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How does EU non-binding law contribute to the scientific concept of biomedical innovations?

Éloïse Gennet, Aurélie Mahalatchimy

Abstract: Whereas EU binding law rather uses the expression "biomedical technology" than "biomedical innovation", the EU legislator seems less hesitant to use the term "innovation" in EU non-binding law. Non-binding EU law plays a significant role in shaping the scientific concept of biomedical innovations and in reflecting on the interactions between innovation and regulation. Firstly, EU non-binding law offers a broader definition of biomedical innovations by emphasizing the central role of society. While reaffirming the dual medical and economic goals of biomedical innovations, it also stresses the importance of public acceptance, aligning closely with the characteristics of biomedical technologies as defined in EU binding law. Secondly, a key finding from the analysis of EU non-binding law is its nuanced approach to the notion of innovation, which sets it apart from binding law in this field. The distinction between incremental and disruptive innovations not only enhances the conceptualization of biomedical innovations but also provides a robust foundation for contemplating the regulatory implications of these innovations. This distinction highlights the mutual influence between regulation and innovation as it is strategically used to justify regulatory decisions. The linked uncertainties have facilitated the emergence of the principle of innovation as a new policy tool for shaping EU-level regulation of biomedical innovations, leading to its recognition in applicable EU binding law.

Keywords: biomedical innovations, technologies, EU law, non-binding law, definition, legal concept, concept of legal science, biological elements, nanotechnologies, principle of innovation.

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How does EU non-binding law contribute to the scientific concept of biomedical innovations?*

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Introduction

Not a day goes by without the scientific literature in the fields of biology and medicine publishing new results for the use of biological elements for therapeutic purposes. Examples include haematopoietic stem cell transplants for certain blood cancers,[1] or the prospects offered by discoveries that have revolutionized the world of research, such as Induced Pluripotent Stem (IPS) cells with faculties similar to those of embryonic stem cells,[2] or the CRISPR-Cas9 technique for genome editing[3] for the most known that have given rise to Nobel Prizes.[4] Nor is there a day that goes by without the mainstream press relaying information in this area.[5] It has to be

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1 O. Penack, M. Marchetti, M. Aljurf, et al., "Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation," *Lancet Haematol*, vol. 11, n° 2, February 2024, pp. e147-e159.

2 R. Netsrithong, L. Garcia-Perez, M. Themeli, "Engineered T cells from induced pluripotent stem cells: from research towards clinical implementation," *Front Immunol*, n° 14, January 2024, p. 1325209.

3 M. Laurent, M. Geoffroy, G. Pavani, S. Guiraud, "CRISPR-Based Gene Therapies: From Preclinical to Clinical Treatments," *Cells*, vol. 13, n° 10, May 2024, p. 800 ; D. V. Parums, "Editorial: First Regulatory Approvals for CRISPR-Cas9 Therapeutic Gene Editing for Sickle Cell Disease and Transfusion-Dependent β-Thalassemia," *Med Sci Monit*, n° 30, March 2024, p. e944204.

4 R. Barrangou, "Nobel Dreams Come True for Doudna and Charpentier," *CRISPR J*, vol. 3, n° 5, October 2020, pp. 317–318; M. Ochi, "Shinya Yamanaka's 2012 Nobel Prize and the radical change in orthopedic strategy thanks to his discovery of iPS cells," *Acta Orthop*, vol. 84, n° 1, February 2013, pp. 1–3.

5 For instance, C. Metz, "Generative A.I. Arrives in the Gene Editing World of CRISPR," *The New York Times*, 22 April 2024 (accessed on 11 June 2024); W. Hague, T. Blair, "Britain must develop a biotech strategy to unlock prosperity," *The Times*, 25 January 2024 (accessed on 11 June 2024).

said that these advances in biomedicine are giving rise to realistic hopes of directly treating the causes of diseases rather than just the symptoms, for diseases where there are no satisfactory treatments, and towards increasingly personalised medicine. But they also raise social, legal and ethical issues regarding for instance the protection of the fundamental rights of donors and recipients,[6] the cost for the health systems,[7] the equitable patients' access,[8] being at the crossroads of many academic sciences, of various interests from multiple actors, and of various regulations. Apart from a limited social sciences literature, the academic approaches generally focus on one specific innovation,[9] covering sometimes some of its linked societal challenges.[10] In social sciences, part of the literature is attempted to cover all or several of these innovations as long as the focus is more on the links the society has with them than on these innovations themselves.[11] In our research works related to the I-BioLex project,[12] we are using the expression 'biomedical innovations' to study a range of innovations in regenerative medicine, nanomedicine and gene therapy, going beyond a specific legal category. We also define biomedical innovations as innovative products, procedures or techniques based on biological elements of human or animal origin which entail high or unknow risks, and which serve a medical goal as well as economic competitiveness. In that context, we consider 'biomedical innovations' as a scientific concept[13] on the basis of its emergence as a concept of legal science[14] in accordance with the language's conventions established in the introduction of this special issue on 'Definitions and concepts in biolaw'.

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6 For instance, K. E. MacDuffie, J. L. Stein, D. Doherty, et al., "Donor perspectives on informed consent and use of biospecimens for brain organoid research," *Stem Cell Reports*, vol. 18, n° 7, 2023, pp. 1389–1393.

7 For instance, C. Iglesias-López, A. Agustí, A. Vallano, M. Obach, "Financing and Reimbursement of Approved Advanced Therapies in Several European Countries," *Value in health*, vol. 26, n° 6, 2023, pp. 841-853.

8 For instance, Q. Tingting, T. Mondher, *Regenerative Medicine; Unlocking Patient Access and Commercial Potential, Pharmaceutical health economics and market access*, 1st ed, CRC Press, Taylor & Francis group, 2023.

9 For instance, A. Collignon, B. Bouchacourt, P. Sfumato, et al., "Autologous Stem Cell Transplant in 2nd Line DLBCL in 2022, Still the Standard of Care ? a Monocentric Experience," *Blood*, 140 (Supplement 1), 2022, pp. 7712–7713.

10 For instance, F. Sanchez-Guijo, J. Vives, A. Ruggeri, et al., "Current challenges in cell and gene therapy: a joint view from the European Committee of the International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT)," *Cytotherapy*, S1465-3249(24), 2024, p. 00054-9.

11 For instance, M. Morrison, A. Bartlett, "Making translational value: Identifying 'good targets' for clinical research on gene editing and induced pluripotent stem cell technologies," *SSM - Qualitative Research in Health*, vol. 2, 100131, 2022, pp. 1–8.

12 Research project funded by the French Agency for Research on "Fragmentation and defragmentation of the law on biomedical innovations," ANR-20-CE26-0007-01.

13 A scientific concept (of philosophy, medicine, sociology, etc.) "is used by a scientific discourse other than the legal discourse," Introduction, this special issue.

14 A concept of legal science "is used in scholarly discourse on the law," Introduction, this special issue.

As per our previous works, we reached several conclusions regarding the existence of a legal concept[15] of biomedical innovations in EU binding instruments.[16] Although the biomedical innovations' denomination/name does not currently exist in EU binding law, some elements of the definition of the concept of legal science, such as the two parallel economic and medical objectives, have been found while new ones, such as ethical concerns and challenges for public trust and confidence, have appeared. One important conclusion also emanating from this first study is the fact that EU binding law seems to actually avoid the term "innovation", to the point where we have considered that the expression "biomedical technologies" would be the most adequate one to correspond to existing binding EU law while designating our object of research.

In contrast, the EU legislator seems to have been less hesitant to use the term "innovation" in EU non-binding law related to biomedical innovations, which is the object of study in this present paper. Indeed, EU law has been framed in a specific context linked to multiple influences, be they economical, ethical, political, legal or societal to name a few main ones, and this is particularly noticeable in non-binding law. Moreover, the interest of non-binding EU law is exacerbated in the field of biomedical innovations. First and contrary to the main legislative process for adoption of binding law, non-binding law can evolve rapidly to take into account the evolutions of science and biomedicine. Second, it is generally richer because it does not aim to be implemented directly and immediately. In this sense, it provides more of an overview of the current thinking, issues, and positions. Identifying trends and changes is therefore easier, given the specific nature of the European Union as representing 27 Member States. Third and last, non-binding law also enables a freer form of reasoning that is not constrained by existing legal categories for a few elected biomedical innovations. This flexibility aligns it more closely with the approach of the science of law regarding biomedical innovations. Thus, how does EU non-binding law contribute to the legal science concept of biomedical innovations? The aim of this article is to analyse EU non-binding law's understanding of the notion of innovation in the field of biomedical innovations in order to, *in fine*, contribute to the conceptualisation of the expression "biomedical innovations" in EU law. As such, it should be useful to any further study of EU law in the field of biomedical innovations, be it an overall analysis of biomedical innovations or a targeted analysis by specific types of, or specific challenges raised by, biomedical innovations. To this end, several types of EU non-binding law's instruments were collected, for

[15] A legal concept "is contained in provisions of positive law (an applicable legal text whatever its source or status is (Act, Decree, Decision of a court…) at a given time in a given legal order)," Introduction, this special issue.

[16] E. Gennet, A. Mahalatchimy, "Is there a legal concept of biomedical innovations in EU binding law?," this special issue.

instance reports and working documents, recommendations, communications from the European Commission; resolutions from the European Parliament; Council conclusions or recommendations; or opinions from the European Group on Ethics. A total of 52 instruments (listed in the Annex) were selected between 1985 and 2022. The inclusion criteria for selecting these instruments were their relevance in the field of biomedical innovations or biomedical technologies, although we acknowledge the subjectivity of such a criterion. In particular, these texts were selected when covering regulatory fields such as biological elements of the human body, medicinal products, medical devices, nanomedicine, gene therapy, or when they were covering transversal topics such as personalised medicine or innovation.

The analysis of these EU non-binding instruments confirms the conclusions reached in our first work regarding EU binding instruments, *i.e.* the definition and characteristics of biomedical innovations as being innovative and complex products, procedures or techniques based on biological elements of human or animal origin aiming at a double objective of promoting health and the internal market, entailing high or unknown risks, causing ethical dilemmas and creating a regulatory gap.

There is no specific definition of "biomedical" innovations in EU non-binding law, but it does give several recurring and defining elements of innovation in general and specifically in the field of health, as including biomedical but also digital innovations. Sometimes, the notion of innovation is used in EU non-binding law when referring to national regulatory frameworks for marketing authorisation and health technology assessment of innovative medicinal products.[17] As has been recently highlighted in a report from WHO's Regional Office for Europe, European countries often define "pharmaceutical innovation" through the perspective of notions of invention and novelty.[18] More specifically, and while admitting there is no globally accepted definition thereof, the report observes that "key components of pharmaceutical innovation are usually its ability to address unmet medical need and its added therapeutic value".[19] However, these references to the term or qualifying adjective of "innovation" or "innovative" are limited in comparison to what seems

[17] For example, the Expert Panel on Effective Ways of Investing in Health (EXPH) in its report on disruptive innovations in health and health care mentions the example of the Czech Republic giving a specific status to "highly innovative products (HIP)" determined mostly with medical/public health efficiency criteria or therapeutic value (notably for the pricing). "The criteria involve: incidence of serious adverse events decreases at least 40%, reduces serious medicine interaction by at least 40%, implies substantial reduction in mortality and prolongation of median survival of more than 2 years, or, in the case of patients where predicted survival is less than 24 months, to extend the life expectancy of at least 50%, at least about 6 months etc." EXPH, *Innovative payment models for high-cost innovative medicines*, European Union, 2018, doi:10.2875/835008, p. 10.

[18] S. Vogler, *Payer policies to support innovation and access to medicines in the WHO European region. Oslo Medicines Initiative Technical Report,* World Health Organisation European Region, 2022, p. 57.

[19] Ibid., p. viii.

to emerge as a more complex concept in the soft law of the European Union. Thus, this analysis highlights how the use of the term "innovation" in EU non-binding law informs the legal science concept of biomedical innovations. First, EU non-binding law partially confirms the definition of biomedical innovations as a concept of legal science (I). Second, EU non-binding law provides for an additional regulatory perspective on the concept of biomedical innovations through an in-depth look at the consequences of regulating innovations (II).

I. A partial confirmation of the legal science concept of biomedical innovations

Interestingly, the way EU non-binding law apprehends or sometimes defines health innovations has common elements with what we have considered to be the legal science concept of biomedical innovations. Yet, while giving a central role to society, it provides for a broader definition of biomedical innovations (A). Moreover, EU non-binding law also established a supplementary element useful for the conceptualization of biomedical innovations through the distinction between continuous and disruptive innovations (B).

A) A broader definition of innovation around the central role of society

In a comparable way to the notion of patentable invention, the Expert Panel on Effective Ways of Investing in Health (EXPH)—an interdisciplinary and independent advisory group established by the European Commission to provide non-binding and independent advice on health systems—defines innovation as "the process of translating an idea or invention into a product/service that creates value or for which customers or society or insurance will pay. To be called an innovation, an idea must be replicable and must satisfy a specific need. Innovation involves deliberate application of information, imagination and initiative in deriving greater or different values from resources, and includes all processes by which new ideas are generated and converted into useful products".[20] According to the European Commission, innovation is a "change that speeds up and improves the way we conceive, develop, produce and access new products, industrial processes and services. Changes that create more jobs, improve people's lives and build greener and better societies".[21] Hence innovation is more than invention, because it brings with itself the notion of improvement and public good, even though sometimes only from the economic point of view of creating jobs and growth.

[20] EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, European Union, 2016, doi:10.2875/881904, p. 17.

[21] European Commission, "Turning Europe into a True Innovation Union," Memo 10/473 accompanying the Innovation Union Communication, 6 October 2010.

The European Political Strategy Center (EPSC), the European Commission's in house think tank, published a strategic note in 2016 which defines innovation with two elements, one aspect of novelty which relates not only "to technical or scientific novelties, but may also pertain to processes and organizational change across sectors"[22]; and the other aspect contains "a teleological criterion", which means that "a technical novelty or a new approach can only be regarded as innovative if it brings economic and societal benefits. Against this backdrop, an innovation is to be understood as a process through which the novelty has to win social recognition and acceptance over time".[23] And in fact, the EPSC also defines innovation as "anything new that changes the society adopting it".[24]

And indeed, the analysis of EU non-binding law reveals that main characteristics of innovation are to be found in its objective to promote societal values and market competitivity as improvements for the society which is seen as the beneficiary of innovation (1) but also in its actual adoption by society where the society is seen as a player, *i.e.* its acceptance by society and its concrete integration into health systems and into the market (2).

1) Society as a beneficiary: the improvement for society

More than a simple medical goal (prevention, diagnostic or cure) as has been described in our previous work on EU binding law, an innovation in the sense of EU non-binding law must bring broader societal benefits and values.

In the specific field of biomedical innovations, this can entail direct benefits to, or focus on, patients. The 2014 Council conclusions on innovation for the benefit of patients recognizes in that regard "that innovations in healthcare can contribute to health and well-being of citizens and patients through access to innovative products, services and treatments that have added value with regard to the existing ones and can also lead to more effective ways to organize, manage and monitor work within the health sector as well as to improve the working conditions for healthcare staff".[25]

However, the notion of innovation in EU non-binding law also entails broader benefits to "patients, healthcare professionals, industry and society" as is stressed in the 2011 Council conclusions on innovation in the medical device sector.[26] In these

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22 European Political Strategy Center (EPSC), *Towards an innovation principle endorsed by better regulation*, Strategic Notes, Issue 14, 30 June 2016, p. 2.

23 Ibid., p. 2.

24 R. Madelin, D. Ringrose (ed.), *Opportunity Now: Europe's Mission to Innovate*, Publications Office of the European Union, 5 July 2016, 348 p.

25 Council conclusions on innovation for the benefit of patients (2014/C 438/06), 6 December 2014, recital 2.

26 Council conclusions on innovation in the medical device sector (2011/C 202/03), 6 June 2011, § 4.

conclusions, the Council puts an emphasis on the changes that the innovation process should entail, like the necessity to increase the involvement of patients in the research and development processes for innovation to be patient-centered and to focus on better defined and targeted public health needs, the necessity to be based on a holistic approach of the health care process (considering medical but also social needs for instance) or a more integrated process with other sectors (IT or new materials).[27]

Interestingly, the notion of innovation can also be directly associated to certain values around market access. In fact, the EXPH published in 2016 a report on disruptive innovation in health and health care. In this report, it states that "talking about innovation" presupposes the respect of the values on which European health systems are based such as "universality, equity, solidarity and access to high quality and safety services" .[28] According to the experts of this panel, "a disruptive innovation would be one that allows generalized access to a product or a service previously accessible only to the ones with a higher need or the ones not facing high barriers to access".[29] Similarly, the European Commission had, in 2008, expressed the importance of incorporating into the EU pharmaceutical framework the regulation of technologies and therapies constituting "breakthroughs" such as tissue engineering and gene therapy and their "translation into marketable products, in particular in areas with unmet medical needs".[30]

Hence, biomedical innovations must bring societal benefits which progress can be measured in the equity of access to high quality medical services on the market. Yet innovation must in particular bring economic benefits. Economic benefits can of course be included into the broader societal benefits of innovation, but the creation of a new market and increase of Europe's competitiveness seems to be a clear area of focus in the EU non-binding law. The EXPH deems the concept of innovation,[31] in the field of health and health care, as "synonymous with risk-taking" in order to develop "revolutionary products or technologies" and thus "create new markets".[32]

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27 Council conclusions on innovation in the medical device sector (2011/C 202/03), 6 June 2011, § 4.

28 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 22

29 Ibid., p. 22

30 Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee - Regulatory aspects of nanomaterials [SEC(2008) 2036], 17 June 2008, COM/2008/0366 final, § 3.2.

31 Notably of "disruptive innovation" but this distinction will be developed at a later stage of this paper.

32 The EXPH also gives further precisions: "Innovation differs from invention in that innovation refers to the use of a better and, as a result, novel idea or method, whereas invention refers more directly to the creation of the idea or method itself. Innovation differs from improvement in that innovation refers to the notion of doing something different rather than doing the same thing better." EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 17.

In a similar way, the EPSC directly and explicitly links innovation to economic growth by considering it as "an essential element of the internal market."[33] The Strategic note from EPSC deduces from Article 3(3) of the Treaty on the European Union that innovation is to be defined by the objective of a "highly competitive social market economy, aiming at full employment and social progress". It concludes that innovation is "a precondition of sustainable and job-creating growth", leading "to higher productivity and competitiveness while yielding social and environmental benefits".[34]

To conclude, health innovations and biomedical technologies have overlapping definitions in EU law as well as with the legal science concept of biomedical innovations as they share at least two essential characteristics: they bring health benefits to patients as well as economic growth to society. However, EU non-binding law provides for a broader definition as long as it explicitly considers the wider societal benefits of health technologies beyond patients, but also for healthcare professionals, industry and society in the context of shared European values. Nevertheless, EU non-binding law also explicitly recognizes the society as a player as regards the adoption of health innovations.

2) Society as a player: the adoption by society

As reflected in EU non-binding law, a health innovation can only be considered as such if its innovative potential has been accepted and adopted by society, which echoes the literature in sociology of political institutions.[35] The EPSC strategic note not only concludes that innovation has to yield economic and social benefits, it also concludes that "innovation is to be understood as a process through which the novelty has to win social recognition and acceptance over time".[36] And in fact, the topic of societal adoption and the idea of (early) integration into practice is a recurring one in discussions related to innovation, especially in science and technology analyses.[37]

Interestingly, in our first work on EU binding law on biomedical innovation, no explicit link could be drawn with any broader theories on the notion of innovation, because EU binding law simply does not use the actual term "innovation" to designate innovative biomedical technologies. On the contrary, the complementary analysis of EU non-binding law, as it explicitly uses the notion of "innovation"

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33 EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit*., p. 1.

34 Ibid., p. 1.

35 V. Tournay, *La gouvernance des innovations biomédicales. Vers une science politique pragmatique*, PUF, Paris, 2007.

36 EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit*., p. 2.

37 S. Besle, É. Schutz, "Utiliser la recherche pour soigner le cancer : l'innovation biomédicale localisée," *Revue française de sociologie,* vol. 16, n° 3, 2020, pp. 405–433.

relatively to biomedical technologies, bridges this gap. One interesting connection relates to the notions of public trust and adoption by society. Without linking it to the notion of innovation, the analysis of EU binding law revealed an unexpected observation, that of the recurring search for public trust from EU legislators when regulating biomedical technologies.[38] Moreover, the latter has been used as part of the European Commission's justification to revise EU binding law applicable to biomedical innovations in its proposal for a regulation on substances of human origin.[39]

Consequently, with the additional analysis of EU non-binding law, we can also link this search for public involvement and trust to the search for public acceptance of an innovation. Public involvement indeed serves the goal of gaining public trust regarding associated high or unknown health risks.[40]

But a health (or biomedical) innovation only becomes "adopted" when it has been integrated into health systems and into the market. In that sense, the EXPH for instance observed in its 2016 report that one of the most important barriers to the development and implementation of disruptive innovations in the European health care systems is the lack of engagement of patients.[41] The early engagement of patients will fluidify the acceptance of an innovation in the field of health. As long as the innovation is not "adopted" by society, it won't qualify as an innovation but only as a potential innovation.[42] Interestingly, this adoption by relevant stakeholders and patients is also fundamental to the future adoption and consumption of the biomedical innovation once on the market.

To conclude, the complementary analysis of EU non-binding law is highlighting the relevance of public trust and confidence as an additional characteristic for the legal science concept of biomedical innovations. It also already leads to reconsider using

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38 É. Gennet, A. Mahalatchimy, "Is there a legal concept of biomedical innovations in EU binding law?," in this special issue. This is also something to be observed in the explanatory memorandum of the proposal for a regulation on substances of human origin: "Insufficient minimum harmonisation was identified as a key reason for reduced trust between Member States, resulting in reduced cross-border exchange and sub-optimal access for patients to SoHOs. A Regulation is considered the most suitable instrument since it does not require transposition and is directly applicable." European Commission, Proposal for a Regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC, COM(2022) 338 final, 2022/0216 (COD), Brussels, 14 July 2022, Explanatory Memorandum § 2, p. 5.

39 "[. . .] lack of adequate procedures does not inspire trust and prevent healthcare actors from developing and adopting innovative processes. [. . .]." Ibid., p. 5.

40 É. Gennet, A. Mahalatchimy, "Is there a legal concept of biomedical innovations in EU binding law?," in this special issue.

41 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 8.

42 Ibid., p. 14.

the expression "biomedical innovations" in our field of study instead of replacing it as the sole analysis of EU binding law suggested with "biomedical technologies"; all the more so as non-binding EU law not only uses the term "innovation", but also distinguishes between several types thereof which actually revolves around the key element of market uptake of an innovation. Using the expression "biomedical innovation" leads to the study of another layer of complexity when trying to conceptualise biomedical innovations in accordance with EU non-binding law: the distinction between incremental and disruptive innovations.

B) An additional element of conceptualisation: the distinction between incremental and disruptive innovations

Some authors have qualified biotechnologies used in the field of medicine as "foundational technologies"[43] which, in themselves, "rarely yield direct societal benefit, but constitute important tools for further research, effectively underpinning important new products and services".[44] In fact, innovation is not a binary notion that either exists or does not, it is rather a gradual concept that implies several levels or degrees of innovation[45] sometimes summarized in a typology distinguishing between incremental and disruptive innovation. Most authors thus distinguish between two types of innovation, with varying qualificatives: regular versus radical, breakthrough versus incremental, disruptive versus sustaining etc. However, these varying qualificatives do have the same general meaning entailing one essential variable to the distinction, measured by the intensity and timeframe of the impact that an innovation has on the market. "Regular innovation involves change that builds cumulatively on established technical and production competences and is applied to existing markets and consumers. Revolutionary innovation, on the other hand, is fundamentally disruptive, involving radical market change and rendering technical and production facilities or resources obsolete".[46] Here we will elaborate on this distinction between incremental and disruptive innovations as useful for the conceptualization of biomedical innovations (1) before highlighting the uncertainties of this distinction at the EU regulatory level (2).

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[43] "such as the ability to grow living cells and tissues outside the body, to establish the sequence of genetic material, to produce recombinant DNA (rDNA), and to multiply DNA sequences using polymerase chain reaction (PCR)." O. Feeney, J. Cockbain, M. Morrison, et al., "Patenting Foundational Technologies: Lessons From CRISPR and Other Core Biotechnologies," *The American Journal of Bioethics,* vol. 18, n° 12, 2018, p. 36.

[44] Ibid., p. 37.

[45] S. Smismans, E. Stokes, "Innovation Types and Regulation: The Regulatory Framing of Nanotechnology as Incremental or Radical Innovation," *European Journal of Risk Regulation*, vol. 8, n° 2, 2017, pp. 364–386.

[46] Ibid., pp. 367–368.

1) A useful distinction for the legal science concept of biomedical innovation

EU non-binding law only gives negative definitions of incremental innovation, *i.e.* it only gives indication of what incremental innovation is not. In fact, the EXPH even uses the expression "non-disruptive innovations" to designate "sustaining innovations".[47] This is also a tendency observed in literature, for example with a similar distinction that is made between "foundational" and "non-foundational" technologies.[48] According to the EXPH, "non-disruptive innovations do not create new markets or value networks but rather better value by continuous improvement within an established system for reward of innovation for the different stakeholders".[49] The European Parliament also seems to make this distinction between disruptive and incremental innovations, yet by recalling that non-disruptive innovations, while not creating new markets, can still bring added value. In fact, in its 2017 resolution it "recalls that incremental innovation may also be beneficial for patients and that the repurposing and reformulation of known molecules may deliver added therapeutic value".[50] This added therapeutic value can of course trigger market evolutions (for instance due to a change in the reimbursement rate) but without creating a "new" market *per se*.

The disruptive part of an innovation may lie, not in the innovation itself, but in the positive and radical transformation it will bring to society and, in our case, in the field of health. According to the EXPH, "disruptive innovations are innovations that create new networks and organizational changes (based on a new set of values) and involve new players, leading to improvements in value as well as changes in the distribution of value between different stakeholders. In fact, disruptive innovations displace older organisational structures, workforce, processes, products, services and technologies".[51]

This idea of a radical transformation is also to be found in non-binding instruments from the European Commission or the European Parliament, noting that these technologies will trigger a change of paradigm by cost reduction of increased efficacy, by turning a generic medicine into a personalised one, a chronic treatment to a one-time treatment, a symptomatic treatment to a curative treatment.[52] Several biomedical innovations seem to be considered as being disruptive in EU non-binding

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47 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 18.

48 O. Feeney, J. Cockbain, M. Morrison, et al., "Patenting Foundational Technologies: Lessons From CRISPR and Other Core Biotechnologies," *op. cit.*, p. 36.

49 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 7.

50 European Parliament, Resolution of 2 March 2017 on EU options for improving access to medicines (2016/2057(INI)), § 49.

51 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 8.

52 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 97; European Commission, Communication from the Commission to the European Parliament, the Council, the European economic and social Committee and the Committee of the regions, Pharmaceutical Strategy for Europe, COM/2020/761 final, Brussels, 25 November 2020, § 3.2.

instruments. A good illustration given by the EXPH is also for instance regenerative medicine.[53] Both the European Parliament and the European Commission have characterized advanced therapy medicinal products as being "fundamentally different from traditional pharmaceuticals as they address the root causes of disease", and as potentially being "the future of medicine".[54] Qualifying an innovation as being disruptive by taking into account its health consequences on society, is very much linked to its actual uptake on the market. EU policy stakeholders seem to agree on the idea that the changes stemming from a disruptive innovation require a new business model.[55] As an example, in its 2008 Communication, the European Commission did not qualify tissue engineering and gene therapy *per se* as biomedical innovations, but it is their translation into marketable products that were considered as "breakthroughs".[56]

The notion of transformation is key in this distinction as it has also been used in literature on innovative biomedical technologies[57] as well as by the European Parliament underlining the "transformative potential" of "novel therapies and technologies", such as ATMPs, gene and cell therapies, personalised medicine, radionuclide therapy[58] and even nanotechnology,[59] although this last example has been and still constitutes a debated example. This radical transformation may not even necessarily come from the innovative technology itself but rather, from its successful combination or implementation with another technology or in a specific domain. As the EXPH notes, disruptive innovations are not necessarily "advanced technologies" but rather, they often consist in the application of an already available technology, or a combination of several of them, to a specific field or market.[60] For instance,

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53 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 8.

54 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 98; see also European Commission, Pharmaceutical Strategy for Europe, *op. cit*., § 3.2: "Advanced therapy medicinal products and some medicines for rare diseases are challenging concepts, both in terms of science and manufacturing. An increasing number of gene and cell therapies under development may offer curative treatments and would require a new business model to address the shift in cost from chronic to one-time treatment. 'Bedside' manufacture of more individualised medicines could be a future trend."

55 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 97; European Commission, Pharmaceutical Strategy for Europe, *op. cit*., § 3.2; EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 20.

56 Communication from the Commission, Regulatory aspects of nanomaterials, COM/2008/0366 final, *op. cit*., § 3.2.

57 M. D. Mehta, "The Future of Nanomedicine Looks Promising, but Only If We Learn from the Past," *Health Law Review,* vol. 13, n° 1, 2004, pp. 16–18.

58 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 97.

59 Ibid. However, there is a disagreement between the European Parliament and the European Commission about the disruptive or incremental character of nanotechnologies. We will say more about this disagreement later on in this paper.

60 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 20.

this is the case of genome editing technologies or the use of biotechnology in food and medicine. A small number of "groundbreaking" developments, "such as the ability to grow living cells and tissues outside the body",[61] have constituted the "building blocks"[62] for later technological developments yielding societal benefits in different fields like healthcare, agriculture, industry or the environment.[63] Indeed, the European Commission's Political Strategy Centre (EPSC), although referring to innovation in general and not disruptive innovations specifically, also is of the opinion that "innovation does not only relate to technical or scientific novelties, but may also pertain to processes and organizational change across sectors".[64] Literature supports this view of foundational innovations only yielding societal benefits and becoming disruptive after the long-term convergence of several technology platforms and disciplines.[65] One example is that of nanotechnologies for which, as S. Lacour describes, empowerment and interdisciplinarity are two specific elements that "best characterize the radical change which they represent": nanotechnologies build matter in a bottom-up approach, which is seen as "revolutionary" and nanotechnologies are not effective (or a lot less) when taken from an isolated/unique discipline perspective.[66] However, nanotechnology is also a controversial example as it highlights the uncertainties of the distinction between incremental and disruptive innovations.

2) The uncertainties of the distinction

The report of the EXPH is not clear regarding the distinction between incremental and disruptive innovations because it contains some contradictions. In fact, it also observes that a disruptive innovation "creates a new market or expands an existing market by applying a different set of values, which ultimately (and unexpectedly) overtakes an existing market".[67] The experts of this panel also later precise that even when this improvement is discontinuous or unexpected, it remains a "sustaining" innovation.[68] These contradictions reflect the difficulties of making and applying such a distinction between a continuous and a radical change,[69] between an incremental and a disruptive innovation.

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61 "such as the ability to grow living cells and tissues outside the body, to establish the sequence of genetic material, to produce recombinant DNA (rDNA), and to multiply DNA sequences using polymerase chain reaction (PCR)." O. Feeney, J. Cockbain, M. Morrison, et al., *op. cit.,* p. 36.

62 Ibid., p. 46.

63 P. Martin, et al., "Genome editing: the dynamics of continuity, convergence, and change in the engineering of life," *New Genetics and Society,* vol. 39, n° 2, 2020, pp. 219–242.

64 EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit*., p. 2.

65 O. Feeney, J. Cockbain, M. Morrison, et al., *op. cit.,* pp. 36–37 ; P. Martin, et al., *op. cit*.; S. Lacour, "Chapitre 7. Nanopatents and their impact on the medical environment," *International Journal for Bioethics*, vol. 22, n° 1, 2011, p. 124 ; M. D. Mehta, *op. cit*., p. 17.

66 S. Lacour, *op. cit*., p. 124

67 EXPH, *Disruptive innovation. Considerations for health and health care in Europe*, *op. cit*., p. 18.

68 Ibid., p. 18.

69 P. Martin, et al., *op. cit.*

The most illustrative example of the difficulties to categorize an innovation is that of nanotechnologies.[70] It is widely accepted that nanotechnologies may impact a variety of domains such as medicine, energy, environment, information technologies and much more. However, the categorization of this innovation is as of today still debated as some authors put forward the revolutionary or radical changes nanotechnologies will provoke[71] whereas others will downplay their effect, warning against the false or too uncertain hopes that are put on them.[72]

Interestingly though, this debate also takes place at the EU institutional level. In fact, the European Commission seems to apprehend nanotechnologies as only necessitating regulation as an "incremental" innovation,[73] bolstered by the concurring opinion of the European Group on Ethics from 2007 in which the ethical experts noted that "in many cases nanotechnology includes technology which has been in use for a long time, and most of the concepts used are not strictly speaking new".[74] Thus, both the European Commission and the European Group on Ethics would advise to not treat nanotechnologies and nanomedicine as something necessitating any new regulatory framework but instead as something to be apprehended within already existing legislation, even if it might necessitate a few clarifications when needed.[75]

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[70] Definition of nanotechnology: "Originating from the Greek word meaning "dwarf," in science and technology the prefix "nano" signifies 10-9, i.e. one billionth (= 0.000000001). One nanometre (nm) is one billionth of a metre, tens of thousands of times smaller than the width of a human hair. The term "nanotechnology" will be used here as a collective term, encompassing the various branches of nanosciences and nanotechnologies. Conceptually, nanotechnology refers to science and technology at the nano-scale of atoms and molecules, and to the scientific principles and new properties that can be understood and mastered when operating in this domain. Such properties can then be observed and exploited at the micro- or macro-scale, for example, for the development of materials and devices with novel functions and performance." European Commission, Communication from the Commission - Towards a European strategy for nanotechnology, COM/2004/0338 final, Brussels,12 May 2004, p. 4.

[71] S. Lacour, *op. cit.*, p. 124.

[72] A. M. Castillo, "La réglementation européenne en matière de nanotechnologies," *Courrier hebdomadaire du CRISP*, vol. 2065, n° 20, 2010, p. 10.

[73] European Commission, Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee - Regulatory aspects of nanomaterials [SEC(2008) 2036], COM/2008/0366 final., Brussels, 17 June 2008, p. 3; European Commission, Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee, Second Regulatory Review on Nanomaterials, COM/2012/0572 final., Brussels, 3 October 2012, p. 11; For a full analysis : S. Smismans, E. Stokes, *op. cit.*; M. Lee, "Risk and beyond: EU regulation of nanotechnology," *European Law Review,* vol. 35, n° 6, 2010, p. 799–821.

[74] EGE, Opinion 21, Opinion on the ethical aspects of nanomedicine, 17 January 2007, pp. 11–12.

[75] Ibid.; European Commission, Regulatory aspects of nanomaterials, *op. cit.*, p. 3; European Commission, Second Regulatory Review on Nanomaterials, *op. cit.*, p. 11.

However, this observation is ambiguous as, simultaneously, the European Commission is praising the "key" and "enabling" potential of nanotechnologies,[76] and the European Group on Ethics admits that "although this discipline is in its infancy, it is advancing very rapidly. It has the potential to change medical science dramatically but it also raises urgent ethical issues. Nanoscience is one of the most rapidly growing branches of science applied to medical questions".[77]

This is all the more ambiguous than the European Parliament has been repeatedly voicing its opinion that nanotechnologies and nanomedicine constitute radical innovations necessitating specific regulatory measures and reform of the existing law,[78] the latest occurrence thereof being in its 2021 resolution on the pharmaceutical strategy in which MEPs underline the "transformative potential" of nanotechnologies and the "enormous benefits" that nanomedicine could bring to patients and society at large,[79] along with all previously mentioned disruptive innovations.[80]

To conclude, we can observe that any categorization of innovation has to be dynamic, *i.e.* able to evolve and maybe switch as the technology is being developed in order to truly reflect reality. However, this flexibility may be instrumentalized as it could trigger potentially demanding regulatory consequences. In fact, as Smismans and Stokes have commented about nanotechnologies, "the categorisation of innovation into certain "types" can be a powerful legitimating tool in justifying a particular course of regulatory action or inaction. By acknowledging that the incremental/radical distinction is not inevitable but depends, at least in part, on different institutional readings of a technology's "innovativeness", it is possible to see innovation "types" not just as objects of governance, but as instruments of governance".[81]

II. An additional regulatory perspective on the concept of biomedical innovations

The previously described distinction can have an important effect on how innovations will be regulated at EU level. Its ambiguity, or lack of clarity, has been instrumentalized for regulatory purposes (A). This strategic categorization is

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76 European Commission, Towards a European strategy for nanotechnology, *op. cit*., p. 4.

77 EGE, Opinion 21, Opinion on the ethical aspects of nanomedicine*, op. cit*., pp. 11–12.

78 For instance, in European Parliament, Resolution of 24 April 2009 on regulatory aspects of nanomaterials (2008/2208(INI)); For a full analysis of the Parliaments position until 2017 : S. Smismans, E. Stokes, *op. cit*.

79 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 97.

80 Ibid., § 97 and § 98.

81 S. Smismans, E. Stokes, *op. cit.,* p. 365.

accompanied by a few drawbacks and disadvantages related to the inherent ambiguity of the distinction and to the poor political attractivity of the yet more flexible category of "incremental" innovations. Interestingly, this strategic categorization may in the future be replaced, not by a new or revised distinction, but by a brand-new principle, the principle of innovation, that has been more and more put forward by some EU institutions, including in the pharmaceutical sector (B).

A) Instrumentalising the distinction between innovations for regulatory purposes

Whether incremental or disruptive, innovations influence regulation, and vice-versa regulation plays an essential part in the development of innovations (1). Yet the distinction between incremental and disruptive innovations is important because it will determine what type of regulatory framework will be elaborated or implemented(2), to the point where the strategic categorization of certain biomedical innovations can and has been instrumentalized by policymakers to steer regulatory responses in certain directions as for nanotechnologies (3).[82]

1) The reciprocal influence between regulation and innovation

The influence between regulation and innovations is reciprocal, a double movement known as co-production in socio-legal studies,[83] and takes place in a constant and renewed interaction as regulatory frameworks have to adapt but also frame the development of innovations before, after or at the same time as innovations are spreading and transforming society.

As mentioned before, disruptive innovations can bring a new professional culture, create new markets and new players and thus transform or disorder old systems. In that sense, disruptive biomedical innovations trigger profound changes that impact human behaviours and norms in many different domains and levels as the use of technology spreads in society, or as society gets organised to promote it. Martin *et al.* talk about "sociotechnical regimes", notably when studying the case of genome editing, "a technology platform that is being powerfully shaped by this existing regime but is starting to disrupt the governance of biotechnology".[84] In fact, according to the author, "the most immediate disruptive effect of genome editing is in terms of governance. Existing regulatory frameworks play an important function in enrolling support for genome editing and are shaping its early development in a familiar fashion".[85]

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82 Ibid., p. 365.

83 S. Jasanoff, *States of knowledge: the co- production of knowledge and social order*, Routledge, 2004.

84 P. Martin, et al., *op. cit.*, p. 237.

85 Ibid.

In fact, biomedical innovations can disrupt regulatory frameworks but conversely, regulation will impact the pace and direction given to innovations, hopefully steering it towards societal needs, be it health needs or market needs. Thus, regulation constitutes a determining and sometimes decisive factor for how research will be conducted, how (or if) a biomedical innovation will be developed and adopted in society.[86] As has been emphasized in the EPSC's strategic note, innovation "thrives in a conducive regulatory environment. However, the relationship between regulation and innovation is not straightforward and some authors regret the lack of solid research and systematic literature on the question.[87] In fact, regulation can both hinder or enable innovation",[88] depending on whether it is comprehensive or not, rigid or flexible, lagging behind innovations or anticipating it etc. Regulation can consist of setting standards and clear frameworks or processes. It can be a "push factor" because giving companies visibility, stability and certainty by making "the yet unknown product more trustworthy", but this is only the case if these standards are not too rigid and thus turning guidance into dissuasive administrative burden.[89]

It is thus a challenge to find the right balance, especially as this balance can evolve in time and necessitate flexibility, between "regulating a technology early and aggressively to protect human health and the environment, or phasing in such regulation slowly to stimulate innovation".[90] Regulatory decisions, for instance on the related ethical issues, will have a major influence on the promotion or restriction of a biomedical innovation. Coming back to the example of genome editing, the possibility to edit embryos, together with the activism of civil association representing patients suffering from rare genetic diseases—who place great hope in gene editing—is "putting pressure on the *de facto* international moratorium on human germline engineering".[91] In fact, innovation is highly dependent on regulation to shape the research design, for instance regarding stem cell research for which some authors have underlined that "any regulatory changes may shape the output of research but also the respective ethics safeguards such as transparency, integrity, and safety".[92]

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86 J. Pelkmans, A. Renda, "Does EU Regulation Hinder or Stimulate Innovation?," *CEPS Special Report,* No. 96, November 2014 (last accessed 14 June 2024).

87 "Does EU regulation hinder or stimulate innovation' is a frequently heard query in the EU, but there is little systematic analytical literature on the issue. Fragmented evidence or anecdotes dominate debates among EU regulatory decision-makers and in European business, insofar as there is a genuine debate at all." J. Pelkmans, A. Renda, *op. cit*., 2014.

88 EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit*., p. 1.

89 Ibid., pp. 4–5.

90 M. D. Mehta, *op. cit*.

91 P. Martin, et al., *op. cit*., p. 237.

92 M. Kritikos, "Governing Technological Innovation: Searching for the Legal and Ethical Holy Grail?," *European Journal of Health Law,* vol. 22, n° 5, 2015, p. 519.

Interestingly, different types of innovations may be tackled with different types of regulatory frameworks; the distinction between incremental and disruptive innovations thus becoming a determining factor in the directions that are given to their regulations.

2) The distinction as a determining factor in the choice of regulation

As pointed out in the 2008 Commission Communication, the emergence of these new technologies and therapies "emphasizes the importance of the proportionality and flexibility of the regulatory framework"[93] that will frame the development of biomedical innovations. These flexibility and proportionality could be implemented in EU law thanks to different regulatory frameworks for different innovations' types.

The qualification of disruptive innovations can be a factor of defragmentation of the EU law on biomedical innovations, *i.e*. a factor triggering the intervention of the EU legislator to harmonize or coordinate corresponding regulatory frameworks at EU level. As mentioned earlier, by qualifying them as innovative and new and by underlining their "transformative potential", the European Parliament seems to consider the following "novel therapies and technologies", most of them corresponding to our legal science concept of biomedical innovations, as being disruptive: "gene and cell therapies, personalised medicine, radionuclide therapy, nanotechnology, next-generation vaccines, including tmRNA derivatives, e-health and the '1+ Million Genomes' initiative". And in fact, in the same paragraph of its 2021 resolution, the European Parliament explicitly "urges the Commission to develop appropriate regulatory frameworks"[94] for these innovations.

Defragmented regulation, here understood as common regulation at the EU level, can constitute a useful mean to promote biomedical innovations. EU legislators can indeed intervene in order to clarify the applicable legal regime and regulatory process, or even elaborate a specific legal and regulatory framework dedicated to disruptive innovations. The clarification of the regulatory process can promote research and innovation as it increases certainty for investigators and sponsors wanting to invest in biomedical innovations. For instance, the European Parliament underlined the repeated and increasing need to strengthen even more the regulatory landscape to facilitate review and approval of ATMPs at EU level, patients' access and Europe's competitive position in ATMP development on the global stage.[95]

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[93] Communication from the Commission, Regulatory aspects of nanomaterials, COM/2008/0366 final, *op. cit*., § 3.2.

[94] European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 97.

[95] Ibid., § 98.

Finally, being qualified or considered as a disruptive innovation can also justify the application of incentives models or EU research funding, as it had been the case with the orphan medicinal products regulation[96] or the advanced therapy medicinal products regulation,[97] although the efficiency of orphan medicines incentives turned out to be underwhelming.[98]

Nevertheless, defragmented regulation can also constitute an obstacle or at least a constraint to the development of biomedical innovations. The elaboration of a specific regulatory regime for disruptive innovation implies taking into account its particular risks towards health, safety, consumers, the environment or ethical risks. This specific regime can thus also be burdensome for researchers and sponsors.

Conversely, when an innovation is deemed "incremental," it is understood to closely align with existing biomedical technologies. As a result, it is not seen as necessitating a dedicated regulatory framework and can instead be governed by existing general legal provisions. Yet except for nanotechnologies as we have mentioned earlier and as we will further develop later on, it is rarely the case that EU institutions explicitly and purposefully "qualify" an innovation as being incremental. Rather, the incremental innovation is often the innovation that does not fulfill the defining requirements of a disruptive innovation.

This fragmentation, understood here as the multiplicity of regulations, whether under different legal orders or a single one, applicable to one type of biomedical innovations can be detrimental to innovation. It can maintain scattered, unclear and thus uncertain regulatory and legal regimes.[99] Yet uncertainty can be quite dissuasive for investigators and sponsors wanting to invest time, human and financial resources in developing a biomedical innovation. Moreover, fragmentation at EU level can also mean fragmentation and divergences of provisions for instance on main ethical issues, health safety or environmental risks, also constituting obstacles to the development of biomedical innovations which are rarely developed within and for a single European country. One example of a "largely fragmented" policy landscape

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96 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1–5, CELEX number: 32000R0141.

97 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), OJ L 324, 10.12.2007, p. 121–137, CELEX number: 32007R1394.

98 The European Parliament observes that many "innovations" are "me-too pharmaceuticals," as well as the need to "better incentivise real breakthrough innovations." It recalls that "it would be beneficial for patients if the framework for the pharmaceutical industry in Europe were to better incentivise real breakthrough innovations." European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), §N.

99 As is sometimes observed about nanotechnologies. A. M. Castillo, *op. cit*., p. 15.

that has been analysed in literature is that of stem cell research,[100] for which the heterogeneity of countries' background results in a plurality of ethics viewpoint creating regulatory uncertainty and thus major barriers to research.[101] More recently for another example, EU institutions have observed the detrimental effects of fragmentation of the regulatory frameworks on the use of substances of human origin. In its proposal for a new regulation, the European Commission observes that "Besides risks and benefits, safety and quality measures also need to take account of the typical economic (public/non-profit) settings where blood, tissues and cells are developed and prepared, and of the often incremental and open-access nature of these innovations. In addition, there are sometimes difficulties in defining the borderlines for novel blood, tissues and cells with other regulatory frameworks, in particular where medicinal products and medical devices are concerned. This creates administrative burdens and implicit disincentives for blood, tissues and cells establishments, healthcare professionals and academia to innovate".[102] As explained by the Commission, stakeholders had highlighted this insufficient legal clarity and distinction from other EU legal frameworks like medicinal products or medical devices, especially regarding ATMPs, resulting in many cases where this had negative impacts on the supply and, in fine, on patient access.[103]

Conversely, fragmentation of the regulatory framework also allows to take account of the specificities of some biomedical innovations or of their context of development, and give freedom and flexibility to the actors. At the beginning of the development of a biomedical innovation notably, it could also allow to take advantage of the confusion to avoid administrative or regulatory burdens, for instance avoiding certain rules linked to risks assessments for health, safety and environment protection. This can, and has, lead to strategic categorization of biomedical innovations, such as nanotechnologies, with the goal to gain time and freedom to develop an innovation and determine if it is worth the investment without dealing with early constraints.

3) The example of a strategic distinction in the case of nanotechnologies

The distinction between disruptive and incremental biomedical innovations can be a determining justification to find the right balance for regulation. It can be an element tipping the scale in an ethical dilemma, in favor of one or the other option or tendency between incentivization on the one hand and appropriate

100 M. Kritikos, *op. cit*., p. 520.

101 Ibid., p. 521.

102 European Commission, Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application, COM(2022) 338 final, *op. cit*., Explanatory Memorandum § 3, p. 5.

103 Ibid., p. 7.

protection of human health and the environment on the other hand. Yet although there have been efforts to conceptualize the notion of innovation, the distinction between disruptive and incremental innovations is not clear cut. It probably cannot and won't be, especially as this grey zone can be instrumentalised by stakeholders, or even by regulators directly, to navigate and pick between different regulatory approaches.

Some authors have observed that "different innovation 'types' can be important strategic resources, in the sense that they actively shape regulatory responses to new technology".[104] Smismans and Stokes show how the contradicting categorization of nanotechnologies by the European Commission and the European Parliament were guided by regulatory purposes, turning the definition of nanotechnology and its categorization in the innovation typology into a part of "discursive politics".[105] They argue that the Commission's "narrow framing" of nanotechnology as incremental innovation "has enabled a strategy of willful nonknowing or deliberate regulatory ignorance [. . .] driven by political convenience, as it relieves policymakers of the need to seek further understanding of the wider social, economic and environmental implications of nanotechnology". The risk assessment of such technology is therefore limited to information on non-specific legislation and the regulatory approach characterized "by a paucity of evidence about the social, economic and environmental aspects of nanotechnology and only limited engagement with the precautionary principle".[106] Moreover, the authors also denounce the fact that with this categorization, the European Commission has also "bypassed more broadly informed and more democratic debate" on nanotechnologies,[107] thus avoiding any public or political conflict susceptible to restrain innovation.

The European Parliament has repeatedly invited the Commission to properly consider the disruptive aspects of nanotechnologies, and notably in the field of health. In fact in its 2021 resolution about the pharmaceutical strategy, it "urges the Commission and the EMA to consider the full lifecycle of all innovative medicines and therapies, including gene and cell therapies, personalised medicine, nanotechnology and next-generation vaccines, and ensure a fit-for-purpose framework for off-patent competition at the time of loss of exclusivity; calls on the Commission to establish a regulatory framework for nanomedicines and nanosimilar medicines, and calls for these products to be approved through a compulsory centralised procedure".[108]

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104 S. Smismans, E. Stokes, *op. cit.*, p. 365.

105 Ibid., p. 365.

106 Ibid., p. 385.

107 Ibid., p. 385.

108 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), § 101.

Reflecting their previously described categorization of nanotechnology as a radical innovation, MEPs clearly call for common binding law on nanomedicine at the EU level, with the goal in mind to clarify the regulatory process and make sure it includes measures to protect patients' safety, to protect the environment and entail a democratic debate and integrated impact assessment taking into account ethical and societal issues beyond the sole economic aspects.

As Smismans and Stokes note, "although the Commission makes broad and often unsubstantiated claims about the radical socio-economic potential of nanotechnology, its regulatory approach has focused on nanotechnology as necessitating the risk regulation of incremental innovation".[109] In fact, categorizing innovation as incremental may be attractive from a regulation perspective because the latter will be less burdensome, unclear but potentially more flexible and permissive. However, the downside of the Commission's strategy is the fact that qualifying an innovation as "disruptive" sounds more appealing and may justify easier access to funding or the allowance of a special status related to the innovativeness and potential market benefits. This drawback may explain the policy solution that the European Commission has been increasingly putting forward in the last decade. The distinction between incremental and disruptive innovations seems to be disappearing. The term innovation is increasingly used by itself, without precising whether it is incremental or disruptive, while it is actually referring to what could have been qualified as a disruptive innovation. More importantly, this distinction seems to be disappearing as the term "innovation" is increasingly referred to as a policy principle.

B) Developing a principle of innovation

Debates in the field of biomedical innovations around the distinction between incremental and disruptive innovations has progressively shifted the past years towards its regulatory consequences. At stake with this debated distinction was the regulatory strategy, and it still constitutes the center of the discussion, only with a more upfront approach. In fact, the debate now revolves around the concept of innovation as a policy principle counterbalancing the precautionary principle. Rather than asking whether innovation is sufficiently disruptive to "deserve" an EU level regulation, *i.e.* a defragmented legal regime which can both be conducive or limitative as we have seen above, the default approach suggested by this principle is to design regulatory instruments so as not to create obstacles to innovation. The goal is to make sure that any EU level regulation does not impede disruptive innovations. As a matter of fact, the principle of innovation seems to be silently directed at "disruptive" innovations as for incremental innovations, the strategy rather consists

[109] S. Smismans, E. Stokes, *op. cit.*, p. 385.

in leaving the regulatory framework as it is and make it flexible enough to adapt to innovative products. This principle of EU non-binding law as a new policy tool for EU level regulation (1) that may be more and more recognised in EU binding law (2) provides for useful insights to the legal science concept of biomedical innovations.

1) A new policy tool for EU level regulation

The innovation principle first appeared in an open letter to the three presidents of EU institutions in October 2013 from the European Risk Forum (ERF) uniting several industries, mainly pharmaceutical industries, which had struggled to obtain EU marketing authorisations for their innovative and thus risky products.[110] In this letter, the principle was formulated as follows: "whenever policy or regulatory decisions are under consideration the impact on innovation as a driver for jobs and growth should be assessed and addressed".[111]

Since 2016, EU organs started to refer to an "innovation principle" in EU non-binding law, emphasizing the benefits that society could gain from innovation and thus the necessity to minimize administrative burden. Both in their own words, the European Economic and Social Committee and the EPSC consider innovation as a "precondition for sustainable and job-creating growth"[112] in Europe and "the basis for the success of the European social market economy".[113] As put by the EPSC and the European Commission, "an innovation principle means ensuring that whenever policy is developed, the impact on innovation is fully assessed. The principle should provide guidance to ensure that the choice, design and regulatory tools foster innovation, rather than hamper it".[114] Hence, according to the innovation principle, European legislation should "avoid unnecessary administrative burdens" and be proactive in order to be "future-proof" and "forward looking".[115] Beyond sole policy documents, the principle was also put forward in the Council of the European Union's 2016 Conclusions on better regulation to strengthen competitiveness, the Council explicitly asked the Commission and Member States to apply, "when considering,

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110 K. Garnet, G. Van Calster, L. Reins, "Towards an innovation principle: an industry trump or shortening the odds on environmental protection?," *Law, Innovation and Technology*, vol. 10, n° 1, 2018, p. 2.

111 European Risk Forum, "The Innovation Principle, Stimulating Economic Recovery," Open letter to Barroso, Van Rompuy and Schultz, 24 October 2013 (last accessed 14 June 2024).

112 Similarly, the EPSC notes that "innovation is a precondition of sustainable and job-creating growth. It leads to higher productivity and competitiveness while yielding social and environmental benefits." EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit.*, p. 1.

113 European Economic and Social Committee (EESC), *Future proof legislation*, Exploratory opinion, SC/045, 7 September 2016, § 3.2.

114 EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit.*; See also European Commission, Directorate-General for Research and Innovation, *Study supporting the interim evaluation of the innovation principle. Final report*, November 2019.

115 EESC, *Future proof legislation*, *op. cit.*, § 1.7 and § 2.2.

developing or updating EU policy or regulatory measures, the 'innovation principle' [. . .], which entails taking into account the impact on research and innovation in the process of developing and reviewing regulation in all policy domains".[116]

The European Commission deplores the fact that the innovation principle is sometimes misinterpreted as an attempt to undermine the precautionary principle in health and environment[117] by using a de-regulatory approach.[118] On the contrary, it would rather be aimed "at complementing the precautionary principle by increasing the salience of impacts on innovation during all phases of the policy cycle".[119] EU organs indeed always recall the need to balance such a principle with the protection of health, consumers or of the environment. The Council, in its 2016 conclusions, did reiterate the primary need, in EU regulation, "to always take into account a high level of protection of consumers, health, the environment and employees".[120] Both the European Economic and Social Committee[121] and the EPSC[122] made similar reminders when advocating in favor of an innovation principle. Yet some authors regret that all these objectives "are thrown into article 3 TFEU, almost like a child's wish-list", although they are potentially contradicting and implemented in a fragmented regulatory landscape for innovations.[123] And indeed, the objective of this principle is quite ambitious as it intends, to sum up, to make EU regulations on innovations friendly by design, to reach a balance between predictability and flexibility of the regulatory framework applicable to innovations, and all of this while embracing EU values and meeting societal needs for protection.[124]

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116 Council conclusions on research and innovation friendly regulation (9510/16), 27 May 2016, Recital 2.

117 European Commission, *The Innovation Principle*, Fact Sheet, 17 May 2022, p. 2.

118 European Commission, *Study supporting the interim evaluation of the innovation principle, op. cit.*

119 Ibid., *op. cit.*

120 Council conclusions on research and innovation friendly regulation (9510/16), 27 May 2016, preamble.

121 The principle of innovation "should however be applied intelligently and carefully, particularly in the areas of social and environmental protection, health and consumer protection." EESC, *Future proof legislation*, *op. cit.*, § 2.15.

122 The EPSC recalled that the innovation principle, even if we would implicitly base it on treaty provisions, should be balanced with environmental protection (11 TFEU and 37 EUCFR), precautionary principle (191 TFEU), human health (168 TFEU and 35 EUCFR), consumer protection (12 TFEU and 169 TFEU and 38 EUCFR) and almost all together with 114(2) TFEU. EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit.*, p. 3.

123 "The regulatory landscape for innovation is fragmented. It lacks internal unity, which sets the scene for tensions between the EU's twin objectives: fostering jobs and growth with scientific advancement, while also ensuring a high level of environmental protection and sustainable development. All objectives are thrown into article 3 TFEU, almost like a child's wish-list; but are these priorities destined for ever to separate and remain stand-alone objectives? Is there an emulsifier that can bind these two priorities and help them form a happy mix that allows the EU to meet both?." K. Garnet, G. Van Calster, L. Reins, *op. cit.*, p. 7.

124 "Specific objectives are to: Improve the design of existing and future EU regulations with regard to their impact on encouraging beneficial innovation; Steer the development of innovative solutions addressing new and complex challenges in a way that embeds EU values and protects Europeans; Achieve an optimal balance between predictability of the regulatory environment and adaptability to scientific and technological progress." European Commission, *The Innovation Principle*, *op. cit.*, p. 1.

According to the European Commission, "EU policy and legislation should be developed, implemented and assessed in view of encouraging innovations that help realise the EU's environmental, social and economic objectives, and to anticipate and harness future technological advances".[125]

Yet the Commission also admitted that the implementation of the innovation principle was not fully materialized, in part due to the lack of a clear definition and legal basis,[126] despite the tentative of the EPSC to give the innovation principle an implicit treaty foundation.[127] But interestingly, the increasing use of the principle of innovation is clearly observable in the EU legal framework applicable to biomedical innovations, thus demonstrating the progression of such a principle initially advocated by the pharmaceutical industry, making its way into EU non-binding law first and now potentially materializing into upcoming binding EU law in the field of pharmaceuticals and health technologies.

2) Towards a recognition in EU binding law?

In a 2021 resolution, the European Parliament had observed that many "innovations" in the field of medicinal products are "me-too pharmaceuticals" and that "it would be beneficial for patients if the framework for the pharmaceutical industry in Europe were to better incentivise real breakthrough innovations".[128] And in fact, the European Commission has been working on a thorough revision of the pharmaceutical legislation notably since publishing its pharmaceutical strategy in November 2020. In the past couple of years, the Commission has thus published several proposals for new binding EU law which will be applicable, if and when adopted, to biomedical innovations. In these proposals, the principle of innovation can be implicitly perceived or sometimes even explicitly mentioned.

First, a few hints to the principle of innovation can be observed, although implicitly, in the reform of the EU legal framework on substances of human origin. As we have defined them through the study of EU binding law, biomedical innovations indeed include the use of biological elements (be it of human or animal origin), hence the relevance of this reform of the framework on human blood, tissues

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125 Ibid., p. 1.

126 European Commission, *Study supporting the interim evaluation of the innovation principle, op. cit.*

127 These treaty foundations would be drawing on article 3.3 TEU according to which the EU "shall promote scientific and technological advances"; drawing on article 173 TFEU which is about EU industry policy aimed at "fostering better exploitation of the industrial potential of policies of innovation, research and technological development"; drawing on article 179(1) TFEU on the European research area to be competitive; and finally drawing on several articles of the Charter of fundamental rights of the European Union: article 13 on the freedom of sciences, article 15 on the freedom to choose an occupation and the right to engage in work, and article 17 on the right to property, including intellectual property. EPSC, *Towards an innovation principle endorsed by better regulation*, *op. cit*., p. 2.

128 European Parliament, Resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)), §N.

and cells. Interestingly, protection of patient's safety seems to constitute the main goal of the reform of the EU legal framework on safety and quality requirements for blood, tissues and cells as they are currently "not fully protected from avoidable risks".[129] The EU legislator has expressed his concern about the lack of adaptation and adaptability of the current legislation when these substances are used or embedded into new technologies or therapies, *i.e.* into biomedical technologies or innovations. These flaws lead to some of the new therapies to remain unregulated or regulated in divergent ways across EU countries.[130] Hence the intention of the EU legislator is both to ensure that "as new technologies or risks will continue to emerge, [. . .] the future framework [will be] more effectively implemented, future proof, crisis resistant and agile enough to accommodate new risks and trends while continuing to provide appropriate safety and quality requirements".[131] Although it is not explicitly cited, the three different objectives of the principle of innovation are clearly expressed in this reform of the EU binding law on substances of human origin: guarantee patient safety, foster innovative technologies such as biomedical innovations by offering a predictable regulatory framework, and finally by offering a framework that is also flexible enough to adapt to innovations.

Second, the Commission has also published in April 2023 a thorough revision of the pharmaceutical legislation, one proposal for a directive, one proposal for a regulation, one proposal for a recommendation and finally, a communication.[132]

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[129] European Commission, Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application, COM(2022) 338 final, *op. cit*., Explanatory Memorandum § 3, p. 5.

[130] "Patients are not fully protected from avoidable risks: the EU safety and quality requirements have not kept up to date with frequently changing scientific and epidemiological developments [. . .]. In addition, while new therapies have emerged since the BTC legislation was adopted, it is not always clear whether, and if so which, of the BTC Directives apply, leaving these substances unregulated or regulated in divergent ways (e.g., breast milk and faecal microbiota transplants). Some of these SoHOs do not meet the definitions of blood, tissues and cells included in the current legislation" [. . .] "Divergent approaches to oversight cause unequal levels of safety and quality and barriers to the exchange of BTC across the EU: divergent national interpretations and implementations of the legislation lead to unequal protection and a lack of mutual trust between national authorities." European Commission, Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application, COM(2022) 338 final, *op. cit*., Explanatory Memorandum § 3, p. 5.

[131] Ibid., § 1, p. 2.

[132] European Commission, Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 COM/2023/193 final, Brussels, 26 April 2023; European Commission, Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC, COM/2023/192 final, Brussels, 26 April 2023.

Among the five main objectives of this wide revision, the Commission mentions the ambition to "offer an attractive, innovation- and competitiveness friendly environment for research, development, and production of medicines in Europe".[133] Not only can we find some of the main objectives of the innovation principle in this communication, but the principle is even explicitly cited. In fact, the Commission explains that "a number of future-proofing measures will ensure that the regulatory system can keep pace with scientific and technological progress, and create an enabling regulatory environment for promising new therapies and breakthrough innovation, in line with the Innovation Principle".[134] In order to do so, the Commission notably suggests to create regulatory sandboxes providing a "structured testing environment in which innovative methods and novel medicinal products can be tried out under the supervision of regulators."[135] These sandboxes would permit to gain more experience and insights to be translated into a tailored regulatory framework which would meet the objectives of being innovation friendly while remaining predictable and without putting the protection of health and safety in jeopardy.[136]

Conclusion

Non-binding EU law contributes to the definition of the scientific concept of biomedical innovations and gives an additional regulatory perspective regarding the distinction between innovation and its consequences. In so doing, it confirms the interest of a legal science concept of biomedical innovations as a mean of taking a step back, through a more holistic approach, from the regulatory processes at work regarding several biomedical innovations in order to understand, discuss, or even challenge their overall relevance. On the one hand, EU non-binding law provides for a broader definition of biomedical innovations in giving a central role to the society, considering it both as a beneficiary and as an actor. While it confirms the double medical and economics objective of biomedical innovations, it also highlights the search for public acceptance of an innovation, and as such gets closer from the characteristics of biomedical technologies as identified in EU binding law, beyond the initial definition of the legal science concept of biomedical innovations. On the other hand, one of the salient results of the EU non-binding law analysis is its use of the notion of innovation, which is also one of the clear and interesting difference between EU binding and non-binding law regarding our field of research.

[133] European Commission, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance, COM/2023/190 final, Brussels, 26 April 2023, p. 1.

[134] European Commission, Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance, COM/2023/190 final, *op. cit.*, p. 12.

[135] Ibid., p. 12.

[136] Ibid., p. 12.

Not only the distinction between incremental and disruptive innovations is a useful supplementary element for the conceptualization of biomedical innovations, it also gives a strong basis for a thorough thinking on the consequences of regulating innovations. While this distinction highlights the reciprocal influence between regulation and innovation, it is also strategically used as a determining and justifying factor in the regulation's choices despite its limits as shown in the case of nanotechnologies. The linked uncertainties have paved the way for the emergence of the principle of innovation as a new policy tool for framing EU level regulation in the field of biomedical innovations, as well as for its recognition in EU binding law applicable to biomedical innovations.