dialogue in nanomedicine field and set the basis for a comprehensive understanding of risks that is based on scientific data and not in perceptions. This thesis tried to create a basis for discussion and recognizes that further research is needed to address those highly debated issues.

Conclusion

Nanomedicine is a very promising field that can benefit areas such as drug development, drug delivery, diagnosis and offers new ways of treatment illness and disease. Nanomedicine may combine various characteristics of action such as chemical, mechanical, immunological that touch upon different disciplines of science and make the boundaries between them blurry. This complex character of nanomedicine applications makes the adoption of a commonly accepted definition that would designate the field a challenging task. This means that an accurate understanding of the complex processes is necessary as different scientific areas are involved. The uniqueness of nanoparticles due to their small size creates another challenge. Although their small size confers on them uniqueness as they can overcome limitations found in the traditional therapeutic and diagnostic agents, this characteristic can have negative implications as well. On the one hand the ultra small size makes them innovative but on the other hand scientists have voiced concerns about the potential adverse effects.

Two areas of application, optical imaging and drug delivery systems are characteristic examples that demonstrate that although the potential benefits can be huge the adverse effects are still emerging and we are not fully aware of them. Studies exploring the toxicological effects of nanomaterials are still emerging and some of them have shown that the ultra small size of nanoparticles can make them more toxic when interacting with human body and more likely to penetrate and be absorbed by the body faster compared to bulk substances. However the inadequacy of data regarding their toxicity in combination with the fact that they are not produced in large volumes does not allow us to answer how and to what extent they can cause harm to human health. This knowledge gap has been mentioned by some scientific reports as the SCENHIR report, the White Paper Risk Nanotechnology Report and the UNESCO report. Although this knowledge gap exists the commercialization of nanomedicine has already taken place. This state of uncertainty in combination with the vague definitions poses challenges to regulators to control the development and use of these technologies. In the absence of specific regulations or provisions in the existing regime that refer to them it is expected that the existing regulatory regime will apply to nanomedicine.

What has emerged form the analysis is that the novel character and the uncertainties that surround nanomedicine are reflected in the current regime. For example some nanomedicine applications as drug delivery systems challenge the boundaries between the medicinal products and medical devices regulatory regime. Another challenge that was also identified is the blurring boundaries between medical devices and in vitro medical devices as the use of nanotechnology results in more advanced devices where the distinction is not clear. Another limitation coming from the European regime is the classification of risk. The complexity of nanomedicine applications makes the identification and classification of risk a challenging task. An example that reflects those challenges is the AcryMed's SilvaGard Surface Treatment that showed that this technology can be used in a wide range of devices and as a result the risk evaluation becomes problematic.

With the chemical industry being the main manufacturer of nanoparticles and with nanomedicine relying on their research and progress, in order to have a complete regulatory approach, REACH was examined to see if it could cope with the uncertainty and the issues that they raise. Although REACH provides a good basis for regulating nanomaterials, limitations have been identified. What emerged when examining nanoparticles under REACH regulation is that the definition of substance that is used under REACH does not use size, shape or other dimensions to identify a substance. So it is considered that it covers all substances and nanoparticles as well. At present under REACH regulation it is not clear whether they are considered equivalent or different when compared to bulk substances. This uncertainty in combination with the lack of information about the risks of nanomaterials and the small volume of their production make both the classification under REACH and registration a difficult task. The limited knowledge about their characteristics calls for additional data in order to conduct an analysis between them and bulk materials.

In an effort to address this complex situation the European Commission in 2011 put forward a recommendation for the adoption of a definition on nanomaterial. Although it is a significant step limitations have been identified. For example the size limitation that is proposed might exclude some applications from regulation. EMA uses a different size range with regard to nanomaterials that are used in medicine. This thesis supports that in case the definition is adopted, REACH will have to be amended in order to include it and the volume

criteria will have to change as well. Also new testing criteria might be necessary due to the novel character of nanomaterials.

With regard to medicinal products and medical devices under REACH, although medicinal products are excluded from registration under REACH, medical devices can fall under this regulation if they include a hazardous substance. But the classification of a substance as dangerous relies on the degree and nature of hazard. At the moment the insufficiency of scientific data and the limited studies about nanomaterials make the classification quite difficult. Besides REACH, the recommended definition on nanomaterial is proposed to be adopted by the new Regulation on medical devices. Although the proposed Regulation will establish stricter assessment criteria it is not without problems with regard to size and it remains to be seen if and in what form it will finally be adopted. So although REACH can be applicable to nanomaterials it has limitations that should be taken into consideration.

The challenging features and the uncertainty that surrounds novel sciences such as nanomedicine, challenge the applicability of the existing regime if we directly apply it to them. At the same time those characteristics, led experts and regulators to develop tools able to assess and manage risks. Risk benefit analysis is a tool that is established under the current regime for medicinal products and medical devices and aims to provide strategies to assess and manage risks. However this thesis argued that the challenging features of nanomedicine and the risks that come along with them cannot be addressed by the current risk benefit analysis. The model of risk benefit analysis that is used in the context of medicine holds a net distinction between scientific data, social and ethical values and cannot capture the multidimensionality of risk in the context of nascent technologies. This separation makes its applicability in nanomedicine inadequate. Conversely a more realistic risk benefit analysis model that can take into consideration the different subsets of risks and scientific data integrated with social and ethical values would be more responsive. Such an approach would help to investigate complex situations as it takes into consideration different variables.

The issue of how to manage risks in nanomedicine has drawn the attention of different interested groups. This thesis showed that the debate evolves around two sides where on the one side are the advocators of a more cautious approach while on the other are those that favor a more risk approach. This thesis argued that in cases of uncertainty some

precautionary measures should be taken together with the adoption of guidelines, codes of conduct and public information that will create a level of safety in order to proceed under uncertainty. Supporting Stirling's view, precautionary measures do not mean ban of everything that can cause harm but instead with the use of guidelines, codes of conduct and communication with the public, the creation of a pathway is promoted that will support the safe development of the technology and the protection of human health.

This regulatory perspective is considered by this thesis not in conflict with novel science, aiming to impede its further development. Instead it is considered as a way to create a path for its safe development. The analysis of the role and scope of guidelines, codes of conduct and communication tools in the context of nanomedicine has shown that their use in the current regime can be a valuable contribution that will help to sustain and promote scientific knowledge without causing harm to human health. Guidelines that will address nanomedicine applications, codes of conduct designed to operate in the context of nanomedicine and communication tools that will inform the public can at the current state of knowledge contribute in establishing a minimum level of safety and promote scientific knowledge process. The complex and multidimensional character of nanomedicine requires a responsive and multidisciplinary mechanism that will deal with all these challenges. The biggest challenge is to promote scientific development that can benefit different disciplines but also interact with policy frameworks in order to ensure safety.

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