



## **New Regulatory Frameworks towards harnessing knowledge, technology and innovation for sustainable Public Health**

*A Policy Brief based on Expert Opinions*

Performed under a working group on “Harnessing knowledge, technology and innovation”, as established under the **Gulbenkian Platform on “Future for Health”**

with the support of the  
**“International Risk Governance Council - Portugal”, IRGC-Portugal**

07 November 2013



**Âmbito:**

O presente trabalho tem por objetivo identificar, de uma forma preliminar, novas condições e formas de regulação de medicamentos incluindo de terapia avançada e de dispositivos médicos, com especial aplicação para Portugal, de modo a facilitar a valorização do conhecimento e da inovação na sustentabilidade do sistema de saúde. Tem como principal objecto de análise mecanismos emergentes de regulação (e.g., “inteligente e integrativa”), assim como as condições necessárias de investigação clínica, em discussão pela *Agência Europeia do Medicamento, EMA*, e pela *Food and Drug Administration, FDA*. Estes mecanismos e condições são susceptíveis de ter um forte impacto na próxima década no estímulo à adopção de novos dispositivos e terapias avançadas, assim como de novos fármacos, estando a ser alvo de uma discussão emergente por comunidades académicas e médicas.

O objectivo deste breve relatório, elaborado entre Setembro e Outubro de 2013 e portanto de um âmbito exploratório, é facilitar a identificação preliminar dos principais aspectos a considerar na eventual evolução para um sistema regulatório mais eficiente, sem prejuízo para a segurança e eficácia terapêutica, de modo a facilitar um impacto positivo a nível científico, social e económico, beneficiando em particular os doentes. Inclui uma lista inicial de recomendações sobre a adopção de políticas e instrumentos de regulação com forte impacto no sector da Saúde.

Esta iniciativa é promovida no âmbito do Projeto “Saúde em Portugal: Desafios para o futuro” promovido através do Programa Gulbenkian para a Saúde, tendo o apoio do “International Risk Governance Council, IRGC-Portugal”.

**Grupo de trabalho:**

Alexandre Quintanilha, IBMC, U Porto

António Portela, BIAL

Catarina Ramos, EUROTRIALS

Cláudia Lobato da Silva, IBB/IST

Daniela Couto, Cell2B (Relatora)

Hélder Mota-Filipe, Fac. Farmácia, U Lisboa; INFARMED

Isabel Morgado, BIAL

Joaquim Sampaio Cabral, IBB/IST

Margarida Menezes Ferreira, INFARMED (Relatora)

Maria João Queiroz, EUROTRIALS

Mário Barbosa, INEB, U Porto

Miguel Amador, IN+/IST, Bolseiro de Doutoramento em Bioengenharia, IRGC-Portugal (Relator)

Nuno Sousa, ICVS/3Bs, U Minho

Paula de Jesus, NOVARTIS

Pedro Granja, INEB, U Porto

Rogério Gaspar, Fac. Farmácia, U Lisboa

Manuel Heitor (IN+/IST; Coordenação)

**Revisores externos (convidados):**

*Ortwin Renn, Universidade de Stuttgart (D)*

*Kenneth Oye, Massachusetts Institute of Technology, MIT (USA)*

*Tom Kirchhausen, Harvard Medical School (USA)*

*Outros a confirmar*

**Nota:**

As opiniões expressas neste relatório são pessoais, e não podem ser entendidas ou citadas como sendo feitas em nome ou refletindo a posição das instituições dos membros deste grupo de trabalho.

**Scope:**

This study aims to identify, in a preliminary way, new forms of regulation of medicines including those for advanced therapies and of medical devices to be promoted and stimulated in Portugal and in a way to help harnessing knowledge, technology and innovation towards sustainable public health. It is based on a comparative analysis of emerging mechanisms of regulation (e.g., “intelligent and integrative”), discussed by the *European Medicines Agency*, EMA, and the *Food and Drug Administration*, FDA. These mechanisms are likely to have a strong impact in the next decade in stimulating the adoption of new and advanced therapies, as well as new drugs, being the target of a discussion by emerging academic and medical communities.

The purpose of this brief report, which was developed during the period September-October 2013 and, therefore, with an exploratory context, is to facilitate the preliminary identification of main aspects to consider in the evolving regulatory system, without prejudice to patient safety and therapeutic efficacy. The ultimate goal is to facilitate a positive impact on scientific, social and economic levels, benefiting in particular patients. It provides an initial set of recommendations on policies and regulatory instruments with a strong impact on Public Health.

This initiative is promoted under the project "Health in Portugal: Challenges for the future" sponsored by the Gulbenkian Programme for Health, with the support of the "International Risk Governance Council - Portugal, IRGC-Portugal".

**Working Group:**

Alexandre Quintanilha, IBMC, UPorto  
António Portela, BIAL  
Catarina Ramos, EUROTRIALS  
Cláudia Lobato da Silva, IBB/IST  
Daniela Couto, Cell2B (Rapporteur)  
Hélder Mota-Filipe, Fac. Farmácia, ULisboa; INFARMED  
Isabel Morgado, BIAL  
Joaquim Sampaio Cabral, IBB/IST  
Margarida Menezes Ferreira, INFARMED (Rapporteur)  
Maria João Queiroz, EUROTRIALS  
Mário Barbosa, INEB, U Porto  
Miguel Amador, IN+/IST, PhD Fellow IRGC-Portugal (Rapporteur)  
Nuno Sousa, ICVS/3Bs, UMinho  
Paula de Jesus, NOVARTIS  
Pedro Granja, INEB, U Porto  
Rogério Gaspar, Fac. Farmácia, ULisboa

Manuel Heitor (IN+/IST; Coordination)

**External Reviewers (invited):**

*Ortwin Renn, Universidade de Stuttgart (D)*  
*Kenneth Oye, Massachusetts Institute of Technology, MIT (USA)*  
*Tom Kirchhausen, Harvard Medical School (USA)*  
*Others to be confirmed*

**Disclaimer**

The views expressed in this report are personal views, and may not be understood or quoted as being made on behalf or reflecting the position of the institutions of the members of this working group.

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# 1. Introduction: towards new regulatory frameworks harnessing knowledge, technology and innovation

Forms of technological innovation and related knowledge-based initiatives have become central to fostering the sustainability of public health. Nations worldwide have promoted specialized public actions and knowledge-driven policies to guarantee sustainable and modern health care systems.

Emerging forms of technological innovation with implications on healthcare are based on new knowledge at the convergence of life sciences, physical sciences and engineering<sup>1</sup>. The diffusion of that new knowledge, together with its potential social and economic impact, requires new regulatory frameworks, and this has driven the present initiative.

Despite the huge evolution in health care in the last decades, new and previous areas of significant clinical need exist and highlight the importance of bringing recent clinical innovations to the patients as a matter of public health. Populations yet suffer of unmet medical needs and/or serious debilitating chronic diseases. Those include cardiovascular diseases, inflammatory and immune conditions, diabetes, orthopaedic indications, ophthalmological indications, haematology, oncology and neurological disease and conditions.

Nevertheless, to address healthcare clinical innovation it is necessary to take into account multiple technology frameworks, each one with its own maturity and challenges. Development of traditional small chemical entities is still a highly active field; understanding the biological pathways gives rise to new formulations of existing drugs with increased performance. Medical devices are another part of traditional innovation frameworks, although challenges emerge in products, which combine different classes or explore technological advances. However, the biggest challenges today arise from the complexity of using biology by itself to develop new biological medicinal products. Long-standing vaccines or the more recent proteins/antibodies obtained from recombinant DNA technologies already have an established industry and market. However, ultimate challenges arise from the use of cells and genes in therapies in the forefront of scientific and regulatory knowledge.

The rationale behind clinical translation of innovations is complex and supported in scientific, economical and sociological aspects. It includes scientific innovations in response to health care needs, conducted in research centres and science-based firms. One of the major constraints in clinical translation is the need for infrastructures to support manufacturing of investigational medicinal products and adequate clinical research teams operating according to good practices (not to mention the anticipated capacity to allow manufacturing scaling-up of new products). To support this process, it is vital the existence of public and private funding (including specialized investment funds), companies interested in engaging in medicine innovations, stakeholders' involvement towards a better and sustainable health, and an adequate reimbursement framework. Regulatory frameworks are a part of this process, by defining practices, usages and accesses to markets.

The process of pharmaceutical and clinical assessment, as we know it today, has its origin in the FDA's 1962 Amendments<sup>2</sup>. It started as a reactive process to problems in existing products, and similar measures were progressively adapted in all industrial countries. Noteworthy is the early introduction of a regulatory path for the authorisation of medicines in Portugal with the creation of a Technical

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<sup>1</sup> Sharp, P. A., Cooney, C. L., Kastner, M. A., Lees, J., Sasisekharan, R., Yaffe, M. B., ... Sur, M. (2011). The third revolution: the convergence of the life sciences, physical sciences, and engineering. Massachusetts Institute of Technology.

<sup>2</sup> Drug disasters such as sulphanilamide and thalidomide led, respectively, to the enactment by the U.S. congress of the Food, Drug, and Cosmetic Act in 1938 and to the Kefauver-Harris Drug Amendments in 1962. The 1938 Act gave the authority to the FDA to oversee the safety of food, drugs, and cosmetics. Later, in 1962, the Kefauver-Harris Drug Amendments mandated pre-market approval and assessment of safety and efficacy of all new drugs. It also granted increased authority to the FDA to access company production and establish good manufacturing practices. At the same time that the 1938 Act and 1962 Amendments enabled the development of safer and more efficient drugs to the patients, they directly increased the time and cost required to bring drugs to market.

Commission for new Medicines (Decree Law 41448, 18 December 1957) prior to those FDA amendments that required FDA to assess the efficacy of all drugs introduced since 1938.

In the European Union (EU), the European Agency of Medicament (EMA) is central for the authorisation processes associated with innovative medicinal products and to set the EU regulatory framework (on behalf of the European Commission) applicable to all medicines. For all processes run at EMA, from management to assessment and approval, the contribution of nominated experts from all member states acting together to constitute the required expertise ensures a strong and harmonised science driven decision process.

Expert judgment remains the cornerstone of benefit-risk evaluation that preside the authorisation of medicinal products. Regulation of medicines as a tool of risk governance has shaped the process of clinical innovation. With the emergence of new technological frameworks, the rationale became more complex, and the approval process requires the introduction of balanced (quantitative and qualitative) analysis for more comprehensive decision on the risk-benefit profile for each new product.

Nevertheless, the potential revision and improvement of legal regulatory frameworks in order to foster innovation is only possible when considered together with new clinical research practices, and by enabling competitive frameworks, providing strategic resources and developing a culture of engagement of different stakeholders.

This study aims to address this complex set of issues. It identifies emerging forms of regulation in the domains of medicines worldwide, namely for advanced therapies and of medical devices, mainly those with particular relevance for Portugal and in a way to help harnessing knowledge, technology and innovation towards sustainable public health. It is aimed to better understand the international context and help improving the current regulatory system and related practices that could evolve towards increasing benefits for patients, with a strong impact on public health, without prejudice to safety and therapeutic efficacy.

The document is structured based on the analysis of work developed in Europe and elsewhere regarding the topics above mentioned. Next chapter presents the context associated the role of new regulatory frameworks in the process of innovation and in the development of a sustainable health care system. It emphasizes uncertainty in risk governance and a multiplicity of associated issues, including the need to consider processes of stakeholder engagement, decision-making and social perception of risk. In addition, emerging regulatory challenges are identified on the development of new regulatory frameworks to deal with the rise of personalized medicine, emerging technological platforms and regulatory exemptions. Chapter 3 analyses processes of uncertainty, together with stakeholder engagement, social perception of risk and decision-making, proposing areas of intervention and potential actions. Chapter 4 focuses on enabling factors for modern clinical research, pointing challenges and efforts performed in improving clinical trials in Europe and Portugal. Regulatory science is presented as a major field of development regarding this topic. Chapter 5 considers the emergence and development of new “smart and adaptive” legal approval schemes. Chapter 6 discusses the need for integrated public and private initiatives to enable the necessary capacities to use new legal frameworks towards sustainable public health. Chapter 7 summarizes opportunities and main recommendations discussed throughout the text.



## 2. The context: emerging regulatory challenges for new therapies, devices and innovative drugs

This chapter considers the context behind the role of regulatory frameworks in the process of clinical translations and the related influence on public health. Emerging challenges influencing current regulatory frameworks are discussed, including forms of personalized medicine, new technological platforms and regulatory exceptions. The analysis supports the needs for developing new regulatory frameworks as described in the remaining chapters.

### 2.1. Regulatory frameworks, clinical translation and public health

Regulatory frameworks are under continuous scrutiny by many different public and private stakeholders with the ultimate goal of promoting public health through access to secure health care innovation. Clinical research is an essential part of the process of innovation, and legal regulatory approvals are supported on the assessment of quality, safety and efficacy regarding public needs, mainly through clinical trials.

Analysis has shown that systematization of conventional clinical assessment in three distinct phases of clinical trials may present advantages for traditional pharmaceutical companies at quantifying probabilities of success, average time spent, and financial resources required to advance a technology to the market. However, for new drugs or therapeutics, in particular for emerging advanced therapies, referencing to previous practices is limited and, above all, it is inhibiting technological innovation. New technologies and approaches require clinical assessments under new regulatory frameworks.

It should be noted that expert views<sup>1</sup> claim “there will always be novel biologic entities that stretch the very limits of our regulatory systems to the point of rendering some aspects obsolete and/or cause for revision. The trick moving forward is to have open, honest and dispassionate communication between clinicians, scientists and Federal and State authorities and professional boards and organizations. When you look back historically on novel therapies such as transplant medicine, IVF (*in vitro fertilisation*) and ICSI (*intra-cytoplasmic sperm injection*), a great deal of prefacing and focus group consensus building was needed to form fair and cogent regulations to monitor safety and allow the fields to move forward.” This process has been lacking in many new therapies, and still awaited for certain cell therapies.

Lack of communication combined with immediate marketability and high patient demand created “a perfect storm in which several clinicians unwittingly (and some intentionally) jumped the gun before a clear understanding could be vetted by professional organizations. [...] Regulations preserving patient safety along with the sanctity of the patient-physician relationship will never be achieved in a vacuum.”

Regulators recognise that conventional regulatory framework may be holding new therapies back, and the causes could be that they do not evolve with the same pace as scientific knowledge and new advances in scientific discovery. The Committee for Advanced Therapies of the European Medicines Agency recognizes “... that the traditional regulatory framework for medicines does not currently fully address the needs of companies and organizations that develop these medicines [advanced-therapy medicinal products]”<sup>2</sup> also due to the fact that the industrial stakeholders are no longer the traditional pharmaceutical industry.

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<sup>1</sup> See, for example, <https://www.ipscell.com/2013/02/interview-with-stem-cell-surgeon-dr-allan-wu/>

<sup>2</sup> Committee for Advanced Therapies, “Committee for advanced therapies adopts five-year work programme to foster development of advanced therapies,” tech. rep., European Medicines Agency, Nov. 2010.

## 2.2. On the rise of personalized medicine

Advances in research in the last decade resulted in the development of genomics (the study of an organism's genes) and proteomics (the study of the translation of genes into proteins). Such development improved our understanding of how individuals are influenced by their genetic makeup, and how it distinguishes them, allowing new personalized approaches in healthcare.

Genentech's Herceptin and companion "HER2 tests" pioneered in 1998 the field of "targeted" therapeutics and diagnostics specific to sub-populations, based on their genetics, and many others have followed. The science enabling personalized medicine provides ways to match therapies to patients based on their genetic profiles, predict susceptibilities to diseases, and foresee patient response to a particular therapy (a field known as pharmacogenomics). Such possibilities would exclude pointless treatments, reduce adverse events, and ultimately, improve patients' results. Modern science is also opening doors to a deeper understanding of molecular interactions, many specific to each individual.

This is opening new paradigms in pharmaceutical and related industries. While their traditional focus was in developing blockbuster drugs that target broad populations, emerging practices of personalized medicine are changing the orientation of large pharmaceutical companies towards tailored therapies for smaller markets (see Box 1). Nevertheless, the concept of tailoring is not new to the industry.

### Box 1: Looking at Novartis

In the past, drugs were developed for the biggest populations, people with things like heart disease or diabetes. It's getting harder and harder to improve on what's there and create the next blockbuster. Novartis has been trying a very different strategy. Instead of targeting giant populations, it targets rare diseases with a small, very similar population. Scientists figured out the molecular pathway by which the disease works and targeted how to interrupt it. From there, they can expand to other diseases that are affected by the same pathway. Novartis' Afinitor, for example, was developed for kidney cancer. Now, after expanded testing, it was approved for breast cancer. "That together will make it a blockbuster," said Joe Jimenez, CEO of Novartis. Finding new uses for existing drugs isn't new. Doing it systematically, scientifically, and aggressively it is.

Source: March 21, 2013 (<http://money.cnn.com/2013/03/21/news/companies/novartis-joe-jimenez.pr.fortune>)

For years, pharmaceutical companies have segmented customers by disease and used biomarkers, e.g. cholesterol levels, to guide treatment decisions. However, the development of new therapeutics based on genomics and proteomics will require an entirely new level of tailoring. This brings a difficulty to perform standard large randomized clinical trials to assess safety and efficacy in a robust manner, increasing the risks and costs of bringing innovative technologies to clinic levels. Likewise, new therapies, including cell therapies or engineered tissues often based on autologous cells, also represent a new approach of personalized medicine (see **Box 2**).

Emerging advances in science and technology capacity call for new measures in regulation policies. The technology in genomic and personalized medicine is growing at an exponential pace. "The thought of doing rapid point-of-care analysis using genomic assays like sequencing, methylation status, RNA expression profiles and proteomics is no longer a pipe dream, but a pending reality due to tremendous strides in nanotechnology and hyper speed computing [...] and will eventually become available for stem cell pre-deployment safety assurance."<sup>1</sup>

<sup>1</sup> See, for example, <https://www.ipscell.com/2013/02/interview-with-stem-cell-surgeon-dr-allan-wu/>

**Box 2: Stem cell treatment for acute myocardial infarction**

“Currently the standard treatment for people suffering a heart attack (due to a blockage in the artery supplying blood to the heart) is to directly open the artery with a tiny balloon in a procedure called primary angioplasty and to introduce a small tube into the artery to keep it open called a stent. The use of primary angioplasty and stents to reopen the blocked artery can lead to a 33% reduction in the mortality (death rate) associated with this condition. Recently, bone marrow stem/progenitor cells have been investigated as a new treatment that may prevent the damage to heart muscle caused by a heart attack in addition to the treatment offered by primary angioplasty. Analysis of randomised controlled trials to 2011 indicates that this new treatment may lead to some improvements over standard treatment as measured by tests of heart function in the short and long term. Over 1,700 patients have participated so far in the 33 trials included in this systematic review.”

Source: Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Watt S, Martin-Rendon E. The Cochrane Library 2012, Issue 2

Adjusting clinical assessment to new drugs or cell technology is opening a window of opportunities for bringing disruptive technologies into clinical trials and demand customization and flexibility from clinical assessment in adjusting to new technological requirements (see **Box 3**). It may involve the gradual adoption of new regulatory frameworks, but it also needs a comprehensive process of “stakeholder engagement” and coordination of the various decision-makers. In the following paragraphs, these two main sets of actions are proposed to deal with emerging “bio-dilemmas”.

**Box 3: Systemic Interactions in Life Science Innovation**

“Pharmacogenomics and pharmacogenetics are related concepts covering a range of new insights into drug responses arising from knowledge gained through gene sequencing. They could potentially improve disease diagnostics and drug discovery and development; lead to more effective design of clinical trials; help to understand the variable response of pathogens to drugs, variable human therapeutic responses to drugs and variable experience of adverse drug reactions. [...] The future of pharmacogenetics will depend on a complex set of interactions across innovation strategies, market potential and regulatory developments. A more complex development process, along with a segmented market, is likely to lead to significantly more expensive drugs. However, if future regulatory systems are modified to favour the use of pharmacogenetics data, fewer drug candidates may be rejected during clinical trials. This could be the key to the systemic impact on innovation systems required to lead to disruptive overall sectoral change. If changes to the regulatory system result in fewer drugs being withdrawn during clinical trials, reducing the cost of drug development, this could make pharmacogenetics-based drugs more affordable. It would at the same time lower the regulatory hurdle that currently prevents new born firms from acting independently to take new drugs through to the market stage, and could potentially undermine the dominance of pharmaceutical multinational companies.”

Source: Tait, J. (2007). Systemic Interactions in Life Science Innovation. *Technology Analysis & Strategic Management*, 19(3), 257–277.

### 2.3. Emerging technological platforms

Analysis has shown that the number of new molecular entities emerging from developmental and licensing pipelines has been declining and the costs of drug development have been rising, as the R&D model for medicinal products is lengthy and slow. Corresponding advances in pharmaceuticals worldwide have not matched the extraordinary advances in life sciences in recent decades. The number of available therapeutics has fallen short of the promise of the newer biologicals medicines. Nevertheless, it is well known that research-based pharmaceutical and biotechnology industries face unprecedented challenges in its quest to bring innovative new medicines to patients. The challenges include patent expirations, restrictive reimbursement, greater regulatory scrutiny, the volatile political environment, and rapidly growing R&D costs and timelines.

New technological innovations also bring challenges to the way of operating and thinking of different stakeholders. This is the case in regenerative medicine, one of several developments arising from stem

cell research, which is seen as being capable of revolutionising healthcare and improving human health. More than impacting only in the regulatory aspects, there is the need to develop a better understanding of uncertainty and where and how value can be created and captured in the complex chains of such emerging technological platforms<sup>1</sup>. A sample analysis of Advanced Therapy Medicinal Products (ATMPs), medical devices and combination products is described in the following paragraphs.

### 2.3.1. Advanced Therapy Medicinal Products, ATMPs

Advanced Therapy Medicinal Products (ATMPs) include medicinal products originated from gene therapy, somatic cell therapy and tissue engineering<sup>2</sup>. These products are at the forefront of innovation in medicine and constitute great promise for the future of healthcare by providing diagnosis and treatment for several diseases. They include those for which there are currently no effective therapeutic options, such as cardiovascular and neurodegenerative diseases and organ failure. Coined in 2003, but fully regulated throughout Europe only since 2009, ATMPs are presently one of the most challenging and innovative pharmaceutical products being developed. This is because of their intrinsic extreme complexity in terms of characterization and control, due to the condition of being often human specific but also due to their dynamic mode of action (see **Box 4**). This not to mention the ethical issues they often rise.

**Box 4: Proposing key tools for technology hurdles in advancing stem-cell therapies**

The California Institute for Regenerative Medicine, Alliance for Regenerative Medicine and Cell Therapy Catapult Elona promoted, recently, a roundtable with the goal to discuss key technology hurdles that are slowing the commercialization of stem cell-based therapies and to propose potential solutions. Participants proposed a publicly accessible Tool Box providing validated, customizable solutions relevant to a large proportion of commercialization efforts (see **Figure 1**). They consider that it would catalyse rapid progress across the cell-therapy industry, by promoting constructive interactions between industry and academic researchers. A work only possible with a substantial financial investment, and support by all stakeholders.

Tool	Rationale
Master cell bank	The foundational cells must be derived in a controlled, documented, pathogen-free environment with appropriate consent and medical history documentation.
Raw materials	Materials contacting process intermediates or product must, where possible, be manufactured under cGMP and tested for quality.
Cell impurities quantification methods	Quantification of impurities is essential for demonstrating the safety of high-dose cell therapies.
Bio-preservation and supply chain systems	Refrigerated or ambient storage systems would enable worldwide distribution of cell products.
Scalable cell culture methods	Large-scale cell therapies require multi-thousand-liter, homogeneous culture systems and, for autologous products, robust platform processes.
Volume reduction methods	This unit operation bridges upstream and downstream processing with product formulation, fill, finish, and distribution.

Figure 1 – Suggested tools (left) and resources (right) for a Tool Box.

Source: Baum, E., Littman, N., Ruffin, M., Ward, S., & Aschheim, K. (2013). Key Tools and Technology Hurdles in Advancing Stem-Cell Therapies. (in alliancerm.org)

Regenerative medicine is now widely spread as an important field of application of ATMPs and can be broadly defined as the administration of cells or tissues to repair, replace or restore deficient or injured parts of the body. In 1996, the first ever cell-based product was approved for commercialization in the USA, consisting of cells for cartilage regeneration. It was followed by several skin substitutes, other

<sup>1</sup> See, for example, Tait, J., Bruce, K., Courtenay, A., Gregson, G., Lowrie, H., Mastroeni, M. Snowden, K. (2010). BUSINESS MODELS AND VALUE SYSTEMS FOR REGENERATIVE MEDICINE THERAPIES: RATIONALE AND METHODOLOGY.

<sup>2</sup> Sample References: Schneider et al. Nat Rev Drug Discov 2010;9:195-201.; Bertram et al. Tissue Eng Part A 2012;18:2187-94.; Plagnol et al.; Regen Med 2009;4:549-59. ; Ancans J. Front Immunol 2012;14:3:253.; Shmulewitz et al. Nature Biotech 2006;24:277-281.

cartilage repair products and bone substitutes for small defects, which include biomedical materials as support structures for tissue regeneration, with or without cells. In 2006, the regeneration of a whole organ was clinically demonstrated, namely the bladder, using a tissue engineering approach, which is known as a strategy involving the use of natural or artificial matrices colonized with cells and additional bioactive molecules such as growth factors. Tissue engineered blood vessels using autologous, and more recently allogeneic cells by *Cytograft Tissue Engineering*, or bladder reconstituted using autologous cells by *Tengion* are examples of products that were recently in the early phase clinical trials. But full maturity is already ascertained to those cell based products that target the wide market of regenerative medicine. In the EU, two marketing authorization have been granted to tissue engineered products composed of Chondrocytes for cartilage repair. Successful long-term results with these complex approaches will certainly pave the way to often-unmet medical needs.

The full potential of these products is foreseen, especially as combined products in association with other emerging technologies, such as nanomedicine, microfluidics, micropatterning, biofabrication, man-machine interfaces, among others. Such combined products pose an additional challenge on the regulatory agencies. New forms of medical treatment, the potential to change medical practice profoundly, the regeneration of diseased tissues and organs providing full functionality, improved healing processes, better quality of life and lower healthcare costs are among the most optimistic previsions. However, these new solutions impose regulatory progress and both EMA, in Europe, and FDA, in the US, are trying to keep up to the pace of technological development.

Besides regenerative medicine, noteworthy is the intense research regarding somatic cell medicinal products. Being developed for quite some time, cell based immunotherapy against cancer constitutes presently the largest number of clinical trials in Europe when classified by disease. One such product has been approved both in the US and the EU while some already reached phase III in Europe.

Gene therapy medicinal products are getting into a mature phase being used already in clinical trials with highly promising results, namely in monogenetic diseases. The first gene therapy product was recently approved in Europe for an ultra orphan enzyme deficiency. It is not surprising that GSK established a partnership to gain an exclusive license to develop an investigational gene therapy for ADA-SCID. *San Raffaele Telethon Research Institute* developed it with strong positive signals in phase I/II trials, allowing GSK to further access to a gene therapy platform and scientific expertise applicable for other genetic diseases.

### **2.3.2. Medical Devices and Combination Products**

Combination products of drugs and devices have been in the market for more than half-century. The metered-dose inhaler developed in 1955 is one of the earliest examples. Nevertheless, the increasing sophistication in combining drug-device products since then became a challenge. Regulatory bodies are adapting their structures and competencies, as well as developing specific guidelines and, for example, the *Food and Drug Administration* (FDA) established a new office in December 2002 – the *Office of Combination Products*. Combination products combine two or three single-regulated entities: drug, biological and/or medical device. They can be physical, chemical, or otherwise combined or mixed and produced as a single entity.

New regulations have contributed to clarify the approval process of combination products in the US. This flexibility did not impose regulatory constraints in the approval of tissue-engineered products where cells are combined with structural components under the medical devices office. In Europe, due to the limiting factor that medical devices cannot incorporate human derived materials, the new class of *Combined Advanced Medicinal Products* was legally established and the combination products became under the jurisdiction of the medicinal product domain. As such, regulatory path became clarified in Europe, but diverging product classification in US and Europe are associated with differences in clinical

development, which have been determinant for limited access of tissue engineering products to the global market (see **Box 5**).

**Box 5: Apligraf – a combination product**

Apligraf is a combination product, containing two types of cells – an outer layer of keratinocytes and an inner layer of fibroblasts within a matrix of collagen, in order to partially mimic human skin. It is used to heal ulcers such as diabetic foot and venous leg ulcers that are not healing after 3-4 weeks. Apligraf from Organogenesis was first approved in 1998 by the U.S. FDA as a medical device. It was later approved in Europe classified as a Combined Advanced Medicinal Product. This had a strong impact in clinical requirements, typically a medical device will require a single clinical trial for safety assessment, while a Combined Advanced Medicinal Product will take a longer clinical path in demonstrating safety and efficacy. This difference is determinant for companies capitalizing on their investment; it defines the time need for marketing authorization. The challenges for this pioneer product revealed to be more than regulatory, but also manufacturing and business challenges. Organogenesis filed for bankruptcy in 2002 because sales never exceeded \$20M per year and the company did not achieve profit. According to Geoff MacKay, Organogenesis' CEO, the company came back from bankruptcy in 2003 with essentially the same product, but a renewed business strategy, and became the first company with a cell-based therapy to achieve profitability ([www.organogenesis.com](http://www.organogenesis.com), A conversation with Geoff MacKay). Since then, the company grew to over 500 employees, exceeded \$100 million in revenue and has shipped over 500,000 units for patients care. This is the most widely used cell-based product in the world today.

Source: [www.organogenesis.com](http://www.organogenesis.com)

## 2.4. Regulatory Exemptions: the example of Orphan Diseases

The variability of technologies and diseases under the umbrella of regulators is increasing significantly. New categories of products, as ATMPs, include different technological platforms. For example, gene therapy is creating therapies to a new set of diseases. As a result, regulatory frameworks in many regions worldwide are adapting to this reality by creating specific frameworks to different technologies and diseases, resulting in bottlenecks or opportunities, while required approaches tend to be case-to-case. An example of these exemptions is the *Orphan Designation* of diseases, which is shaping the process of clinical innovation and translation.

The *European Organization for Rare Diseases* (EURORDIS) estimates that there are between 5,000 and 7,000 distinct rare diseases, and 6% - 8% of the EU population is affected by one of these diseases. *Orphan Designation* is a special incentive granted by regulatory authorities to companies developing new therapies or drugs that affect rare diseases, given that it provides significant benefit over what is already existent.

In Europe, *Orphan Designation* is based on the criteria laid down in Regulation (EC) No 141/2000 (Article 3). To qualify for orphan designation, a drug must meet a number of criteria:

- a) it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating, or;
- b) the prevalence of the condition in the EU must not be more than 5 in 10,000, or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development, and;
- c) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

One notable incentive is the 10 years of market exclusivity in EU, or 7 in the USA, which can only be broken by other products with similar active substance demonstrating superiority. Another important incentive is the significant reductions on regulatory fees and tax incentives. But, possibly, the most attractive condition related to the orphan status is the possibility to “validate” a product or a technology

fulfilling the clinical demonstration on a smaller population in a narrow indication, later extending the authorisation to other non-orphan broader indications. This is especially relevant for those products that are obtained by complex and innovative manufacturing processes, including gene therapy medicinal products that use adeno-associated viral vectors to transfect the therapeutic gene (see **Box 6**).

**Box 6: The First Gene Therapy in the Western World, an Orphan Designation**

Glybera was the first gene therapy approved in the Western World. Glybera targets familial lipoprotein lipase deficiency (LPLD) an ultra-rare genetic disease, with severe complications to patients. As an ultra-rare condition, only 250 treatable patients were estimated to exist in Europe, smaller than the total patients need to perform a clinical trial. The marketing authorization request to EMA was constituted by preclinical data and data from only 27 patients in all clinical trial phases. It started with the initial submission in December 2009 that was turned down by the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Advanced Therapy (CAT) in June 2011. Also during re-examination later that year, one of the two committees maintained its negative position. Such news resulted in the bankruptcy of its initial promoter, Amsterdam Molecular Therapeutics, however it continued by the hands of uniQure. Finally, in January 2012, when the European Commission asked for re-evaluation of the application of Glybera for a more restricted use, namely for most severe LPLD patients, both CHMP and CAT gave their consent. This complex process clearly illustrates the challenges of dealing with an ultra-orphan disease and thus very small patient numbers. Furthermore, the complexity of the dataset and the definition of the endpoints were likely important issues. Although, EU approval for the use of Glybera is narrow than originally planned by UniQure and the regulatory authorities obliged the company to monitor and report on the patients' outcome.

Source: Büning, H. (2013). Gene therapy enters the pharma market: the short story of a long journey. *EMBO molecular medicine*

### **3. Uncertainty and risk governance in health care: stakeholder engagement, social perception of risk and decision-making**

This chapter introduces the rationale behind regulation, together with an inherent uncertainty and the need of risk governance in association to multiple dimensions in health care innovation. It considers the relative relevance of processes of stakeholder engagement in driving technological innovation, with supporting examples at different levels. In addition, the need to consider processes of public awareness and the social perception of risk are discussed. Under this context, the paragraphs below also briefly explore processes of decision-making and the importance of expert training and opinion leaders in the development of efficient regulatory frameworks.

#### **3.1. Uncertainty and Risk Governance practices**

Biotechnology was expected to disrupt drug discovery, manufacturing, and regulation, but very often it has adapted to traditional processes of drug development. This is partly due to the inherent uncertainty and the need of adequate risk governance practices. How to make decisions under risk and uncertainty remains a fundamental challenge in the process of new drugs and therapies.

This is primarily because there exists no *rule of thumb* as to the level and nature of acceptable risk, in spite of the extent of multi-stakeholder dialogues. The availability of relevant information across decision contexts also varies and, for instance, it is hard to impute a value on human life, health and happiness. To inform decisions, patients, physicians, scientists, managers and politicians should address these uncertainties by exercising sound technical, economic and ethical judgments.

Technology development strategies and risk governance policies are commonly treated as separate spheres, and this has driven several new initiatives worldwide, including the “International Risk Governance Council”, IRGC (<http://www.irgc.org/>). According to Kenneth Oye, precautionary approaches to risk governance displace or forestall technological innovation. Past examples include EU fears on food GMOs and US limitations on embryonic stem cell research. In other cases, risks are under-addressed until health, environment, and/or security interests are compromised, with public alarm limiting acceptance. Past examples include US stasis on gene therapy after early patient deaths. Neither approach is satisfactory.

Still regarding applications to pharmaceuticals, the number of new molecular entities emerging from developmental and licensing pipelines has been declining, and the cost of drug development has been rising. As mentioned above, extraordinary advances in the life sciences have not been matched by corresponding advances in pharmaceuticals. This calls for the need to better exploring the governance of risks, efficacy, and effectiveness of drugs and advanced therapies and the way they affect pharmaceuticals innovation.

Overall, a systematic approach to organizational and policy learning is required in institutional settings that are conducive to improving risk management and make risk communication more effective. The paragraphs below address these issues under three main perspectives: i) processes of stakeholder engagement; ii) Public awareness and the social perception of risk; and iii) decision-making and the importance of expert training and opinion leaders.

#### **3.2. Stakeholder engagement towards health care innovation**

The IRGC risk governance framework augments the classical model of risk analysis (risk assessment, management, communication) by including steps of pre-estimation, interdisciplinary risk estimation, risk characterization and evaluation, risk management, as well as monitoring and control. At each of these



phases issues of uncertainty play a major role. The inclusive nature of the risk governance framework suggests different communication and involvement strategies for each phase of the governance cycle. This assists risks managers to address different aspects of uncertainty and ambiguity in relation to the nature of the problem and the specific needs of the stakeholders in each phase of the governance process.

Related modifications introduced by new forms of R&D organization are becoming a reality. Besides industry, other stakeholders are likely to play a more active role in the development of new drugs and cell therapies. Patients, physicians, hospitals and research universities are examples of more active sponsors, either at individual or institutional levels. Their involvement can be associated with the need to consider complex and modern technical infrastructures, but it also increasingly depends on the nature of modern health sciences. Physicians and hospitals are playing a more active role in their development and providing feedback for technological improvement. Universities and hospitals are playing active roles in new forms of clinical trials while patients engagement are increasingly relevant in determining the success of new therapies.

It is under this context that patients are also becoming central to regulatory systems, together with an active role in the process of innovation. The relevance of patients' engagement surpasses their role as "recipients" and it is becoming a vital part of clinical research, namely through patient associations (see **Box 7**).

#### **Box 7: The role of Patients Associations in Health Care Innovation**

"The emergence and empowerment of patient organisations has a long history in most Western countries, dating back to the 1940s and 1950s when the first organisations for people with chronic diseases were founded. [...] Patients with the same disease become aware of the similarity of their individual experiences; they are no longer alone, for they have alter egos with whom they share a collective identity. [...] Patients consider that their shared experience constitute knowledge of their diseases that is different from professional knowledge but essential for understanding and improving their condition. [...] With their special concern about their disease, patients consider it legitimate to have a say in decisions concerning their situation."<sup>1</sup> "In France in the 1950s, haemophilia and diabetes led to the first associations being created to lobby doctors and public authorities in order to improve everyday conditions for patients. [...] In many countries the fight against AIDS constitutes a paradigmatic example of transformations in patients' individual and collective relationships with the medical world."<sup>2</sup> "The arguments brought to bear in the public debates about AIDS groups, the role of the media, or the ethics of clinical trials have often referred to their supposed experience of health care and of the information surrounding their treatment. [...] The ethics and methodology of clinical trials are another source of polemical debate, bringing to light the strongly contrasting concepts held by the specialists (doctors and statisticians) regarding the relationship between scientific knowledge and clinical practice."<sup>3</sup>

Source: <sup>1</sup>Rabeharisoa, V. (2006). From representation to mediation: the shaping of collective mobilization on muscular dystrophy in France. *Social science & medicine* (1982), 62(3), 564–76. ; <sup>2</sup>Barbot, J. (2006). How to build an "active" patient? The work of AIDS associations in France. *Social science & medicine* (1982), 62(3), 538–51; <sup>3</sup>Barbot, J., & Dodier, N. (2002). Multiplicity in Scientific Medicine: The Experience of HIV-Positive Patients. *Science, Technology & Human Values*, 27(3), 404–440.

Patients are often highly motivated to have a role in the innovation process. For instance, patients of chronic diseases have to deal with long-lasting conditions and everyday challenges. They have been shown to develop valuable innovations in medical treatments and devices to improve their quality of life and even treat their own disease; sometimes even saving their own lives<sup>1</sup> (see **Box 8**).

<sup>1</sup> Habicht, H. and Oliveira, P. and Shcherbatiuk, V. (2012), User Innovators: When Patients Set Out to Help Themselves and End Up Helping Many. *Die Unternehmung*, Vol. 66, Issue 3, pp. 277-294, 2013; Oliveira, P. (2013), "Users as Service Innovators," in K. Lakhani and D Harhoff (eds.), *Revolutionizing Innovation - Users, Communities and Open Innovation*, MIT Press;

**Box 8: Patient Innovation – a social network to diffuse innovations created by patients**

*Patient Innovation* is a non-profit international, multilingual and free platform<sup>1</sup>, designed to allow patients and caregivers to show and share their answers and practical solutions developed to fight their diseases. By sharing, patients may help themselves and others, stimulating value creation from the network effect – the contributions of others for the same solutions or alternatives helps create a unique database of solutions developed by patients with different diseases. This database is searchable by diseases, solutions and symptoms, and is self-managed by patients. Prestigious institutions and reputable individuals, including several Nobel Laureates, distinguished scholars and associations of patients and caregivers, have endorsed this project.

Source: <sup>1</sup><http://www.patient-innovation.com>

The challenge of processes of stakeholder engagement is on articulating different institutions, individuals and their specific goals. In the case of clinical translation, it has been promoted in many regions worldwide through the creation of knowledge networks to support efficient processes, and habilitate infrastructures and human capital. The example of IATA, in Andalusia, is worth noting in terms of a public initiative at regional level (see **Box 9**). Still in this regard, *Health Cluster Portugal* is a positive example of engaging stakeholders at national level (see **Box 10**).

**Box 9: The Andalusia Initiative for Advanced Therapies (IATA): fostering translational biomedical research**

The “Andalusia Initiative for Advanced Therapies, was established to promote the development of new therapies to improve the population’s health and to incorporate innovative advanced therapies in the health care and progress of our region. To do this we seek alliances with the academic world, research institutions, health centers, patients’ associations, small and medium enterprises, and the pharmaceutical industry. This requires us to identify, organize, and provide the support needed to maximize the development of multidisciplinary research in the field of advanced therapies in Andalusia. By facilitating the training of technologists and basic and clinical researchers, and by fostering translational research in this field—as well as promoting the generation of a business structure beneficial to such research—we hope to ultimately provide a source of wealth for the region and enable the potential benefits of advanced therapies to be passed on to the population in as short a time as possible. [...] defining our strategy and action plan involved seven working groups, an advisory committee, and a governing committee composed of scientific leaders, clinical researchers, research managers, representatives from patients’ associations, and responsible parties from both the public and the private sectors.”

Source: Cuende, N. (2013). Andalusian Initiative for Advanced Therapies: Fostering Synergies. *Stem cells translational medicine*, 2(4), 243–245.

**Box 10: Health Cluster Portugal – engaging stakeholders towards a common vision**

Health Cluster Portugal (HCP) ([www.healthportugal.com](http://www.healthportugal.com)) brings together over 130 organizations, including universities, R&D institutions, hospitals and companies in the areas of pharmaceuticals, biotechnology, medical technology and services. All these stakeholders are engaged towards a common mission: to strengthen the competitiveness of Portugal in the research, design, development, manufacturing and commercialization of health-related products and services, in selected market and technological niches, targeting the most demanding and relevant international markets, based on the recognition of its excellence, technological level and competences in the field of innovation. The health sector in Portugal has experienced remarkable gains in terms of quality and competitiveness during the last couple of decades, and factors such as the historically prevalent lack of cooperation amongst the stakeholders and the limited investment in innovation are progressively being reverted. Under the auspices of HCP, academia, industry and hospitals are, more than ever before, working together in the creation of health and wealth.

Source: Health Cluster Portugal, 27 September 2013

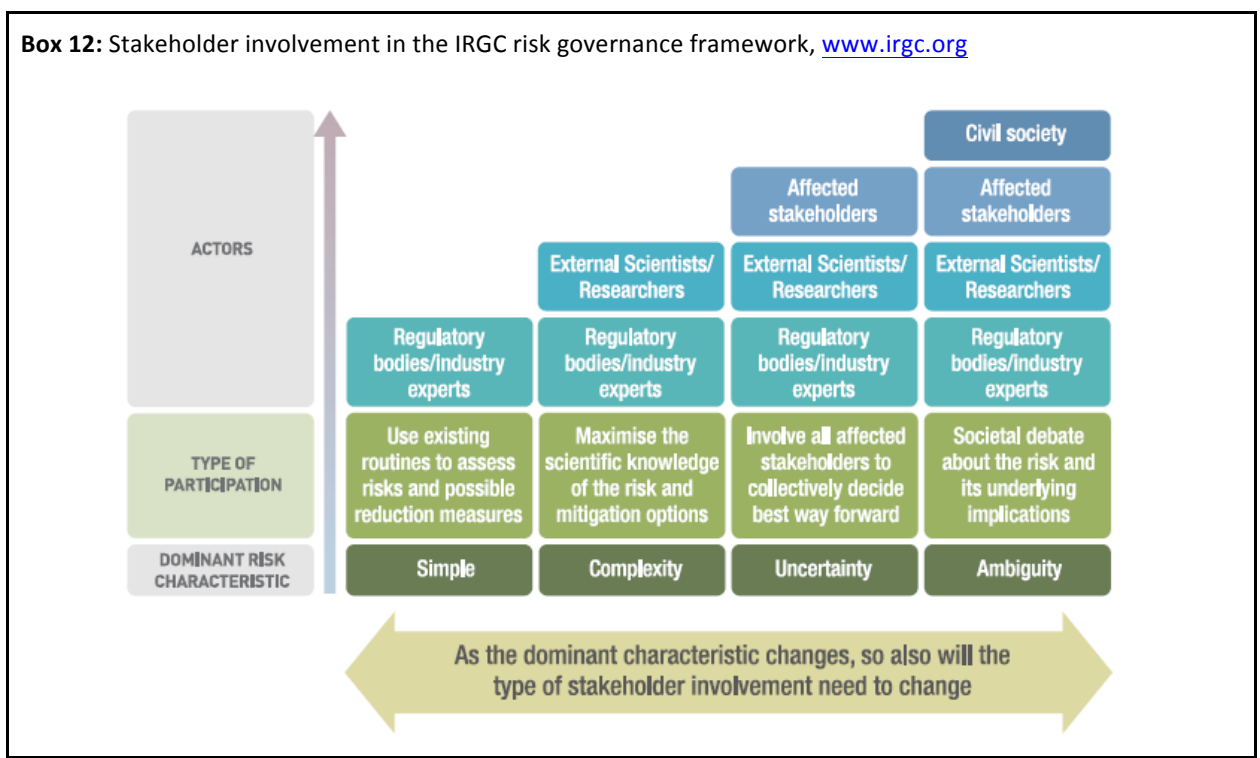
Other major initiatives to help engaging stakeholders in innovative biomedical research are also found at the European level (see **Box 11**), bringing together patients, governmental bodies, regulatory agencies and funding bodies, to name but a few. The social acceptance of these evolving patterns provides an illustrative example that drug development can be challenged and successfully adapted. We shall take this as an inspiring example in aligning new product and firm development to emergent challenges.

**Box 11: European Advanced Translational Research InfraStructure (EATRIS) – engaging stakeholders in knowledge networks in Europe**

“A number of European countries decided to establish EATRIS. EATRIS aims for faster and more efficient translation of basic research into innovative products, by providing academia and industry access to the state-of-the-art expertise and highly capital-intensive facilities residing in Europe’s top translational research centers and hospitals.” EATRIS offers a platform for debate and interaction between all the stakeholders in translational research, and operates around five focus areas - the Product Platforms - namely Biomarkers, Imaging & Tracing, Advanced Therapy Medicinal Products, Vaccines and Small Molecules. Portugal is member of this network.

Source: Dongen, G. A. Van, Ussi, A. E., Man, F. H. De, & Migliaccio, G. (2013). EATRIS , a European initiative to boost translational biomedical research. *American Journal of Nuclear Medicine and Molecular Imaging*, 3(2), 166–174.

The main objective of involving stakeholders is to prepare better decisions. It is meant to improve the understanding of the rationale behind people’s interests, motivations and decisions. In risk-related matters, stakeholder involvement should not be seen as an attempt to convince or persuade people to adopt the judgement of the risk manager or communicator about the tolerability or acceptability of risks. It is rather the attempt to help people to make better-informed judgments and enable them to control the risks that they face in their own lives. When the general public is involved, in public participation programmes, it is an opportunity for all citizens to take an active part in contemporary discourses about matters such as modern technologies, economic activities or other collective risk bearing events such as the codetermination of projects for designing and shaping our natural and social environment. Stakeholder involvement and citizen participation are hence key topics in risk governance and management.



### 3.3. Public awareness and the social perception of risk in health care

We now turn to issues of public awareness and the social perception of risk. Public discourse about risks is part of a broader societal debate over social concerns, ranging from social justice to societal responsibility for personal growth and well-being. Regulatory agencies as well as industrial representatives are expected to participate in such debates, as this is part of the legitimizing efforts of social forces in a plural society. At the same time, issues of ambiguity in risk management demand discourse-based activities that provide reassurance to each actor that all views are taken into account and that provide sufficient incentives for reaching common grounds or, even, a common consensus.

Data from Eurobarometer 2011 show that 75% of EU citizens feel positive about science and two thirds believe that science is making their lives healthier, easier and more comfortable. But, since 2005, the share of Europeans experiencing broad trust in science has declined from 78% to 66%. Interestingly, much of the data shows that their trust in scientists and knowledge-producers continues to be extremely high (at the top of most lists). But that their trust in the mechanisms that lead to the application of new knowledge in particular domains remains quite low. There are probably several reasons for this, one of the most important being the complex nature of our perceptions regarding risk.

Several factors have a strong impact on our understanding of risk. Among them, we can certainly list the following:

- a) What is the current state of knowledge and, even more relevant, what are the uncertainties (kind and level) associated with the outcome of the interaction between the components of complex systems;
- b) Whether there is any evidence that control mechanisms (natural or man-made) are either sufficiently robust or remain fragile in dealing with unpredictability;
- c) To what extent do we trust the institutions and/or the individuals that are providing the information needed for the decision process;
- d) Issues such as equity (who benefits?), governance (who controls?), personal involvement (do I have a choice?) and many others.

Sympathy or aversion towards risk by individuals is clearly determined by a complex combination of these factors (see, for example, the evidence provided in **Box 13**). Their relative weight varies considerably among citizens in different countries. While some observers are convinced that better communication would help clarify many of the unresolved issues, particularly those associated with trust, the empirical evidence for this claim is not particularly convincing. Transparency in decision-making and an effective interplay of checks and balances are just as important.

The emergence of disruptive and promising technologies in health care imposes new challenges to the role of patients in the process of innovation, as discussed above. The information of the population regarding these new potential therapies shapes the acceptance of participating in clinical trials and supporting initiatives of clinical translation. Clinical trials are an essential part of the current development of new treatments, and are managed to constitute a minimal exposure to risk. However, knowledge of the risks associated to some new therapies is yet limited. It is crucial the awareness of patients of the risks taken when exposing to clinical trials, but mainly the benefits of going into it, as they are essential to enable innovative technologies into clinic.

Regulators are likely needed to invoke precautionary principles increasingly often as risk analysis of advanced science-based therapies become more complex and more long-term. However, it is clear that they need to learn to use precautionary principles more effectively so as to treat the various issues and stakeholders in the new drug and new therapies debate in a balanced way. The increasing role of patient associations (as mentioned above), among other stakeholders, was only recently acknowledged as a step forward in empowering patient decisions in the European authorisation process at EMA,

among those organisations participating actively in the specialised committees for Advanced Therapies and Pharmacovigilance.

**Box 13: Frustrated Amyotrophic Lateral Sclerosis (ALS) patients manufacture their own drug**

“Some patients with fatal Lou Gehrig's disease, frustrated by the slow pace of clinical drug trials or unable to qualify, are trying to brew their own version of an experimental compound at home and testing it on themselves. [...] The patients who are experimenting with these do-it-yourself drugs say it is a calculated risk worth taking, given the average life expectancy is only two to five years after diagnosis and there are no effective treatments. Many patients say they want to slow down the progression of the disease, in hopes that an effective therapy will be found in time to save their lives. [...] Around 28 patients have shared data at the site run by PatientsLikeMe (found on <http://www.patientslikeme.com/>), a Cambridge-based health-data-sharing company that helped analyse results and publish findings from a do-it-yourself drug trial involving lithium. Jonathan D. Glass [...] is one of the NP001 site investigators. He said he is concerned that "these people could hurt themselves. Who knows what they are actually making in their kitchen." He says patients need to work with doctors and regulatory officials to find ways to speed up the drug development process. "I feel their pain that they really want it to happen faster, but I don't think you can do it without the medical establishment," he said.

Source: Marcus, A. D. (2012, April 15). Frustrated ALS Patients Concoct Their Own Drug. The Wall Street Journal. Retrieved from <http://online.wsj.com/article/SB10001424052702304818404577345953943484054.html>

The involvement of patients in the regulatory process has to be viewed as focused in the patient's health and, above all, as a process fostering the social perception of risk. Unregulated shortcuts are examples of an unmet fit of regulations to individual risk perception (see **Box 13**), and in extreme situations, an unbalanced risk perception supports a prejudicial tendency to ignore the rationality, which shape current regulatory frameworks. At European level, several initiatives took place over last years to adapt European and National regulatory frameworks to new advanced therapies. For example, simplified (national) approaches have been introduced in legal frameworks of innovative products on a named patient basis in order to facilitate introducing early phase developments.

However, it is found that several nations worldwide (including in Europe) fail to establish/ implement adequate mechanisms and/or lack supervision (see **Box 14**), or demonstrated (publicly and deliberately) some complacency with the use of unproven therapies (see **Box 15**).

**Box 14: A case study: relative failure of European mechanisms of regulatory compliance on cell therapy**

Few reports exist on the operation of not approved cell therapy clinics, but one of these examples came to light after the close of the biggest cell therapy clinic operating in Europe, XCell. “The closure of the XCell-Center in Dusseldorf follows an undercover investigation by The Sunday Telegraph into its controversial practices, which attracted hundreds of patients from the UK. The clinic charged patients up to £20,000 for stem cell injections into the back and brain despite a lack of scientific proof that the treatments actually worked. While most other European countries - as well as the US, Canada and Australia - have banned stem cell treatments unless shown to be safe and effective, XCell had exploited a loophole in German law allowing it to charge for the experimental procedures. [...] The clinic had come under increasing scrutiny following the death of an 18-month-old boy. [...] The centre had previously had permission to practice for a transitional period because it was already up and running when a law came into force in 2009 banning the commercial exploitation of unproven stem cell treatments. It appears German authorities have now decided to close the loophole with immediate effect. They deny the law has changed and sources suggested they decided abruptly to re-interpret it instead.”

Source: Mendick, R., & Hall, A. (2011). Europe's largest stem cell clinic shut down after death of baby. The Telegraph. Retrieved from <http://www.telegraph.co.uk/news/worldnews/europe/germany/8500233/Europes-largest-stem-cell-clinic-shut-down-after-death-of-baby.html>;

**Box 15: European (De-)Regulation on Cell Therapy**

“Clinics that offer unproven stem-cell treatments often end up playing cat and mouse with health regulators, no matter which country they operate in. In Italy, however, one such treatment now has official sanction. The country’s health minister, Renato Balduzzi, has decreed that a controversial stem-cell treatment can continue in 32 terminally ill patients, mostly children — even though the stem cells involved are not manufactured according to Italy’s legal safety standards.”<sup>1</sup> Months later, “parliamentarians further eroded protection for vulnerable patients targeted by stem-cell companies. On 10 April, they amended an already controversial ministerial decree with a clause that would redefine stem-cell therapy as tissue transplantation, thereby releasing it from any regulatory oversight. If the second parliamentary chamber endorses this amendment, Italy will be out of step with the rules of the European Union and the US Food and Drug Administration, both of which define stem cells modified outside the body as medicines.”<sup>2</sup> “The Italian case is the first in which unproven ‘stem cell therapies’ may be de facto made legal, rather than being stopped by regulatory bodies and the government.”<sup>3</sup>

Source: <sup>1</sup>Nature 495, 418–419 (28 March 2013); <sup>2</sup>Nature 496, 269–270 (18 April 2013); <sup>3</sup>Bianco, P., Barker, R., Brüstle, O., Cattaneo, E., Clevers, H., Daley, G. Q., ... Smith, A. (2013) Regulation of stem cell therapies under attack in Europe: for whom the bell tolls. The EMBO Journal, (32), 1489–1495.

The active involvement of patient organisations and the need to provide clear information for an informed decision is crucial for the good conduction of personalised medicine, namely for the authorisation process of autologous products that are manufactured from patients cells or tissues.

### 3.4. Decision-making in health care innovation: Expert training and opinion leaders

Despite the fact that biotechnology has been at the forefront of science policy worldwide, and has been both financed through both public and private funds in many world regions, successful new bio-industries are concentrated in few and very specific locations (or ‘bio-intensive hot spots’). More biotechnology companies were created in California and Boston than the rest of the world together. How far this is affecting public health beyond those regions? Are social and historical contexts impacting the development of new products and therapies across countries and regions?

It is clear that the dynamics of the geography of innovation is a complex technical, economic and social process, mainly resulting from a long path of technical change and the accumulation of a knowledge base over many decades, together with large investments in that knowledge base. As a result, decision-making in health care innovation is particularly important in those “less-favoured” regions (including Portugal and other southern European regions), where expert training and opinion leaders are playing a critical role in dealing with existing uncertainty.

It is under this context that the role of the regulators in those regions is becoming critically important to foster health care innovation and help harnessing knowledge, technology and innovation towards sustainable public health (see **Box 16**). These mechanisms are likely to have a strong impact in the next decade in stimulating the adoption of new and advanced therapies, as well as new drugs, being the target of a discussion to guarantee expert training in the regulators, as well as in academia and firms.

On the other hand, it should be noted that clinical practice is constantly questing for innovative approaches. Often those good practices generate ideas that remain hypothetical in part due to the absence of a clear view from academic and clinical staff about *where* and *how* to proceed within a regulated environment. Clinical expectations have to make their case and the process to do it follows codes of good practices that require previous knowledge of the many issues related to regulatory affairs.

**Box 16: Regulatory Authorities Guiding Innovation – the case of INFARMED in Portugal**

Cell2B is a Portuguese-based biotech developer of cell therapies for immune and inflammatory diseases. It was incorporated in 2011 with technology developed by its founders and licensed from the Massachusetts Institute of Technology (MIT) in Boston and Instituto Superior Técnico (IST) in Lisbon. The leading product, ImmuneSafe® is being developed based in the orphan designation that has been granted in Europe for the treatment of Graft-versus-Host Disease. INFARMED has assumed a strong role in supporting Cell2B development as other SMEs. The first scientific advice was requested in 2010 when seeking regulatory clarification about a cell-based therapy classification. Since then, multiple scientific advice meetings were requested on the GMP facility planning and functioning and in preparing the Request for Orphan Designation and Scientific Advice with the European Medicine Agency. INFARMED is assuming a strong role in supporting and preparing SMEs in developing their technologies and manufacturing units. Also, they are a key element to consult with and request advice before approaching the centralized authorities, namely the European Medicine Agency.

Not particular to Portugal, but as relevant as elsewhere, academic and translational research should be strongly supported by opinion leaders, while regulatory practices and related expert training is developed at a stage where it can be well assimilated and used by various stakeholders. For example, the tendency for “paternalistic regulations and behaviours”, in the absence of adequate expertise, may give rise to different and unexpected outcomes (see **Box 17**). This strengthens the uncertainty under which the introduction of basic regulatory concepts is very critical to all those that deal with pharmaceutical domains and health care innovation.

**Box 17: Regulation for conservatives: behavioural economics and the case for “asymmetric paternalism”**

“Paternalistic regulations that are designed to help on an individual basis. Paternalism treads on consumer sovereignty by forcing, or pre-venting, choices for the individual’s own good. [...] Recent research in behavioral economics has identified a variety of decision-making errors that may expand the scope of paternalistic regulation. To the extent that the errors identified by behavioral research lead people not to behave in their own best interests, paternalism may prove useful. But, to the extent that paternalism prevents people from behaving in their own best interests, paternalism may prove costly.”

Source: Camerer, C., Issacharoff, S., Loewenstein, G., O’Donoghue, T., & Rabin, M. (2003). Regulation for conservatives: behavioural economics and the case for “asymmetric paternalism.” *University of Pennsylvania Law Review*, 151(1211), 1211–1254.

## 4. Enabling modern clinical research and practices towards sustainable public health

This chapter discusses the critical role of clinical research in the context of new and evolving regulatory frameworks. This is because local capacity for clinical research is determining the impact of any modern legal framework, as well as critically influencing the attractiveness of any region for innovation in health care (including private funding from pharmaceutical and other industries). To face the challenges in clinical translation, industry and regulators (and also patient organisations) are committed in advances at the level of clinical research. Developments regarding procedures and design of clinical trials aim to reduce related burdens and improve the efficiency of clinical translation of new drugs.

Next section explores current clinical research frameworks, stressing current changes in European and Portuguese legislations of clinical trials. Then, we focus on the need to develop regulatory science. The chapter concludes by briefly discussing emerging technology challenges, with emphasis for medical devices, ATMPs and nanotechnology.

### 4.1. Promoting and strengthening clinical practices for research and trials

The design of Clinical Trials (CTs) is being continuously challenged by improvements in regulatory science and by attempts to promote flexibility of regulators and regulation, without affecting safe operation.

New strategies tend to increase the likelihood that data collected during a clinical trial will demonstrate the effectiveness of drugs (see **Box 18**). Better understanding of pathologies leading to personalized therapies is helping drug promoters to better target their clinical trials. Recently FDA provided a draft guidance regarding the use of such strategies known as *clinical trial enrichment*. Such improvements, although beneficial to a successful clinical translation, are only possible when articulated with the regulator and legal approvals of CTs. It is therefore necessary to create conditions so that data extrapolation is scientifically credible and valid to support medicines authorization (e.g., a clear effort in the use of the results from PK/PD models and from animal testing in clinical trial simulations are surely a possible way ahead).

New technological advances at this stages, as the use of simulations, allow to design more efficient trials and modelling processes will enable both efficacy and safety extrapolations. They may also facilitate designing clinical trials towards more efficient and predictable practices. Acceptance of biomarkers, instead of the classic endpoints in trials, may also be considered and accepted on a case-by-case basis by authorities.

In addition, advances in clinical research have to be complemented and matched by CTs frameworks, as an essential component of medical research, being one of the greatest focuses of attention in modern health care innovation. Clinical Trials provide evidences of safety and efficacy prior to approval by competent authorities in order to become available to patients who need them. *Good Clinical Practice* (GCP) guidelines join the individual trial subject's rights, ethical principles and general standards to be respected in CTs.



**Box 18: Four ways to fix the clinical trial**

“Although a promising compound can fail for many reasons, from safety concerns to corporate decisions, many say that a significant number of good drugs are being lost to outdated and impractical clinical-trial designs (see ‘The clinical-trial cliff’). The drugs may work, says Lillian Siu, an oncologist at Princess Margaret Hospital in Toronto, Canada, “we just don’t know how to test them appropriately. Solving the problem may require fundamental changes to the clinical-trial system to make it faster, cheaper, more adaptable and more in tune with modern molecular medicine. [...] Patient recruitment has been a major stumbling block. At least 90% of trials are extended by at least 6 weeks because investigators fail to enrol patients on schedule. [...] The result: longer, more expensive trials — some of which may never be completed. [...] forming networks are likely to face technical barriers. They need to develop appropriate patient-consent forms, unified databases and ultra-secure networks to connect hospitals. [...] In 2006, the FDA and EMA introduced guidelines for testing very small ‘microdoses’ of drugs in humans. [...] Proponents of phase 0 testing argue that it makes sense to get human data quickly. About one-quarter of the molecules entering clinical trials fail because of “poor pharmacology” [...] Although phase 0 trials could help to wean researchers off pharmacology studies in animals, moves are also afoot to bring mouse experiments closer to the clinic. [...] Pier Paolo Pandolfi, a cancer researcher at Harvard Medical School in Boston, has therefore pioneered a technique called the ‘co-clinical trial’, in which mice with similar disease characteristics are treated in a similar way to the humans. [...] looking just once at the data is “like driving home from work and only opening your eyes once to see where you’re going”, says Donald Berry, a statistician at the MD Anderson Cancer Center. Berry specializes in designing ‘adaptive’ trials, which can change course as the data roll in. If one treatment regimen seems to be more successful, for example, researchers might increase the proportion of participants that should receive that treatment. These trials can also be used to identify biological markers, such as mutations or altered metabolite levels, associated with the success or failure of a given regimen. [...] While researchers dream up new, better ways to design clinical trials, many involved acknowledge that the changes with the biggest impact will probably be more bureaucratic than conceptual. Simply standardizing the forms used to record clinical-trial data would reduce costs and cut down on record-keeping errors and omissions.”

Source: Ledford, & Heidi. (2011). 4 ways to fix the clinical trial. *Nature*, 477, 526–528.

#### 4.1.1. The evolving regulatory pattern of clinical trials in Europe

Clinical research is being the subject of extensive analysis at European level to strengthen attractiveness for clinical trials in Europe. Initiatives towards new legislation for clinical trials are ongoing and main challenges can be summarized as follows:

- to help reducing administrative burdens for conducting clinical trials, avoiding redundancy of procedures at national and Community levels;
- to maximize the level of harmonization in practices and interpretations at Community level, and expedite the evaluation of clinical trials for all member states.

To achieve these objectives, the new proposed regulation foresees several changes, including submission of a single *Clinical Trial Application* (CTA) with defined and harmonized requirements through a single-EU Portal electronic submission. It provides access to an information system for clinical trials, integrated at EU level, and improves transparency about the recruitment of participants in a clinical trial and the results of the clinical trial.

The draft regulation under discussion also establishes a clear distinction between aspects where Member States cooperate in the assessment and other issues of an intrinsic ethical or national/local nature, where the assessment is made by each Member State individually (e.g. liability, informed consent, suitability of clinical trial site etc.). Besides these aspects, some other innovative aspects of this legislative proposal should be highlighted, introducing a proportionality approach to risk, and changes to insurance rules and compensation, as well as (co) promotion and inspections.

This draft regulation completed its first reading in the Council and the Report of the ENVI Committee of the European Parliament was approved and published.

#### **4.1.2. The evolving regulatory pattern of clinical trials in Portugal**

Directive 2001/20/EC has brought important improvements in the safety and ethical soundness of clinical trials in EU and in the reliability of clinical trials data. However, despite the efforts of that Directive to generate harmonized environment for ethical review in Europe for CTs with investigational medicinal products, its national implementation resulted in different outcomes regarding ethical reviews. It resulted in a complex preparation of applications and a rather difficult integration of opinions regarding one protocol for sponsors of multinational clinical trials. All stakeholders - patients, industry, and academic research - voice this criticism.

Directive 2001/20/EC was transposed in Portugal into local legislation in 2004 (Law nº. 46/ 2004, of 19th of August). Nevertheless, the directive national implementation did not reduce the administrative burden or the already lengthy timelines for implementing and conducting clinical trials in Portugal. In fact, the decline in the number of clinical trials conducted in Portugal, when compared with other EU countries, reveals the loss of progressive competitiveness. It is necessary to recover efficiency and implement new measures to promote clinical research and trials activity.

Various stakeholders involved in the process met to identify obstacles to the development of clinical research. They include several initiatives of INFARMED (which led to PNEC, the national platform for clinical trials) and, recently, a study conducted by *PriceWaterhouseCoopers* for APIFARMA, as discussed by key stakeholders at a meeting on "Clinical Research in Portugal". All these exercises have identified weaknesses and opportunities to improve, including: i) to reduce timelines between CTAs and beginning of patient recruitment; ii) to improve sites capabilities and competencies to conduct clinical trials by creating dedicated structures; and iii) to create and foster incentives for clinical research and related healthcare professionals.

It is under this context that a new national legal framework for clinical research is being discussed in Portugal. INFARMED held in 2012 an enlarged meeting with various stakeholders to facilitate a consensus position and a draft legal document about clinical research is under discussion (Law proposal nº 146/XII), addressing many areas of clinical research (including medicines, medical devices and cosmetics, among others). It is based on the following key measures:

- a) A new framework for clinical research;
- b) A national network of ethics committees;
- c) A national register of clinical trials;
- d) Shorter time required for evaluation and decision;
- e) Rationalization and streamlining the approval process for clinical trials.

This framework will promote the role of the *Ethics Committee for Clinical Research* (CEIC) and the *Ethics Committees for Health* (CES). It will create a *Clinical Trial's National Network* (RNEC) to try to facilitate information transmission during the process, as well as increase access and knowledge about the clinical trials conducted in Portugal. Nevertheless, some aspects of the current proposal still create some concerns that are important to highlight:

- a) Specific and dedicated infrastructures need to be implemented in order to have any regulatory framework in full effect. A clear transition plan should be defined in order to avoid jeopardizing current CTs approval and avoid unattractive environment for new CTs.
- b) Following the process of other EU countries, the *Ethics Committee for Clinical Research* (CEIC) should not be involved in assessing financial contracts. This can cause an unnecessary additional step, creating time constraints. Current inspection procedures should guarantee full transparency and accountability.

- c) Timelines should be reviewed and aligned with EU guidance, which foresees one year for non-pediatric, and six months for pediatrics clinical trials, for sponsors to provide the clinical trials summary report.

In addition, it should also be noted that data protection committees in most EU countries are not involved in approvals of CTs, although the proposal under discussion still considers this additional step for Portugal. Also, no timelines are defined for evaluation purposes by the *National Commission for Data Protection* (CNPD) and it may not have the capacity to achieve competitive approval timelines following best practices in Europe.

Regarding capacity for CTs, it should be noted that much effort is ongoing to increase attractiveness of the clinical environment for more regulated trials (see **Box 19**), although the present scenario of trials is still very much oriented for late phase trials, missing the most innovative early phases. Changing this pattern and moving towards modern clinical research requires significant investments in new skills and procedures, including experimental material to be sufficiently studied and controlled to ensure safety of participating patients. While R&D funding has been adequately structured in the last decade in academy, clinical translation and research, particularly in hospitals, is still in its infancy and requires dedicated incentives and programs.

**Box 19: On the experience of Eurotrials in Portugal**

Based on the experience gained during the last 18 years on clinical trials implementation and management, it is clear that Portugal has an underexplored potential for developing good clinical research. However, positive experiences exist in *Eurotrials*. For instance, the recruitment in one site regarding the implementation of multinational, multicentre clinical trials in Cardiology area was very successful, comparing the recruitment worldwide, and is one of several examples in a wide range of areas. The Hospital Administration Board considered clinical research as a priority and the site has the equipment, the infrastructure, the dedicated clinical research team (study nurses, study coordinators, etc.), the organization and the motivation to ensure that a clinical trial is performed as committed. High patients' compliance, reduced patients dropouts rates from clinical studies, surely related with the patient doctor relationship culture, supported generally by medical records of quality represent also an important strength for the clinical research country selection.

Source: Eurotrials

In addition, it should also be noted is the increasing awareness on the importance and value of performing clinical research, both at public and health care professional level, mainly as result of various stakeholders work and investment in sharing information and training. It will be crucial for the recognition of Portugal as a relevant country for conducting clinical studies that such strategy and interest is extended to primary care units, where significant diseases and populations are followed and are still missed from the context of clinical trials.

Still to be addressed is the need to foster adequate research cultures in clinical practice, entitling health professionals to perform research as part of their scientific and professional development. The formation of independent research centres in hospitals should be encouraged and staffed with professionals that support a culture of ethical research and compliance.

Considering new trends on risk based monitoring, clinical research sites will also need to address organizational issues and to ensure efficient patient recruitment and related data entry timeliness and quality, with independency and reliability.

## 4.2. Developing regulatory science: a systemic approach to regulation

The role of regulatory authorities in the authorisation and supervision of pharmaceutical products is unquestionable - only regulated industrial products can enter the global market. In this regard, regulatory authorities are constantly challenged by an increasingly complex science driven decision

process that require specialisation, expertise and training. It is only achievable by a systematic approach to regulation and the adequate understanding of regulatory science as an upcoming discipline (see **Box 20**).

**Box 20: From molecule to market access: Drug regulatory science as an upcoming discipline**

“Regulatory science as a discipline has evolved over the past years with the object to boost and promote scientific rationale behind benefit/risk and decision-making by regulatory authorities. [...] building a regulatory framework that is not challenged continuously in terms of deliverables for public health and cost-effectiveness, might be counterproductive in the end. Regulatory science and research can help understand how and why regulatory decisions are made, and where renewed discussions may be warranted. The MEB supports regulatory science as an R&D activity to fuel primary regulatory processes on product evaluation and vigilance, but also invests in a ‘looking into the mirror’ approach. Along the line of the drug life-cycle, publicly available data are reviewed and their regulatory impact highlighted. If made explicit, regulatory research can open the door to evidence based regulatory practice and serve the regulator’s contribution to innovative drug licensing today.

Source: Gispen-de Wied, C. C., & Leufkens, H. G. M. (2013). From molecule to market access: Drug regulatory science as an upcoming discipline. *European journal of pharmacology*, 1–7. doi:10.1016/j.ejphar.2013.07.021

The authorisation process became progressively more complex as companies seek new tools. On quality development, quality by design approaches require data collection and processing with statistical tools that are not part of the armamentarium of regulatory authorities and require increased specialisation and burden to inspections. Decisions on bioequivalence or on comparability for biosimilars are also more and more based on statistical tools. Quality control is based on increasingly sophisticated equipment and data processing, leaving a narrow margin for market supervision activities based on analytical tools. New methodologies for safety are at stake. Very importantly, in 2009, the European Medicines Agency began a three-year project on benefit-risk methodology. The project aimed to identify decision-making models that can be used by regulators, to make the assessment of benefits and risks of medicines more consistent, more transparent and easier to audit<sup>1</sup>.

Involving regulatory bodies in continuous adaptation has become a critical step and, in this regard, FDA is a good example of a sound approach. Their critical path initiative in 2004 and their strategic program of 2011 set eight priority areas for FDA to advancing regulatory science<sup>2</sup>, which are interesting examples of a concerted strategy to ensure their access to relevant tools and expertise for a competent risk benefit decision. Such reorganization and adaptation is also taking place in recent years throughout Europe, namely at the European level, in EMA (see **Box 21**), and at the national level, in France (see **Box 22**).

**Box 21: Reorganizing the European regulator: changing approaches at EMA**

EMA reorganized itself recently to provide scientific integrated approach in the decision making process. Since September 2013, the European Medicines Agency (EMA) has a new organisational structure to support better its public health mission and its role as part of the European medicines regulatory system. The new structure reflects a renewed focus on three key elements: How to better support the scientific work of the EMA committees; How to better share the knowledge and information the Agency holds throughout the European Union (EU) medicines regulatory network; How to better meet the need of the Agency’s stakeholders and partners. The reorganisation introduces a new operating model for how medicines with separation of the scientific and procedure management with increased scientific input from the Agency to support and complement the competencies available in the network. Reinforced competencies are organised in the therapeutic areas related to the medicinal products being evaluated, as well as those specialist scientific disciplines that are necessary to ensure a comprehensive assessment.

Source: Guide to the European Medicines Agency at 16/set/2013

<sup>1</sup> See more: <http://www.ema.europa.eu/> (EMA/Home/Special Topics/Supporting research/Benefit-risk methodology)

<sup>2</sup> See more: JL Goodman Clin Pharm Ther 91: March 2012

**Box 22: Strategic reorganization of national regulators: looking at ANSM, France**

At national level, the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé – ANSM) also reorganized itself recently to provide scientific integrated approach in the decision making process. ANSM was created by the Act of 29 December 2011 relating to the increased safety of medicines and healthcare products. They introduced regular measuring variations in the benefit-risk ratio of medicines on the market – different strategies defined for old and new drugs. ANSM promotes quick access to therapeutic innovation before receiving Marketing Authorisation (MA) by the renewal of the premarket approvals scheme (PMA) and supervision of prescriptions without MA by means of issuing recommendations for temporary use (RTU). They focus in the promotion of academic research on medicine safety, through calls for projects aimed at public research bodies, non-profit private research bodies and healthcare institutions in order to develop a high-level scientific research strategy. ANSM gave access to the CNAMTS databases for surveillance and epidemiology studies, in particular in the context of a public interest group. And seek to improve relations with healthcare professionals and patients by setting up task forces that bring together healthcare professionals, calls for projects to promote associative initiatives aimed at encouraging correct use of healthcare products and reducing the risks linked to usage, participation of associations of patients and users of the healthcare system in the Board of Directors and committees of the Agency, etc. ANSM also focused in a better supervision of advertising

Source: ANSM Presentation brochure (20/11/2012)

Regulatory science recognised as a new academic discipline would significantly enhance decision making as a science driven process and would improve the flow of information amongst all the stakeholders involved.

### **4.3. Evolving regulatory framework for medical devices, ATMPs and nanotechnology**

The paragraphs above argue in favour of regulatory science, so that regulation tends to be proportionate (to what needs to be done), targeted, consistent, transparent and accountable. All new technologies face the challenge of proportionality and targeting. Increasing uncertainty in the context of health care innovation requires a regulator to adopt precautionary approaches, although more flexible regulation should encourage innovation. This, in turn, requires constructive risk sharing and stakeholder engagement processes (including consideration of risks and the costs/benefits of new technologies), trust building (and here scientists need to be balanced and not merely advocates) and time and resources.

Under this context, the following paragraphs briefly address specific emerging issues in new areas of applied biosciences towards the development and usage of medical devices, ATMPs and nanotechnologies.

#### **4.3.1. Medical Devices**

Medical Devices legislation, presently under revision in Europe, should aim to meet the needs for an appropriate framework, solid, transparent and sustainable, assuring the safety and effectiveness of medical devices. This framework should also stimulate the sector viability, promoting innovation.

Main issues included in the proposal under current consideration include the following:

- a) For high-risk or innovative medical devices or using innovative technology, a more direct intervention of regulatory authorities combined with more flexible procedures is under discussion to facilitate access to markets. This approach prevents predictable delays associated to a pre-market approval, as adopted in the USA.
- b) Clinical evaluation prior to placing devices in the market will be associated with a post-market clinical follow-up, which jointly represents an ongoing process of clinical evaluation of medical devices.

- c) The application of regulation about new devices to other studies is under discussion, such as those carried out within the framework of research and development of new devices.
- d) A new mechanism is proposed that will allow promoters of multinational clinical research to present a single application for evaluation through an electronic system to be created at EU level.
- e) With the goal of increasing the overall transparency of the system, part of the information resident on European database EUDAMED will become available to the public.
- f) Products that combine a drug and a device are regulated under the medical devices regulatory framework or under the legislation of the medicines. In this context, the EU Commission intends to facilitate interaction between the two regulatory frameworks. Medicines legislation should be amended in a manner concordant to that proposal.
- g) The proposed general safety requirements and performance should be adapted to scientific and technical progress. This includes the use of nanomaterials in medical devices, devices containing non-viable tissues or cells of human origin, and the invasive products without medical purpose, if they resemble medical devices.

In addition, EU directives for Medical Devices concerning *in vitro* diagnostics are under revision towards immediate application in all member states and to follow new trends on regenerative medicine and increasing difficulties with borderline products. It should also be noted that recent challenges imposed by pharmacogenomics raise the issue of companion diagnostics that are not sufficiently regulated to adequate access and independent use.

#### **4.3.2. Nanotechnology**

High levels of uncertainty and, in many cases, ignorance are involved in the assessment of risks to human health and the environment of current applications of nanotechnology. The long-term impacts are still unknown but current knowledge is sufficient to make regulatory agencies, governments, industry, insurance companies, NGOs and consumers extremely apprehensive. Downplaying risks should not be part of the solution in risk management strategies.

Under this context, the conceptual framework proposed by IRGC for risk governance of nanotechnology ([www.irgc.org](http://www.irgc.org)) is based on analysing and managing anticipated risks, challenges and opportunities that concern multiple stakeholders. The model presented seeks and defines roles for all actors in a spirit of collaboration between agencies and stakeholders. It presents a model of civil convergence with consideration of contextual factors; as such, it shies away from a top-down governmental or legislative approach.

Nanotechnology opens new perspectives for innovation in the pharmaceutical sector, with particular applications (namely in the short term), in cosmetics industry, which accounts currently to more than 4000 manufactures and manages, involving more than 1.5 million jobs in the European Union. In this context, new cosmetics regulations have been adapted to accomplishing requirements for increased safety.

It should be noted that various international organisations (OECD, UNIDO, ISO, ASTM), international industry (SRC International, International Electronics Manufacturing Initiative, ICON) and NGOs (ETC Group, Greenpeace, Woodrow Wilson Centre) have explored questions associated with nanotechnology and related regulatory frameworks. Other key players include WHO, NONS and REACH. Their involvement and approach, however, to the issue of risks differ significantly. Crucial questions pertaining to regulation are still at an early stage of development. How much precaution is necessary? Should nanoparticles be regulated? What is the role of regulatory agencies at the national and international levels? These questions remain unanswered and are still a main issue for debate at international levels.

### 4.3.3. Advanced Therapy Medicinal Products, ATMPs

Specific legislation for Advanced Therapy Medicinal Products (ATMPs) has been developed in Europe (and US) to encompass challenges faced by this particular field. The regulatory framework established in 2007 includes several specific provisions that represented a step forward in pharmaceutical legislation. To support an effective development of these important products, new regulatory approaches were foreseen for fuelling drug development without jeopardizing public safety. Most importantly, it was the first piece of EU regulation that: i) accepted a risk based approach to justify omissions on the conventional submission dossier (Directive 120/2009/EC); ii) accepted particularities such as specific GMP provisions for the human starting materials (Revised GMP guide Annex 2); iii) accepted long term safety and efficacy follow-up data to be provided post-marketing (Regulation 1397/2007/EC); and iv) recognised and included in the specialised Committee both academy and patient organisations.

In order to ensure continuous therapeutic innovation in Member States, the legal regulatory framework kept an opened door to a national authorisation system. It allows the use of ATMPs, within its borders and under the responsibility of the health care provider, the so called *Hospital Exemption*. A regulatory path for hospital exemption is under finalisation in Portugal to grant innovative hospital organisations the necessary authorisation to manufacture and use ATMP's under defined conditions.

Nevertheless, innovative ATMPs, and more generally biological and biotechnological medicinal products, require a multidisciplinary approach where the leading role is often from biomedical engineers, medical doctors, biochemists and biologists. In addition, industrial pharmacists (that have less exposure to medical and biological domains triggering similar innovation patterns) usually lead the general knowledge required to ensure pharmaceutical quality. One recommendation for Portugal would be to set high level post-graduate training courses, like those existing in several EU countries, to qualify experts in biological pharmaceutical domains.

## 5. Promoting new legal frameworks towards sustainable public health

This chapter discusses new legal frameworks towards approval approaches. At first, the emergence of new forms of regulation is introduced. It intends to respond to new technological platforms, and to new challenges faced by traditional regulatory frameworks. Then, the chapter presents examples of legal frameworks integrating complementary aspects of stakeholder engagement, clinical research and enabling resources. The discussion considers main areas of intervention and potential actions towards “intelligent and integrative” regulatory frameworks.

### 5.1. The changing patterns of legal approvals

It has become a *common place* to argue that extraordinary advances in many areas of current research in life sciences have not been matched by corresponding advances in pharmaceuticals and have fallen short of the promise of biologicals. Some believe that, within the global arena, this may be the result of approval frameworks that are not “smart” or “adaptive” enough (see, for example, **Box 23**). New paradigms call for the need of new legal framework to face challenges emerging in recent years to facilitate the diffusion of new drugs and therapies.

#### **Box 23: Appropriate Governance of the Life Sciences - The Case for Smart Regulation**

“... comparing the lightly regulated information and communication technology (ICT) sector with the heavily regulated life sciences, the former sees a much greater degree and rapidity of change in products and capabilities arising from technological innovation and small start-up companies are able to build up rapidly to become major players on the basis of innovations that effectively challenge the status quo. Innovation in the life sciences, on the other hand, is dominated by a relatively small group of multinational companies. Regulation now forms an insurmountable barrier to entry for any start-up company with an innovative idea that might challenge the status quo. [...] Because of their influence on this balance of power between multinational companies and other companies in the health care sector, regulatory agencies have a particularly important role in shaping the sectors of the future, through major structural reforms of the regulatory system or through more targeted approaches to particular technologies. [...] Regulatory systems can, by a series of incremental changes over a long period, become increasingly dysfunctional and out of step with innovation in the technologies they regulate. Also, as a regulatory system builds up in this way it becomes increasingly complex and a change or addition to one set of regulations can have unpredicted implications, for example for new products in development or for companies outside the expected range of the regulations. However, the de-novo development of path-breaking regulation for path-breaking technology is also fraught with difficulties and may equally discourage, rather than encouraging innovation.”

Source: Tait, J., Chataway, J., & Wield, D. (2007). The Case for Smart Regulation, ESRC Innogen Centre

Risk governance approaches for the coming years should facilitate dealing with uncertainty and the complex interactions between modern, science-based, drug and therapy developments, safety precautions and industrial development. The ultimate goal is also to foster new regulatory frameworks that facilitate new firm creation and survival in specific social, geographic and regulatory contexts (including Portugal), without prejudice to patient safety and therapeutic efficacy. This requires a better understanding of the increasingly relevant convergence of the life sciences, physical sciences and engineering, so that new policy frameworks can be developed to promote public health across geographies.

Global environment for the development of medicinal and health products is changing at an accelerated pace. Several public initiatives have been launched in recent years worldwide, either by direct financial



support or by accelerating the necessary review process for granting access to clinical experimentation. Most programs aim at facilitating the development of prospective products and/or by simplifying the regulatory path.

Conventional pharmaceutical regulatory frameworks are being challenged by several initiatives worldwide to reduce the stringency in terms of timing and, above all, to foster a generalised access of innovative products to patients. On a case-by-case basis, FDA is accepting more products for an accelerated review process whereby the clinical demonstration is progressively generated through pre-defined post-marketing studies. In Europe discussions are on going to replace traditional approaches to a more risk based system based on prospectively planned evidence gathering<sup>1</sup>. A key component is the potential need of post-assessment clinical practices and tests during a long time period after drug release, making use of independent clinical research facilities and competences.

## 5.2. “Intelligent and integrative” legal approval frameworks

New considerations to legal regulatory frameworks are mainly focused in providing fast-track approvals, providing stepwise approaches and risk-sharing pathways of approval. For instance, high-risk therapies maybe acceptable in consequence of their potential benefits, namely in frameworks focused on diseases (e.g., the pathways provided to therapies to orphan diseases in Europe), or in breakthrough therapies associated with important clinical hurdles (e.g., in the United States). On the other hand, some new regulations intend to provide fast-track approval frameworks with a technology focus, accepting limitations of evaluating risks in standard frameworks in a timely manner. A long-standing example is the special pathways of flu vaccines, combining a technological perspective with the evolving characteristics of flu. More relevant is the acceptance in Europe of conditional marketing authorisations and exceptional circumstances authorisations, which is being used in new technologies, such as gene therapy (see **Box 6**).

For traditional drugs, phase I trials are designed to assess safety of human exposure to new investigational agent, often in healthy patients. This could stop a trial if toxicity is detected. For advanced-therapy medicinal products, safety aspects such as toxicology, are less likely and phase I trials are designed to assess safety and often dose-escalation, which is typically an aspect of traditional phase II trials. Analysis shows that clinical trials with cell based medicinal products (and with other advanced therapies) consider (indeed) pivotal and extended studies, rather than the typical three-phases clinical trials established for traditional drugs and biologics. More than adapting already existing procedures from traditional drugs, emerging advanced therapies require original considerations in designing clinical trials. Efforts to address these challenges can be found recently in Japan and South Korea (see **Error! Reference source not found.**).

### **Box 24: Japan to offer fast-track approval path for stem cell therapies**

“Japan has recently been trying to shake its 'drug lag', a term used to describe its historically slow review process that sometimes translates into therapies reaching the market well after they have received the green light elsewhere. But the country is now ready to speed the translation of regenerative medicine to the bedside. [...] The move comes in response to the potential offered by its homegrown induced pluripotent stem (iPS) cell technology, which netted Shinya Yamanaka, of the University of Kyoto, last year's Nobel Prize in Medicine or Physiology. [...] The proposed amendments to the pharmaceutical law will create a new, separate approval channel for regenerative medicine. Rather than using phased clinical trials, companies will have to demonstrate efficacy in pilot studies of as few as ten patients in one study, if the change is dramatic enough, or a few hundred when improvement is more marginal. According to Toshio Miyata, deputy director of the Evaluation and Licensing Division at the Pharmaceutical and Food Safety Bureau in Tokyo, if efficacy can be “surmised,” the treatment will be approved for marketing. At that stage, the treatment could be approved for commercial use and, crucially for such expensive treatments, for national insurance coverage.

<sup>1</sup> See more: Eichler et al Nature 91:426-436 march 2012

Source: David Cyranoski, Japan to offer fast-track approval path for stem cell therapies, Nature Medicine 19, 510 (2013)

Improvements in legal regulatory frameworks are also possible by enabling new approaches to clinical trial design, including adaptive clinical trials<sup>1</sup> and the definition of newer endpoints (e.g., the acceptance by FDA of new endpoints of pathological complete response in cancer). However, new technologies highlight the uncertainty in the regulatory process. Enabling fast-track approval frameworks is frequently made through changing the perspective of acceptable risk by the regulator, as well as increasing the post-market follow-up of approved medicinal products (see **Error! Reference source not found.**). The ultimate goal is to foster technological innovation, but without prejudice to patient safety and therapeutic efficacy. It highlights the need of enabling new forms of “adaptive” licensing (see **Box 25**), making use of a stepwise learning process under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation (i.e., “intelligent and integrative”). The ultimate goal is to align approvals closely with patient needs for timely access to new technologies and for data to inform medical decisions (i.e., “careful and coherent”).

**Box 25: Adaptive Licensing (AL): Taking the Next Step in the Evolution of Drug Approval**

“Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, *adaptive licensing* (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation.”

Source: Eichler, H.-G., Oye, K., Baird, L. G., Abadie, E., Brown, J., Drum, C. L., ... Hirsch, G. (2012). Adaptive licensing: taking the next step in the evolution of drug approval. *Clinical pharmacology and therapeutics*, 91(3), 426–37.

Overall, *equity* among industry goals and societal needs are to attempted and this requires continuously and systematic processes of stakeholder engagement. In addition, independent clinical research facilities and competences are required for post-assessment clinical practices and tests during a long time period after drug release.

<sup>1</sup> Adaptive clinical trials designs use data to allow sponsors or CROs (contract research organizations) to adjust parameters for ongoing clinical trials, including dosage, subject population or sample size. The adjustments typically come after the analysis of statistically significant safety or efficacy data can be seen to accelerate clinical development and improve efficiency.

## 6. Enabling initiatives (public and private) to complement and foster the impact of new legal frameworks towards sustainable public health

The previous chapters show that the potential revision and improvement of legal approvals to foster innovation in health care is only possible when considered together with new clinical research practices. In addition, they should enable competitive frameworks, providing strategic resources and developing a culture of engagement of different stakeholders. It is under this context that this chapter complements the previous analysis by briefly introducing the need for other enabling initiatives (public and private) to complement and foster the impact of new legal frameworks towards sustainable public health.

The rationale is that clinical innovation plays a vital role to foster the sustainability of public health systems. Above all, early treatment reduce health burden to patients, allows long term health care savings and result in natural economical benefits to society. On the other hand, adequate reimbursement systems play a crucial role in the process and need to be taken into account in the development of regulatory frameworks.

Patenting offices may also have a crucial role, particularly in the case of emerging medicinal products derived from human materials, such as genes, stem cells or embryonic products, although they are challenging the existing frameworks of intellectual property (see **Box 26**). Patents are a form of regulation, and play a decisive role in biotechnology, as a guarantee of technical credibility. But, in general, developing new regulatory frameworks with short-term impact on public health requires other (public and private) enabling initiatives. They should encompass networks, resources and strategies supporting the development of breakthrough areas.

### **Box 26: Intellectual Property on Stem Cells**

The European ban in 2011 on the patenting of embryonic stem cells is seen for some as blocking the development of new treatments. “Scientists working in stem-cell medicine will not be able to deliver clinical benefits without the involvement of biological industry. But innovative companies must have patent protection as an incentive to become active in Europe. [...] European discoveries could be translated into applications elsewhere, at a potential cost to the European citizen.”<sup>1</sup> The response of industry was shaped in the protection of process rather than the product. “Growth media, equipment and chemicals that help scientists to work with stem cells could all be patented in Europe without running afoul of the high court's ruling. For instance, Peter Coffey at the Institute of Ophthalmology in London and his team are working with the drug giant Pfizer to develop a human-ES-cell-based treatment for macular degeneration [...]. Their patents cover the placement of their retinal cells in the eye, not the cells themselves.”<sup>2</sup> On the other hand, induced pluripotent Stem Cell (iPSC) emerges as the solution to ethical problems of embryonic cells. Possible to be patented, gave rise to thousands of patents worldwide. With extensive research after the first reported iPSC, and some companies in active efforts engage clinical trials, the question is if anyone can go further with the commercialization of iPSC without the infringement of intellectual property rights, which become unclear to whom they really belong.<sup>3</sup>

Source: <sup>1</sup>Austin Smith, 'No' to ban on stem cell patents. *Nature* 472, 418 (28 April 2011); <sup>2</sup>Ewen Callaway, European ban on stem-cell patents has a silver lining. *Nature* 478, 441 (2011); <sup>3</sup>See more in <http://www.ipscell.com/2013/05/putting-the-ip-in-ips-cells-patent-war-looming/>

### 6.1. Brief survey of strategic initiatives to complement and foster the impact of new legal frameworks

Strategic initiatives towards bringing technological advances to clinical practice are found in different regions worldwide and a few sample examples are listed below. Among many others, sample initiatives include the *Andalusia Initiative of Advanced Therapies*, in Spain (see **Box 29**), the *California Initiative of*

*Regenerative Medicine*, in USA, namely with new Alpha Stem Cell Clinics<sup>1</sup>, as well as the *UK Regenerative Medicine Platform* (see **Box 27**). The recently Japanese initiative on sound translational research (see **Box 28**) is also worth noting, as it considers a new institution dedicated to regenerative medicine based specifically on iPS cells.

**Box 27: UK Regenerative Medicine Funding Strategy**

UK Regenerative Medicine strategy defined in 2012 set an investment on the development of the defined national needs. In order to promote the clinical translation of regenerative medicine therapies, the focus was set in the creation of resources to habilitate the scale-up of manufacturing (production and quality), clinical assessment, namely next generation in vivo imaging technologies, and facilities that provide new interdisciplinary capabilities addressing key translational bottlenecks, for example to support specialised manufacturing processes in clean room environments, or the integration of acellular approaches or the physical sciences to provide new tools and technologies of wide applicability.

Source: See more <http://www.mrc.ac.uk/Fundingopportunities/Calls/CapitalFundingtoSupportRegenerativeMedicineResearch/MRC009149>

**Box 28: Japan: Towards leadership on iPSCs**

“Japan wants to lead the way, particularly with applications that focus on a relatively new kind of stem cells called induced pluripotent stem cells or iPS cells. Japanese researcher, Shinya Yamanaka, first reported production of iPS cells in 2006 in mice and in 2007 in humans. Japan has raced ahead of other countries and they appear to have the intellectual property rights and drive to do so (see **Box 26**). [...] While I worry that researchers in Japan may be moving a bit too fast to human studies, at the same time I have to admire their dedication and commitment to translating iPS cells into clinically relevant medicines. In addition, the Japanese government has definitely stepped up to the plate, committing more than \$1 billion USD specifically to iPS cell research. [...] CIRM (California stem cell agency) budget for 10 years is \$3 billion for all kinds of stem cell research. CIRM has funded a sizable amount of iPS cell research so the state of California is a serious competitor to Japan on iPS cells. [...] Still Japan is remarkably committed to being the iPS cell leader and iPS cells are understandably a source of pride for Japan given Yamanaka’s achievements including the Nobel Prize. [...] It’s tricky when it comes to getting iPS cell-based therapies to patients. The sweet spot—not too slow or too fast—for the speed of iPS cell clinical translation is not entirely clear today.”

Source: <http://www.ipscell.com/2013/09/japan-aiming-for-a-commanding-position-on-new-stem-cells/>; Nat. Biotech. 31:272-273 April 2013

**Box 29: Outcomes of Andalusian Initiative of Advanced Therapies (IATA)**

Spanish Ministry of Health and Social Welfare has signed in August 14<sup>th</sup>, 2012 “a licensing agreement with the company Innovaxis biopharmaceutical in order to develop the phase III of a cell therapy clinical trial aimed to avoid amputation of lower limbs in diabetic patients.” The agreement “was born with the objective of establishing public-privates partnerships that facilitate the momentum of clinical trials led by the Andalusian authorities.” The agreement provides funding to continue the phase III in the Andalusian health service, in which the initial phase was led. Managed by the Andalusian Public Foundation Progress and Health, IATA promoted lines of research that support the promotions of 18 clinical trials in therapy and tissue engineering in different stages of development in several areas of the Andalusian Public Health System such as Immunology, Cardiology, Neurology, Digestive, Ophthalmology, Hematology, Peripheral vascular and Gastroenterology. In collaboration with the University of Granada, IATA set up a Master Programme, pioneer at the international level, on manufacturing of advanced therapy products, which reached its third edition, and allowed the region to lead the training in this field. “These actions are intended to place the Region in a leading position in the field of translational biomedical research, a field of activity that aims to find solutions to diseases which currently do not have them and, at the same time, as part of the strategy of sustainable economy, since investment in research works as an engine of economic and social development in Andalusia and its results therefore, they revert to citizenship.”

Source: <http://www.investinandalucia.es/accesible/new/show/id/31/title/>; Maciulaitis et al Mol. Ther 20:479-82 2012

<sup>1</sup> Trounson, A., DeWitt, N. D., & Feigal, E. G. (2012). The Alpha Stem Cell Clinic: a model for evaluating and delivering stem cell-based therapies. *Stem cells translational medicine*, 1(1), 9–14.

## 7. Summary: recommendations for Portugal

Emerging forms of technological innovation with implications on healthcare are mainly associated with new knowledge at the convergence of life sciences, physical sciences and engineering. This context can be favourable to Portugal in the present stage of early R&D developments that normally precedes the involvement of “big pharma” industry.

This is important because emerging new therapies, medical devices and innovative drugs may allow addressing unmet needs or improving current health solutions in a personalised scale, reducing economical burdens and promoting innovation in public health. But this is strictly associated with revisiting existing regulatory frameworks, which should facilitate the governance of risks and define how new products are translated into clinical practice, without prejudice to patient safety and therapeutic efficacy.

It is under this context that this report calls for the need to consider uncertainty in risk governance in association to multiple dimensions in health care innovation. It shows that the potential revision and improvement of regulatory approvals to foster innovation in health care is only possible when considered together with new clinical research practices. Also, the diffusion of that new knowledge, together with its social and economic implications, challenges the current regulatory frameworks and legal approval practices. In addition, they should enable competitive frameworks and public and private initiatives, providing strategic resources and developing a culture of engagement of different stakeholders.

The main challenge is to consider a large European-wide context, as well as the need to balance the *idea* of "smart and adaptive" regulatory frameworks (which seems to focus on "quick and easy" practices), with the *idea* of "**intelligent and integrative**", that would consider "careful and coherent" practices. Equity among stakeholders (private and public) is required. In addition, independent clinical research facilities and competences are required for post-assessment clinical practices and tests during a long time period after drug release.

In other words, the rationale for regulating new products and therapies is becoming more complex and approvals require the introduction of balanced risk analysis for comprehensive decisions on their risk-benefit profile.

Emerging challenges facing regulatory frameworks for new therapies, devices and innovative drugs include the following:

- *Fostering New pharmaceutical products*: Adjusting clinical assessment to new drugs or cell technologies is opening a window of opportunities for bringing disruptive technologies into clinical trials. New technological innovations also bring challenges to the way of operating and thinking of the different stakeholders. They challenge the scientific knowledge of regulators and patients, while offering breakthrough innovations and the putative improvement of public health;
- *Considering Regulatory Fragmentation* - Variability of technologies and diseases under the umbrella of regulators justifies the creation of particular and specialized frameworks to different products and conditions, resulting in emerging both bottlenecks and opportunities. This increases the complexity of regulatory frameworks and reduces the predictability of the path of new products, creating high levels of uncertainty, which may jeopardize the capacity to allocate resources in product development.
- *Understanding Trends towards Personalized Medicine*: therapies target specificities of individuals or small groups of individuals, with improvements in the treatments provided, challenge development and funding the strategies.

Our analysis shows that beyond revising legal approval aspects, there is also a need to develop a better framework for clinical practices and research, together with deepening current understanding of *how* value can be created and captured in the complex chains of emerging technological innovations. We conclude that new regulatory frameworks oriented to harnessing knowledge, technology and innovation towards sustainable public health is only possible together with:

- Understanding **uncertainty and risk governance**, as well as developing a culture of engaging different stakeholders for targeted objectives;
- Promoting **clinical research practices and trials**, together with other enabling public - private initiatives for the establishment of joint infrastructures and shared knowledge;
- Providing strategic new **qualifications**: training for qualified person in emerging advanced therapy medicinal products; introducing regulatory science and advanced training on risk benefit assessment, risk communication and risk governance;
- Stimulating new and evolving **legal approaches**.

## 7.1. Understanding uncertainty and risk governance

How to make decisions under risk and uncertainty remains a fundamental challenge in the process of new drugs and therapies. This is primarily because there exists no *rule of thumb* as to the level and nature of acceptable risk, in spite of the extent of multi-stakeholder dialogues. The availability of relevant information across decision contexts also varies and, for instance, it is hard to impute a value on human life, health and happiness. To inform decisions, patients, physicians, scientists, managers and politicians should address these uncertainties by exercising sound technical, economic and ethical judgments.

New forms of pharmaceutical innovation are becoming a reality worldwide. Besides industry, other stakeholders are likely to play a more active role in the development of new drugs and cell therapies. Patients, physicians, hospitals and research universities are examples of more active sponsors, either at individual or institutional levels. Their involvement can be associated with the need to consider complex and modern technical infrastructures, but it also increasingly depends on the nature of modern health sciences. Physicians and hospitals are playing a more active role in their development and providing feedback for technological improvement. Universities and hospitals are playing active roles in new forms of clinical trials, while patients engagement are increasingly relevant in determining the success of new therapies.

It is under this context that patients, beside regulators, are also becoming central to regulatory systems, together with an active role in the process of innovation. The relevance of patients' engagement surpasses their role as "recipients" and it is becoming a vital part of clinical research, namely through patient associations.

The main objective of involving stakeholders is to prepare better decisions. It is meant to improve understanding of the rationale behind people's interests, motivations and decisions. Stakeholder involvement and citizen participation are hence key topics in risk governance and management.

The involvement of patients in the regulatory process has to be viewed as focused in the patient's health and, above all, as a process fostering the social perception of risk. Unregulated shortcuts are examples of an unmet fit of regulations to individual risk perception, and in extreme situations, an unbalanced risk perception supports a prejudicial tendency to ignore the rationality, which shape current regulatory frameworks.

The active involvement of patient organisations and the need to provide clear information for an informed decision is crucial for the good conduction of personalised medicine, namely for the authorisation of autologous products that are manufactured from patients cells or tissues. This

involvement is facilitated when clear high level decisions are taken on which are the targeted development areas to be considered strategic.

## **7.2. Promoting Clinical Research Practices and Trials, together with other enabling initiatives**

Clinical research is an essential part of the process of innovation in health care. Moreover, clinical research is key in establishing regional attractiveness to develop new products, foster local pharmaceutical industry, and ultimately providing a direct impact in the early access to breakthrough treatments. Regulatory practice has to be able to support advances in clinical research, under a suitable clinical trial framework.

It is under this context that clinical trials framework in Europe is being reviewed to increase its attractiveness. The goal is to help: i) reducing administrative burdens for conducting clinical trials; ii) avoiding redundancy of procedures at national and Community levels; iii) maximizing the level of harmonization in practices and interpretations at Community level; and iv) expediting the evaluation of clinical trials for all member states. The articulation with changes at European level must be carefully considered in Portugal and this requires specific actions regarding clinical trials, including:

- Infrastructures to support clinical trials;
- Incentives to undergo in clinical trials;
- Clinical research professional careers.

Analysis suggest that national competitiveness, in an European framework, depends above all on the ability to: i) reduce the timelines between CTAs and beginning of patient recruitment; ii) improve sites capabilities and competencies to conduct clinical trials by creating dedicated structures; iii) create incentives for clinical research and other healthcare professional practices.

## **7.3. Providing strategic new qualifications**

Regulatory authorities are recurrently challenged by an increasingly complex science driven decision process that require specialisation, expertise and training. It is only achievable by a systematic approach to regulation and the adequate understanding of regulatory science as an upcoming discipline. It is under this context that analysis suggests there is an opportunity in focusing attention in Portugal in emerging technological niches, including medical devices, ATMPs and nanotechnologies. It is only possible to encourage innovation in health care if new regulatory frameworks are supported to be proportionate (to what needs to be done), targeted, consistent, transparent and accountable.

In addition, the preliminary analysis in this report suggests that a national initiative to promote clinical research and practices should focus on early-phase trials. It requires investments in people and resources to enable a competitive and sustainable research environment for clinical translation, under an effective international context. Strategic international partnerships help promoting best practices and should be extended. Training for qualified person in emerging advanced therapy medicinal products is required as often development has been conducted by non pharmacists.

It should be clear that creating an attractive framework to foster clinical innovation goes beyond regulatory frameworks. It has to be supported in clinical networks, namely at an international level and following emerging specialization patterns, as well as by enabling physical and human resources to support clinical translation. This rational has driven many strategic initiatives worldwide, namely in the development of Regenerative Medicine. The main lessons to learn are about the need to capacitating clinical research to address emerging challenges in new technologies.

Patients, governments and hospitals have to engage in a more efficient process of clinical innovation, as well as, promoters and investors. The necessary scrutiny required for targeted decisions cannot be strictly based on peer scientific review, but requires a throughout revision of the conditions for clinical practices, together with business practices. Introducing regulatory science as well as advanced training on risk benefit assessment, risk communication and risk governance will help leveraging strategic decisions at different levels by the various stakeholders.

#### **7.4. Stimulating new and evolving legal approaches**

New technological paradigms call for the need of new approval procedures. However, there is no evidence that abandoning a traditional precautionary principle is the answer. In addition, the regulatory framework in Portugal is mostly defined at the European level, but analysis shows that there are several countries competing with Europe to lead the development in emerging fields of advanced therapies, devices and pharmaceutical technologies.

Signs exist in Europe going towards a more risk based assessment framework. Overall, new technologies highlight the uncertainty in the regulatory process. Enabling fast-track approval frameworks is frequently made through changing the perspective of acceptable risk by the regulator, as well as increasing the post-market follow-up of approved medicinal products. However it has to go beyond “quick and easy” licensing approaches. It highlights the need of enabling new forms of “adaptive” licensing, making use of a stepwise learning process under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation (i.e., "intelligent and integrative"). The ultimate goal is to align approvals closely with patient needs for timely access to new technologies and for data to inform medical decisions (i.e., "careful and coherent").