Eliana B. Souto *Editor*

Patenting Nanomedicines

Legal Aspects, Intellectual Property and Grant Opportunities

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Preface

As a Ph.D. Professor of Law, my opinion of this book has to be seen as that of a "non-expert" in the medical field. Nevertheless, I can surely testify to the absolute relevance of the theme to today's perception of legal issues that arise from an interdisciplinary[1] approach of bioethical discussions regarding patenting nanomedicines.[2] Indeed, as the presentation states, "the multidisciplinary aspect of nanomedicine provides a unique opportunity for patenting the innovations. But at the same time it poses several challenges also."

1. In 1959, Richard Feynman in Pasadena, told the world "*[T]here is plenty of room in the bottom*". He continued: "What I want to talk about is the problem of manipulating and controlling things in a small scale ... What I have demonstrated is that there is room—that you can decrease the size of things in a practical way. I now want to show that there is plenty of room. I will not discuss how we are going to do it, but only what is possible in principle ... We are not doing it because we haven't yet gotten around to it".[3]

   But it is important to stress that "the positive attitude to nanotechnology is based not on knowledge but on hope and fascination. The perceived risk is low because of a lack of vivid and frightening images of possible hazards. If new flashes were to link nanotechnology to concrete hazards or actual harm to people, attitudes might suddenly change".[4]

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[1] On this multidisciplinary context, SARGENT, Ted, The Dance of Molecules How Nanotechnology is Changing our Lives, New York: Thunder's Mouse Press, 2006, p. xiii.

[2] About the emerging threats, FIOLHAIS, Carlos, "Nanotecnologia: o Futuro Vem Aí" in Biologias na Noite (coord: Amadeu Soares), Porto: Edições Afrontamento, 2007.

[3] *Apud* ROUKES, Michael L. "Plenty of Room, Indeed" in Understanding Nanotechnology (coord: Sandy Fritz), New York: Warner Books, 2002, p. 18.

[4] SIMONS, Johannes, ZIMMER, René, VIERBOOM, Carl, HÄRLEN, Ingo, HERTEL, Rolf, e BÖL, Gaby-Fleur, "The Slings and Arrows of Communication on Nanotechnology, Journal of Nanoparticle Research, 2009, n. 11, pp. 1555 e ss.

From this perspective, it is both a privilege and responsibility to be able to contribute to an objective review of this book, from a legal perspective.

2. The first guarantee of quality arises from the biosketch of the Editor. Presenting a brilliant *curriculum vitae* as a researcher, Eliana B. Souto also has a most singular interest in law regulation, which grants the scope of the book an in-depth and thorough text dissection and conceptual reasoning even from a comprehensive legal perspective. That circumstance ensures the high quality and commitment of the result to be presented.
3. It is stated that the book "is primarily addressed to professionals from the field of patent examiners, academics, researchers and scientists, as well as post graduating students, developing their research in the area of nanomedicines in general, and intellectual property in particular" and that "pharmaceutical companies are also potential targets since the book will also be a guideline in the design and process development of novel drug delivery systems, dealing with ethics, socio-political policies and regulatory aspects". And it is also relevant that the target market is expected to be broad because of further recommendations and search for potential market players and stakeholders such as professional associations working in nanomedicines.
4. The "emerging threats" and "grant opportunities" of the nanomedicines are well explained in the scheme into which the book is divided. Not only is the *summa division* between Parts I and II,[5] clear and helpful, but the scope of the chapters is also clearly pointed out.

Thus, from a legal perspective, the book seems to be a relevant collection of cases regarding the most recent developments in the nanomarket, which requires reflective attention from the legislative authorities and administrative and judicial bodies.

In all chapters the so-called ELSI (ethical, legal and social issues) to which bioethics must adjust are self explanatory.[6]

In fact, and again from a legal point of view, it is most essential to address questions that deal with the ethical fundamentals of legal rights, such as "protection of identity, privacy, obtaining informed consent and communicating benefits and risks". Given the scenario of limited information being available, we must question the validity of some medical uses and patenting.[7]

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[5] Regarding this issue, OSTROWSKI, Alexis D., MARTIN, Tyronne, CONTI, Joseph, HURT, Indy, e HARTHORN, Barbara Herr, "Nanotoxicology: Characterizing the Scientific Literature, 2000–2007", Journal of Nanoparticle Research, 2009, n. 11, p. 255 and SAWANT, Rishikesh M., SAWANT, Rupa R., GULTEPE, Evin, NAGESHA, Dattatri, PAPAHADJOPOULOS-STERNBERG, Brigitte, SRIDHAR, Srinivas, e TORCHILIN, Vladimir P., "Nanosized Cancer Cell-target Polymeric Immunomicelles Loaded with Superparamagnetic Iron Oxide Nanoparticles", Journal of Nanoparticle Research, 2009, n. 11, pp. 1777 e ss.

[6] CORMICK, Craig, "Why Do We Need to Know What the Public Thinks About Nanotechnology?", Nanoethics, 2009, n. 3, p. 167.

[7] MEILI, Christoph, "The 'Nano Information Pyramid' Could Help to Solve the 'No Data—no Market'—Problem of Nanotechnologies", in "No Data, no Market?" Challenges to Nano-Information and Nano-Communication Along the Value Chain, 5th International "NanoRegulation" Conference 25–26 November 2009, Rapperswil (Switzerland) Conference Report (coord: Stephan Knébel e Christoph Meili), Switzerland: The Innovation Society, 2010, p. 2.

Furthermore, it is important to question the relationship between intellectual property[8] and the limits to science activity (Part I, Chaps. 1 and 2). In fact, it is not only a question of deciding the regulatory framework (Part I, Chap. 3[9]) but also, more thoroughly, questioning its ethical roots.

5. In addition to the consideration of health and safety precautions[10] in the Chap. 3 of Part I, it would also be important to address the issues of consumer safety,[11] particularly when we are considering synthetic nanoparticles (as "engineered or manufactured nanoparticles") or buckyballs (as buckminsterfullerenes).

The application and lessons that arise from the precautionary principle must also be brought into light.[12]

[8] KOEPSELL, David, "Let's Get Small: An Introduction to Transitional Issues in Nanotech and Intellectual Property", Nanoethics, 2009, 3, pp. 157 e ss., and SEEMAN, Nadrian C.,"Nanotechnology and the Double Helix", Scientific American, June 2004, pp.35 e ss.

[9] About this issue LEE, Robert, and STOKES, Elen, "Twenty-FirstCentury Novel: Regulating Nanotechnologies", Journal of Environmental Law, 2009, vol. 21, n. 3, pp. 469 e ss.; CALSTER, Geert van,"Regulating Nanotechnology in the European Union", European Law Review, Agosto – Setembro de 2006, pp. 238 e ss and JOHNSON, Robbin, "Emerging Technologies Oversight: Research, Regulation, and Commercialization", Journal of Medical Ethics, vol. 37, n. 4, Inverno de 2009, pp. 587 e ss.

One of the most important legal instruments applicable to nanomaterials is Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). REACH provides a general framework of the manufacture, marketing and use of chemicals within the European Union.

[10] HOWARD, John, and Murashov, Vladimis, "National Nanotechnology Partnership to Protect Workers", Journal of Nanoparticle Research, 2009, n. 11, p. 1674. Also confront Working Conditions Committee of the Social and Economic Council of the Netherlands, Nanoparticles in the Workplace: Health and Safety Precautions, 2008.

[11] "Nanomaterials in Consumer Products, Availability on the European Market and Adequacy of the Regulatory Framework", RIVM/SIR Advisory Report 11014, European Parliament, Policy Department Economic and Sicnetific Policy (April 2007), p. iii.

[12] About this specific issue, Agência Europeia do Ambiente, Late Lessons from Early Warnings: the Precautionary Principle 1896–2000, Copenhagen, 2001; CASTAING, Cécile, "La mise en œuvre du principe de précaution dans le cadre du référé suspension", in: Actualité Juridique Droit Administratif, n 43, 15 de Décembre de 2003; DOVERS, Stephen, "Precautionary policy assessment for sustainability", in: Implementing the Precautionary Principle. Perspectives and Prospects, Edward Elgar, Cheltenham, 2008; FISHER; Elisabeth, Judith Jones, René von Schomberg, "Implementing the Precautionary Principle. Perspectives and Prospects", Edward Elgar, Cheltenham, 2008; O'RIORDAN, Timothy e James Cameron, "Interpreting the Precautionary Principle", Earthscan, 1994; SUNSTEIN, Cass R., "Beyond the Precautionary Principle", University of Pennsylvania Law Review, Janeiro de 2003, p. 1004 and SUNSTEIN, Cass R. (2005), Laws of Fear Beyond the Precautionary Principle, Cambridge: Cambridge University Press, pp. 36 e ss.

The investment policies and the patenting of nanomedicines in underdeveloped countries[13] must also be addressed, particularly when related to the issue of nano-waste.[14]

It is clear that all those issues mentioned here are central and not merely peripheral to the objective(s) of the study, hence the usefulness of this book to a legal professional who needs to master the ultimate subject of legal reasoning and expertise.[15]

Porto, Portugal, 2012

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[13] FOLADORI, Guillermo, INVERNIZZI, Noela and ZÀYAGO, Edgar, "Two Dimensions of the Ethical Problems Related to Nanotechnology", Nanoethics, 2009, n. 3, p. 123; JAMISON, Andrew, "Can Nanotechnology Be Just? On Nanotechnology and theEmerging Movement for Global Justice", Nanoethics, 2009, n. 3, pp. 129; KISS, Alexandre, "L'Irreversibilité et le Droit des Generations Futures", in: Révue Juridique de l'Environnement, numéro spécial, 1998 and NISSEN, Ulrik B., "Justice in Nanotechnological Development (Symposium Introduction)", Nanoethics, 2009, n. 3, p. 119.

[14] BUTTI, Luciano, "Harzardous Waste Manegement and the Precautionary Principle", Waste Management, 29 (2009), pp. 2415–2416 and TELLENBACH, Mathias, "How to Treat Nano-Waste: Challenges and Information Needs along the Value Chain" in "No Data, no Market?" Challenges to Nano-Information and Nano-Communication Along the Value Chain, 5th International "NanoRegulation" Conference 25–26 November 2009, Rapperswil(Switzerland) Conference Report (coord: Stephan Knébel e ChristophMeili), Switzerland: The Innovation Society, 2010, p. 32.

[15] WILLIAMS, Linda and ADAMS, Wade," Nanotechnology Demystified", New York: McGraw-Hill, pp. 3 e ss.

Editor's Note to Readers

The scientific community today faces an exciting time with Nanomedicine and Nanotechnology-based research. Even as research on this progresses very fast, questions of ethics, socio-political policies and regulatory aspects are sometimes left behind. Issues such as protection of identity, privacy, obtaining informed consent and communicating benefits and risks are amongst the many ethical queries researchers should always bear in mind. The most significant concerns involve risk assessment and management of novel Nanomedicine-based products that are currently under development for diagnosis and treatment of different types of diseases, as well as risk communication in clinical trials. It is the duty of researchers in medical and medically related research to promote and safeguard the life, health, privacy and dignity of the research subjects. The search for new knowledge has to take place within the limits imposed by such responsibilities. For instance, although in vivo animal experiments and ex vivo laboratory analyses can increase the understanding of the interaction of Nanomedicine-based products with biological systems, the former cannot eliminate all of the uncertainty surrounding the exposure of a human subject to these products in clinical trials. It is the duty of researchers to carry out experiments aimed at safeguarding the future applications of novel therapeutic strategies with clinical relevance.

The protection of intellectual assets is essential to the competitiveness of research in the field of nanomedicines, where the threat of dual use competes with novel and potential grant opportunities. This book discusses the difficulties in producing principles and policies that are rooted in practice of Nanomedicine, aimed at ultimately creating a dialogue between the public and science.

Registered patents in Nanomedicine and Nanotechnology-based research are increasing globally and the large majority are focused on drug delivery systems, highlighting an important application of these patents. Furthermore, many of them are related to non-communicable diseases (e.g. cancer, infectious diseases, hepatitis). Nanomedicines are among the first products to create nanotechnology patent disputes as the multi-billion dollar pharmaceutical industry begins to adopt them.

This work has received contributions from different research groups worldwide, i.e. Brazil, India, Italy, Malaysia, Portugal, South Africa, Taiwan, Thailand,

Turkey, and United Kingdom, locating patented nanomedicines in drug delivery (e.g., lipid/polymeric nanoparticles, nanoemulsions, nanogels, liposomes, nanofibres, dendrimers, nanotubes, micelles), employing pertinent key terms while searching the patent databases to provide a comprehensive state-of-the-art review of diverse patent applications. Written by experts in their respective fields, the different chapters expose the reader to the theories and threats, applications and challenges that are part of the application process to obtain a patent.

This book is primarily addressed to professionals in the field of patent examiners, academics, researchers and scientists, as well as post graduate students, developing their research in the area of nanomedicines in general, and intellectual property in particular. Pharmaceutical companies are also potential targets since the book may also provide guidance in the design and process development of novel drug delivery systems, dealing with ethics, socio-political policies and regulatory aspects. Potential market players and stakeholders are not only the academics and researchers, but also patent examiners, the pharmaceutical industry, and members from pharmaceutical associations.

The Editor is grateful to this outstanding group of international researchers, who have contributed their valuable expertise to this book bringing to it a first-hand account of their professional experience. In particular acknowledgment is due to Dr. Tatiana Andreani for her most valuable technical assistance while preparing the manuscripts received for editing. The Editor is thankful to *Fundação Ensino e Cultura Fernando Pessoa* and *Fundação para a Ciência e Tecnologia*, for the exceptional support of this task. Sincere thanks are addressed to the editing and managing staff at *Springer* for their tireless efforts and assistance.

Finally the editor's would like to thank Professor Luisa Neto from the Faculty of Law, University of Porto, for finding time to assist us in this work with her outstanding professional legal view, to fill a "much-needed" void in Patenting Nanomedicines.

Porto, Portugal 2012 Eliana B. Souto

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Abbreviations

γ-PGA	Poly-γ-glutamic acid
AAV	Adeno-associated virus
ADME	Absorption, distribution, metabolism and excretion
ADMET	Adsorption, distribution, metabolism, excretion and toxicity
Ads	Adenoviruses
AE	Arteether
AEG-1	Astrocyte elevated gene-1
AIDS	Acquired immune deficiency syndrome
AL	Artemether/lumetantrine
ALA	Aminolaevulinic acid
AMP	Amphiphilic peptides
ANDA	Abbreviated new drug application
AONs	Antisense oligonucleotides
AQ	Amodiaquine
ART	Artemisin
AS	Artesunate
ASODN	Antisense oligonucleotides
asODNs	Antisense oligodeoxynucleotides
AUC	Area under curve
AUTM	Association of University Technology Managers
BAB	Blood aqueous barrier
BBB	Blood brain barrier
BCC	Basal cell carcinoma
BCS	Biopharmaceutical classification system
BCSFB	Blood cerebrospinal fluid barrier
BM	Basement membrane
BP	Base pairs
BRB	Blood retinal barrier
BSA	Bovine serum albumin
CA	Camptothecin

CAP	Calcium phosphate nanoparticles
CDK	Cyclin-dependent kinase
CDs	Cyclodextrin
CFD	Computation fluid dynamics
CHOL	Cholesterol
CLG	Cross-linked gelatin
CLSM	Confocal laser scanning microscopy
CMC	Carboxymethylcellulose
CME	Clathrin mediated endocytosis
CNA	Circulating nucleic acids
CNS	Central nervous system
CNT	Carbon nanotubes
COX-2	Cyclooxygenase-2
CP	Carbopol
CPP	Cell penetrating peptides
CQ	Chloroquine
CQP	Chloroquine phosphate
CS	Chitosan
CsA	Cyclosporin A
CSA	Condroitin sulfate A
CSF	Cerebrospinal fluid
CVOs	Circumventricular organs
DA	Degrees of acetylation
DARC	Duffy antigen receptor for chemokines
DBPC	Dibehenoylphosphatidylcholine
DC-CHOL	3β[*N*-(*N*′,*N*′-dimethylaminoethane)-carbamoyl] cholesterol
DDAB	Dimethyldioctadecylammonium bromide
DHA	Dihydroartemisin
DLenDMA	1,2-Dilinolenyloxy-*N*,*N*-dimethylaminopropane
DNA	Deoxyribonucleic acid
DODAC	*N*,*N*-dioleyl-*N*,*N*-dimethylammonium chloride
DODAP	1,2-Dioleyloxy-3-dimethylamino-propane
DODMA	*N*,*N*-dimethyl-2,3-dioleyloxy)propylamine
DOGS	Dioctadecylamido-glycylspermine
DOPE	Dioleoylphosphatidylethanolamine
DORI	*N*-(I-(2,3 dioleoxyloxy)propyl)-*N*-(l-(2-hydroxy)ethyl)-*N*,*N*-dimethyl ammonium iodide
DOSPA	2,3-Dioleyloxy-*N*-[2(sperminecarboxamido) ethyl]-*N*,*N*-dimethyl-1-propanaminium trifluoroacetate
DOTAP	1,2-Dioleoyl-3-trimethylammoniumpropane
DOTMA	*N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethyl-ammonium chloride
DOX	Doxorubicin
DPPC	Dipalmitoylphosphatidylcholine

dsRNA	Double stranded ribonucleic acid
EC	Ethylcellulose
ECM	Extracellular matrix
ECVAM	European Central of Validation of Alternative Methods
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth-factor
EGFR	Epidermal growth-factor receptor
EMEA	European Medicines Agency
EPC	European Patent Convention
EPN	Evaporative precipitation of nanoemulsion
EPO	European Patent Office
EPR	Enhanced permeability and retention effect
ESD	Emulsification solvent diffusion
ESF	European Science Foundation
FAE	Follicle associated epithelium
FDA	Food and Drug Administration
FFR	Fibroblast growth factor receptor
FTM	Flutamide
G	Gelatin
GALT	Gut associated lymphoid tissue
GBM	Glioblastoma multiforme
GI	Gastrointestinal
GIT	Gastrointestinal tract
GRAS	Generally regarded as safe
GUV	Giant unilamellar vesicles
HA	Hydroxyapatite
HBsAg	Recombinant hepatitis B surface antigen
HBV	Hepatitis B virus
HDM2	Human double minute 2
Hf	Halofantrine
HGF/SF	Hepatocyte growth factor/scatter factor
HIF	Hypoxia inducible factor
HIV	Human immunodeficiency virus
HLB	Hydrophile-lipophile balance
HMW	High molecular weight
HPH	High pressure homogenization
HPMA	Hydroxypropyl methacrylate
HPMCP	Hydroxypropyl methylcellulose phthalate
HPV	Human pappilomavirus
HSA	Human serum albumin
HSK	Herpes stromal keratitis
HSPG	Heparin sulphate proteoglycans
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type 1

HTAS	High throughpot ADMET system
HTS	High throughpot screening
IARC	International agency for research on cancer
ID	Injected dose
IGF	Insulin-like growth factor
IGF-I	Insulin-like growth factor I
IGF-IR	Insulin-like growth factor I receptor
IgG	Immunoglobulin G
IN	Intranasal
INK4a	Inhibitor of cyclin dependent kinase 4a
IP	Intellectual property
IPA	Institutional Patent Agreement
IRBC	Infected mouse erythrocytes
IV	Intravenous
IVISIV-R	In vitro–in silico–in vivo relationship
IVIVC	In vitro–in vivo correlation
JPO	Japan Patent Convention
LCST	Low critical solution temperature
LDL	Low density lipoproteins
LEs	Lipid emulsions
LMW	Low molecular weight
LN	Lipid nanoparticles
LNCs	Lipid nanocapsules
LPM™	Lipid polymer micelle
LRP	Low density lipoprotein receptor-related protein
LUV	Large unilamellar vesicles
M&S	Modeling and simulation
MAL	Methyl aminolaevulinate
ME	Microemulsion
MEs	Microemulsions
MFH	Magnetic fluid hyperthermia
miRNA	Microribonucleic acid
MLV	Multilamellar vesicles
MMP	Matrix metalloproteinases
MMs	Mixed micelles
MMS	Mohs micrography surgery
MOL	Molecular structure format
MPS	Mononuclear phagocytic system
MQ	Mefloquine
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRT	Mean residence times
mTPP	Meso-tetraphenyl porphine
MWCNT	Multi-walled carbon nanotubes

NAI	Naturally acquired immunity
NC	Nanocapsules
NCE	New chemical entity
NCI	National Cancer Institute
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NE	Nanoemulsion
NIH	National Institute of Health
NLC	Nanostructured lipid carriers
NLS	Nuclear localization signal
NMSC	Non melanoma skin cancers
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NP	Nanoparticles
NPC	Nuclear pore complexes
NPs	Nanoparticles
NRBC	Normal erythrocytes
NSCL	Non-small cell lung
NSF	National Science Foundation
nt	Nucleotides
ODN	Oligodeoxynucleotide
ODNS-NS	Oligo-di-nucleotide nanoparticles
OVA	Ovalbumin
PAA	Polyacrylic acid
PACA	Poly(alkylcyanoacrylate)
PALAM	Poly(allylamine)
PAMAM	Polyamidoamine
PBCA	Poly(butylcyanoacrylate)
PBPK	Physiologically based pharmacokinetic
PC	Physicochemical
PCL	Poly(ε-caprolactone)
PDGF	Platelet-derived growth factor
pDNA	Plasmid DNA
PDT	Photodynamic therapy
PEC	Polyelectrolyte complex
PEG	Poly(ethylene glycol)
PEG2000-DSPE	Polyethylene glycol-distearoyl phosphatidylethanolamine
PEI	Polyethyleneimine
PGA	Poly-glutamic acid
PGES-1	Prostaglandine E 1 Sinthase
PHB	Poly(h-hydroxylbutyrate)
PK	Pharmacokinetic
PK/PD	Pharmacokinetic–pharmacodynamic
PKA	Protein kinase A-type I
PKC-α	Protein kinase C-α