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The Multifaceted Definition of Organoids in Law

Adrien Bottacci

Abstract: This article examines the definitions applicable to organoids in European Union (EU) law and French law to outline the state of their fragmented regulatory landscape. By analysing relevant European and national hard law and soft law, we will extract key definitional features of organoids. While the field is still relatively new, elements of definition are sprouting in various instances. By comparing this early understanding of organoids in law to the myriad of future applications possible -as research tools, as medicines or even as commodities-, it will become apparent which technological pathways are still in lack of regulatory attention. Only by paying attention to the road less travelled will we ensure fostering innovation, promoting responsible research practices, and balancing societal benefits with potential risks. This article contributes to the ongoing discourse on regulatory concepts used in science and technology by shedding light on the complex interplay between law, ethics and innovation through an analysis of definitions applicable to organoids in law. This article ultimately highlights the importance of proactive yet nuanced regulatory measures that keep pace with the rapid technological developments in organoid research.

Keywords: organoids, embryoids, assembloids, definition, french law, European Union law, substances of human origin, medicinal products, new approach methodologies.

Référence électronique

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The Multifaceted Definition of Organoids in Law

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Any attempt at reaching the essence of an object should strive to follow Plotinus's dictum: "If one wants to know the nature of one thing, one must examine it in its pure state, since every addition to a thing is an obstacle to the knowledge of that thing".[1] Formulating a definitive statement about the nature of an object can only be made by setting aside all superfluous elements and focusing on its necessary and sufficient characteristics. However, such an essentialist approach can prove thorny when each element of the so-called pure state can manifest endless variations. This is the crux of the matter when attempting to define organoids. They do not constitute a pure and uniform class of objects. Instead, organoids are a fuzzy category composed of different clusters of objects. Broadly speaking, they are self-organising three-dimensional cellular structures derived from stem cells[2] that can reproduce some physiological and structural features of an organ. Thus, the biological definition of organoids has been narrowed down to three main characteristics: (1) the presence of multiple cell types, (2) that are undergoing a process of self-organisation in three dimensions, (3) which reproduce structural and physiological features of an *in vivo* tissue.[3] However, each variation on these criteria produces different types of organoid models. Following are a few examples of these possible variations:

– Organoids can be made from induced pluripotent stem cells (iPSCs)[4] or embryonic stem cells (ESCs)[5] though they can be made from adult stem cells, tissue-specific progenitor cells and cancer cells too. They can be made with human cells or non-human animal cells. They can also reproduce all kinds of tissues.

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1 Plotinus, the enneads, IV.7.10.

2 Stem cells: they are undifferentiated cells that can transform into various types of cells and replicate indefinitely to produce more of the same stem cell.

3 S. N. Boers, K. M. de Winter-de Groot, J. Noordhoek, V. Gulmans, C. K. van der Ent, J. J. M. van Delden, and A. L. Bredenoord, "Mini-Guts in a Dish: Perspectives of Adult Cystic Fibrosis (CF) Patients and Parents of Young CF Patients on Organoid Technology," *Journal of Cystic Fibrosis*, 17, n° 3, 2018.

4 Induced pluripotent stem cells: a type of pluripotent stem cell that can be generated from a somatic cell which is reprogrammed to reach a more "naive" state. A pluripotent stem cell will self-renew itself and can be differentiated into every cell type of the body.

5 Embryonic stem cells: a type of pluripotent stem cell that is obtained from the inner cell mass of a blastocyst, an early stage of the embryo. They can self-renew and develop into any embryonic cell type.

Their name reflects the tissue modelled: *liver organoid*, *cardiac organoid*, *brain organoid*, *blood vessels organoid*, *gonadal organoid*, etc. Structures made with cancerous cells are called *tumoroids.*[6] A single organoid can even be made with cells from different donors.[7]

– Different organoids can be put together to form *assembloids*. They are used to reproduce more complex structures or to study inter-organ interactions.[8] For instance, fusing together retinal, thalamic and cortical organoids allows the study of the visual pathway.[9]
– Organoids can also be placed on microfluidic devices to reduce variability during their development. These devices mechanically control environmental parameters such as the flow of nutrients or mechanical constraints. These microfluidic systems are called *organs-on-chip (OoCs).*[10] They are expected to be used for high-yield, high-throughput methods, especially in human regulatory toxicology.[11]
– Finally, stem cell-based embryo models (SCBEMs) are also often classified as organoids despite not modelling an organ *per se* but rather specific stages of the embryonic development. They are called blastoids[12] or gastruloids[13] depending on the developmental stage being modelled. For the purposes of this article, we will use the umbrella term of *embryoids.*[14]

From these first few examples one might quickly appreciate how diverse organoid models can be. Yet these first considerations relate only to what organoids *are* at a biological (or ontological) level. If we turn then to what organoids can be

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6 N. K. Finnberg, P. Gokare, A. Lev, S. I. Grivennikov, A. W. MacFarlane, K. S. Campbell, R. M. Winters, et al., "Application of 3D tumoroid systems to define immune and cytotoxic therapeutic responses based on tumoroid and tissue slice culture molecular signatures," *Oncotarget* 8, n° 40, 2017.

7 N. Caporale, D. Castaldi, M. T. Rigoli, C. Cheroni, S. Trattaro, A. Valenti, M. Bonfanti, et al., "Multiplexing Cortical Brain Organoids for the Longitudinal Dissection of Developmental Traits at Single Cell Resolution," *bioRxiv*, 2023.

8 S. Kanton, and S. P. Paşca, "Human assembloids," *Development* 149, n° 20, 2022.

9 C. M. Fligor, S. S. Lavekar, J. Harkin, P. K. Shields, K. B. VanderWall, Huang K.-C., C. Gomes, and J. S. Meyer, "Extension of retinofugal projections in an assembled model of human pluripotent stem cell-derived organoids," *Stem Cell Reports* 16, n° 9, 2021.

10 C. M. Leung, P. de Haan, K. Ronaldson-Bouchard, Kim G.-A., Ko J., Rho H. S., Chen Z., et al., "A Guide to the Organ-on-a-Chip," *Nature Reviews Methods Primers* 2, n° 1, 2022.

11 S. Schmeisser, A. Miccoli, Martin von Bergen, E. Berggren, A. Braeuning, W. Busch, Chr. Desaintes, et al., "New Approach Methodologies in Human Regulatory Toxicology – Not If, but How and When!" *Environment International* 178, 2023.

12 A blastoid is a model of the pre-implantation blastocyst. In humans, this stage is reached 5 to 7 days post-fertilisation.

13 A gastruloid is a model of the post-implantation conceptus, when gastrulation occurs. In humans, this stage is reached 14 to 21 days post-fertilisation.

14 M. Simunovic, and Ali H. Brivanlou, "Embryoids, organoids and gastruloids: new approaches to understanding embryogenesis," *Development*, 144, n° 6, 2017.

used for, we can identify several more definitions applicable to organoids. They are currently being used as research tools for basic and preclinical research to investigate developmental biology, phylogenetics, host-microbe interactions, disease modelling, drug discovery, toxicology, gene editing, and in "omics".[15] They might soon be used as preclinical models[16] for regulatory toxicology, or as medicinal products for diagnostic and therapeutic purposes in precision medicine[17] and regenerative medicine.[18] Some organoids could even be made for bioproduction[19] or biocomputing.[20]

Distinguishing an ontological description of organoids and a functional description of their uses will be important when it comes to their legal classification. Indeed, in the scientific literature, organoids are usually classified by the organ they model first, and by reference to their practical uses second (if at all). Indeed, a liver organoid could be used for any of the purposes listed above. Consequently, from a

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15 Developmental biology is the study of the processes by which animals and plants grow and develop. Phylogenetics is the study of the evolutionary history and relationships between individuals, populations and species. Host-microbe interactions describe how microbes behave within host organisms on a molecular, cellular, organismal or population level. Disease modelling is the creation of representative biological systems that aim to mimic the behaviour of diseases in a controlled environment. Drug discovery is the process by which new candidate medications are discovered. Toxicology is the study of the adverse effects of chemical substances on living organisms. Gene editing is group of techniques aiming at modifying the genetical material of an organism through deletion, insertion, replacement or modification of DNA. Omics are a group of techniques used in biology that end with the suffix -omics, such as genomics, proteomics, metabolomics, metagenomics, transcriptomics etc. They aim at characterising and quantifying pools of biological molecules which help understanding the structure, functions and dynamics (the phenotype) of an organism. To read more about these uses of organoids, see C. Corrò, L. Novellasdemunt, and Li V. S. W. , "A Brief History of Organoids," *American Journal of Physiology*, *Cell Physiology,* 319, n° 1, 2020.

16 In particular "[drug repurposing] represents a very practical and imminent application where [organs on chips] could rapidly supersede conventional experimental approaches used to support medicines repurposing applications (e.g. in vivo animal studies)," CEN, CENELEC, FGOoC, "Focus Group Organ-on-Chip Standardization Roadmap," 2024, p. 64.

17 Patient-derived organoids have successfully been used to identify potential drugs to treat pancreatic cancer. Clinical trials are currently underway: E. Driehuis, , A. Van Hoeck, K. Moore, S. Kolders, H. E. Francies, M. Can Gulersonmez, E. C. A. Stigter, et al., « Pancreatic Cancer Organoids Recapitulate Disease and Allow Personalized Drug Screening », *Proceedings of the National Academy of Sciences* 116, n° 52, 2019.

18 A few trials of organoid-based therapies are underway. See, Choi W. H., Bae D. H., and Yoo J., "Current status and prospects of organoid-based regenerative medicine," *BMB Reports* 56, n° 1, 2023.

19 Bioproduction: manufacturing process using biological systems to produce molecules. These molecules usually are used as therapeutics (protein-based therapeutics, vaccines, gene therapies). For discussion of this possibility, see, for instance: J.-L. Galzi, Th. Jouault, and J. Amédée, « Les organoïdes : des mini-organes au service de la biomédecine », *médecine/sciences* 35, n° 5, 2019.

20 Biocomputing: methods using biological materials and functions to perform computation. Neural organoids could be used to perform computation with far lower energy consumption than standard silicon based computation. For more discussion of this possibility, see L. Smirnova, B. S. Caffo, D. H. Gracias, Huang Q., I. E. Morales Pantoja, Tang B., D. J. Zack, et al., "Organoid Intelligence (OI): The New Frontier in Biocomputing and Intelligence-in-a-Dish," *Frontiers in Science*, 2023.

scientific point of view, classifying organoids according to their type and according to their use are two distinct tasks. Classifying them according to their type relies on ontological criteria such as their cellular make-up, their biological functions, their morphology or their gene expression. Classifying them according to their use depends on the reason why an organoid was created in the first place (for basic research, for preclinical research, for medicinal purposes, etc.).

If this clarification may appear trivial, it is, however, important when it comes to biolaw where function often comes first. The legal classification of organoids among the different legal regimes often hinges on criteria targeting the use made of that object rather than what that object is made of. Under this functional approach, we will see how organoids can be defined as *new approach methodologies, medicinal products*, *specimen* in an in vitro medical device, *genetically modified organisms,* etc.

Consequently, as demonstrated by Marie Glinel, the interplay between these ontological and functional threads is an important feature in biolaw.[21] Indeed, there is a real tension in biolaw between naming things as they stand in the biological world and naming them after their function.[22] When it comes to defining organoids in law, it will not be as simple as transplanting the scientific definition into law. While this could be done in a number of instruments or in case law, it is not clear which broader legal purpose it would serve. A definition of organoids could well appear in a given legal regime or in the context of a case. Yet, the regulatory landscape applicable to organoids is so vast and fragmented that it is unlikely that an isolated definition will become applicable to other legal regimes. Indeed, defining an organoid is highly context-dependent and varies with its ontology and its use. Organoids find themselves at the crossroad of many different policy objectives (promoting human health, promoting innovation, managing environmental risk, protecting societal values).[23] As suggested by the Hybrida project, "[organoids] may be exceptional due to the fact that this breadth of potential applications renders organoid research a focal point, where virtually all ethical, legal and research integrity-related issues converge".[24] Consequently, there is probably no framework that can singlehandedly tackle all of these issues under a unified approach.[25] It is then unclear that a unified

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21 M. Glinel, *L'influence de la qualification juridique dans la répartition des compétences France-Union européenne – L'exemple des biotechnologies*, PhD Thesis, dactyl., Université Toulouse 1 Capitole, 2023.

22 Ibid., p. 411.

23 An object that can be classified under different regimes is more likely to be fragmented than an object regulated by a single regime, ibid., p. 410.

24 P. Kavouras, E. Spyrakou, V. Stavridi, A. Deligiaouri, C. Pence, C. A. Charitidis, and J. Helge Solbakk, "D3.1: Map Report of Normative, Research Ethics and Research Integrity Frameworks," Hybrida Project, 2020, p. 89.

25 A. J. Barnhart, and K. Dierickx, "Too-Many-Oids: The Paradox in Constructing an Organoid Ethics Framework," *Molecular Psychology: Brain, Behavior, and Society* 2, 2023.

definition of organoids in law would be possible. Since organoids are scattered among different legal regimes, identifying a definitive set of criteria that are precise enough to single them out while remaining relevant for all regimes is quite challenging. In other words, instead of elaborating a *concept* of organoids, we might be limited for now to discuss the broader *notion* of organoids in law.

As a preliminary work on the definition of organoids, this article will focus on identifying common threads among the different legal regimes applicable to organoids and to elaborate what might be the typicality of organoids in law. This requires that we identify what sets organoids apart from similar entities such as 2D cell cultures, tissue and cell therapies, organs or embryos.[26] In short, are organoids novel enough to deserve a definition in law?

Our assumption will be that the novelty of organoids will depend on a specific field of application. As long as organoids fit existing definitions and criteria of a legal regime, they do not pose definitional challenges. For instance, in some applications, organoids are clearly regulated and are subsumed in broader categories of objects. When organoids easily fit definitions, it suggests that the applicable framework is quite robust and generally forward looking. However, when we find organoids (and especially their subtypes) that challenge existing legal classifications, then we will have identified areas that highlight their typicality. Some might even exhibit enough specificities to question the relevance of their current legal classification. When definitions become harder to interpret, it demonstrates that we might be reaching the limits of a legal concept. In such case, definitional work is required, as well as a possible regulatory overall of that field of application.

While there is currently no definition of organoids in law, there are actually several definitions applicable to them. We will start by conducting a scoping review of the legal regimes applicable to them in European Union (EU) law and French law[27] and extract the definitions provided therein. These legal regimes and definitions will be analysed to gather classification criteria. On that basis, we will see that organoids can be classified depending on their biological make-up (their essence, their ontology) but most often on their specific use-case (their purpose, their function). This scoping review will offer a first picture of the complex regulatory landscape applicable to organoids technologies (I). To make sense of this complexity, we will see how the various definitions interact with one another and how different stakeholders intervene at various stages of their elaboration. In such a fragmented landscape, the coherence of organoid regulation will be an important subject of interest.

[26] The typicality of organoids in regard to these other structures is not only a question of legal science, but also in fact an open question even for life sciences.

[27] Both choices motivated by linguistic and scientific competence of the author.

We will see that a lot of thought goes into building a consistent system of definitions to avoid gaps and overlaps in the scopes of nearby legal frameworks. However, definitions are not a pure exercise of legal systemic. They also reveal underlying legislative choices and balances of interests that are made when laws are passed. From these considerations, we will be able to extract core features that seem to uniquely characterise the notion of organoids in law (II.).

I. Scoping the Legal Regimes and Definitions Applicable to Organoids

In the following sections, we will present the most relevant legal regimes and definitions applicable to organoids, both in French and EU law. Since our goal in this part is to offer a first look at the key legal regimes applicable to organoids, we will not linger on their substantial provisions but rather focus on the definitions and classification criteria.

There are several regulatory pathways to consider when creating organoids. They can be roughly broken down into three stages,[28] starting with the donation and procurement of human biological material, that needs to be transformed into a product of interest, which can eventually be distributed or stored. Following this approach, we will see that the production of organoids is first governed by legal regimes applying to the elements of the human body (A). Then, other legal regimes will apply to organoid-based products depending on their intended use (B). Finally, regardless of their specific use-case, organoids might also be applied the transversal regime of GMO regulation (C).

A) Organoids and Their Connection to the Human Body

Insofar as organoids can be made from human biological elements, we could expect definitions found in the following legal regimes to reflect a close proximity to the biological reality of the human body. For instance, it would be reasonable to expect that the difference between a cell, a tissue and an organ is a biological matter of fact. Yet, the various frameworks applying to the human body and its elements are not so straightforward in their approach. This section particularly highlights how ethical conversations often focus on ontological criteria, while functional criteria favour a more efficient and utilitarian classification of the human body and its elements.

[28] We are building on the analysis conducted by Aurélie Mahalatchimy in EU law and extending it to include French law. See, A. Mahalatchimy, "Challenges for the implementation of the current EU legal frameworks to organoids," *Les Cahiers de TESaCo*, n° 4, June 2024, pp. 49–58.

The first step of any organoid culture involves procurement of cells, tissues and more generally a substance of human origin (1). From these, organoids are grown to maturity, where they start reproducing some structural and functional features of a given tissue or organ. However, some organoids raise questions regarding their legal classification. First, it is becoming necessary to clarify where organoids stand in relation to actual organs and parts of organs (2). Second, it is also becoming urgent to clarify the relation between embryoids and actual embryos (3).

1) Origins of the Starting Material

One main cluster of regimes applying to organoids relates to the procurement of human biological elements. Cells that are used to create organoids are either obtained directly from donors (for instance by collecting skin cells or tumour cells from surgical waste) or from cell lines managed by biobanks. Despite targeting the same material reality, the European approach (a) and the French approach (b) differ remarkably when it comes to defining elements of the human body.

a) European Approach to Defining Substances of Human Origin: from Ontology to Function

In the European framework, these starting cells and their related activities are now governed by Regulation 2024/1938 on standards of quality and safety for substances of human origin intended for human application (SoHO Regulation).[29] Tissues and cells now fall under the catch-all category of *substances of human origin* (SoHOs). A SoHO is:

> "any substance collected from the human body, whether it contains cells or not and whether those cells are living or not, including SoHO preparations resulting from the processing of such substance."[30]

In turn, these *SoHO preparations* are:

> "a type of SoHO that: (a) has been subjected to processing and, where relevant, one or more other SoHO activities referred to in Article 2(1), point (c); (b) has a specific clinical indication; and (c) is intended for human application to a SoHO recipient or is intended for distribution."[31]

Thus, elements from the human body are defined with a functional overtone: SoHOs are not merely *from* the human body, they are *collected* from it. Similarly, the very broad definition of SoHO preparations refers to operations conducted on

[29] Regulation 2024/1938 of the European parliament and of the Council of 13 June 2024 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, *JO L*, *2024/1938*, 17 July 2024.

[30] Art. 3 (1), ibid.

[31] Art. 3 (37), ibid.

the substance rather than referring to the biological properties of the substance itself. These broad definitions are necessary to achieve the wide encompassing scope intended for the SoHO Regulation. Yet, this leaves us with no definition of cells and tissues.[32] This is a striking departure from the previous Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (T&C Directive).[33] There, *cells* and *tissues* were defined by biological criteria.[34] Even in the proposal for the SoHO Regulation,[35] *cells* and *tissues* were defined on the basis of biological criteria.[36] The SoHO Regulation, in its final version, is therefore a major shift as it almost completely rids itself of ontological definitions in favour of functional definitions. This is in line with the goals pursued by this revision, to design an instrument with a broad scope of application in order to catch under a single regime most of the elements of the human body that are intended for human application. Biological and ontological considerations are set aside to pursue a regulation based on the function of the element. Organoids, as *SoHOs* or *SoHO preparations*, are obviously included in that trend. However, between ontological and functional definitions exists a third possibility as illustrated by French law.

b) French Approach to Defining Substances of Human Origin: Avoidance Strategies

French law is not as thorough in its definitional approach of the elements of the human body. The first French laws governing uses of substances of human origin never defined the biological material to which they applied.[37] For instance, *postmortem* collection of substances of human origin is regulated under two distinct legal frameworks. However, no definitions were provided for cells and tissues, on the one hand, and for organs on the other. To determine which provisions applied

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[32] Only an exemplar list of cells and tissues is provided in recital 7 of the SoHO Regulation, *op. cit.*

[33] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, *OJ L 102*, 7.4.2004, p. 48–58, CELEX number: 32004L0023.

[34] Cells were "individual human cells or a collection of human cells when not bound by any form of connective tissue" and tissues were "all constituent parts of the human body formed by cells," art. 3, ibid.

[35] 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, 14.7.2022, COM/2022/338 final.

[36] A cell was "a mass of cytoplasm with or without a nucleus, that is bound externally by a cell membrane. Usually microscopic in size, cells are the smallest structural and functional unit of an organism" and a tissue was "a group of cells that function together as a unit," art. 3 (3) and (4), ibid.

[37] The law of 7 July 1949 (known as the 'Lafay' law) allowed corneal graft; the law of 21 July 1952 covers therapeutic use of human blood; the law of 22 December 1976 (known as the 'Cavaillet' law) regulates organ harvesting and the law no. 93-5 of 4 January 1993 overhauled the organisation of blood transfusions.

to a given element, one had to refer to lists found in decrees which enumerated cells, tissues[38] and organs[39] that could be obtained *postmortem*. With time, however, definitions were adopted. They are usually found in annexes rather than actually binding provisions. They take the form of entries in a glossary and are copied from those found in EU law.[40] This is why, to this day, elements of the human body are still classified on the basis of the original lists rather than the later definitions. In fact, the single statutory definition found in the Public Health Code (PHC) for an element of the human body is about human iPSCs (hiPSCs).[41] It is noticeably recent in the context of French biolaw as it was introduced in 2021 after the revision of the bioethical law.[42] As it stands, it is more of an oddity than a systemic departure from previous methods.

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[38] The tissues and cells listed are the skin, bones, soft tissues of the musculoskeletal system, corneas, heart valves, arteries and veins. Arrêté 2 août 2005 fixant la liste des tissus et cellules pour lesquels le prélèvement sur une personne décédée présentant un arrêt cardiaque et respiratoire persistant est autorisé, *JORF* n° 0182, 6 August 2005, p. 12902.

[39] The organs listed are the kidney, liver, lung and pancreas. Arrêté du 2 août 2005 fixant la liste des organes pour lesquels le prélèvement sur une personne décédée présentant un arrêt cardiaque et respiratoire persistant est autorisé, *JORF* n° 0182, 6 August 2005, p. 12901.

[40] "Selon la définition prévue par le droit [de l'Union], on entend par 'organe' 'une partie différenciée du corps humain, constituée de différents tissus, qui maintient, de façon largement autonome, sa structure, sa vascularisation et sa capacité à exercer des fonctions physiologiques ; une partie d'organe est également considérée comme un organe si elle est destinée à être utilisée aux mêmes fins que l'organe entier dans le corps humain, les critères de structure et de vascularisation étant maintenus,'" arrêté du 29 octobre 2015 portant homologation des règles de bonnes pratiques relatives au prélèvement d'organes à finalité thérapeutique sur personne décédée, *JORF* n° 0273, 25 November 2015, p. 21839 ; "Cellules : des cellules d'origine humaine isolées ou un ensemble de cellules d'origine humaine non reliées entre elles par un tissu conjonctif, devant subir une ou des étapes de préparation ou de conservation," "Tissu : toute partie constitutive du corps humain constituée de cellules reliées entre elles par une trame conjonctive," Agence française de sécurité sanitaire des produits de santé, décision du 27 octobre 2010 définissant les règles de bonnes pratiques relatives à la préparation, à la conservation, au transport, à la distribution et à la cession des tissus, des cellules et des préparations de thérapie cellulaire, *JORF* n° 0265, 16 November 2010, p. 20447 ; "Organe : Partie différenciée du corps humain, constituée de différents tissus, qui maintient, de façon largement autonome, sa structure, sa vascularisation et sa capacité à exercer des fonctions physiologiques ; une partie d'organe est également considérée comme un organe si elle est destinée à être utilisée aux mêmes fins que l'organe entier dans le corps humain, les critères de structure et de vascularisation étant maintenus," décision nº 2017-14, 22 sept. 2017 de la directrice générale de l'Agence de la biomédecine fixant le modèle du rapport annuel prévu au 9º de l'article R. 1211-37 du code de la santé publique, *BO Santé, protection sociale, solidarité*, 15 November 2017, p. 27.

[41] "On entend par cellules souches pluripotentes induites humaines des cellules qui ne proviennent pas d'un embryon et qui sont capables de se multiplier indéfiniment ainsi que de se différencier en tous les types de cellules qui composent l'organisme," art. L 2151-7 PHC.

[42] X. Bioy, "La loi de bioéthique 2021, plus sociétale que jamais," *Actualité Juridique Droit Administratif*, n° 32, 2021, p. 1826 ; P. Egéa, "La condition embryonnaire," *Actualité Juridique Droit Administratif*, n° 32, 2021, p. 1866.

In conclusion, it is debatable whether the coexistence of older lists alongside newer European-influenced definitions does provide greater clarity or if it instead undermines the coherence of the regulatory framework. From these first considerations, it is remarkable how technical, yet straightforward EU definitions can be when compared to the French approach which suffers from a lack of consistency and clarity. While European definitions of SoHOs is moving towards functional criteria, French definitions do not follow a clear trend. It never really relied on firm ontological or functional definitions, instead favouring lists. These lists do not linger on questions of ontology, nor do they functionally define elements of the human body. For this reason, a definition of organoids in French law seems unlikely: definitions of elements of the human body have never been deemed necessary. However, if a future hypothetical European instrument were to define organoids, then its definition would surely be transposed in French law. Even so, this would not ensure that this definition carries much weight across the French legal system.

Going back to the European level, it is interesting to note that while the SoHO Regulation did repeal the T&C Directive, it did not modify the existing framework on organs. One of the reasons why lies in biology.

2) Are Organoids Organs?

Directive 2010/45/EU on standards of quality and safety of human organs intended for transplantation (Organ Directive)[43] has been kept separate from the SoHO revision. This is due to the fact that the organ legal framework is substantially different from the broader framework on SoHOs. What sets organs apart from other SoHOs is their vascularisation as well as the following risks of ischaemia during their transport.[44] Even if the Directive regulates the *use* of organs for transplantation (their function), it is their *vascularisation* (an ontological feature) that justified that a wholly separate legal regime be put in place. Now that SoHOs are defined by functional criteria, organs are the last element of the human body defined with ontological criteria in hard law. An organ is :

[43] Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation, *OJ L* 207, 6.8.2010, p. 14–29.

[44] Recital 26 of the SoHO Regulation, *op. cit.*: "Solid organs are excluded from the definition of SoHO for the purposes of this Regulation and, thus, from the scope of this Regulation. Their donation and transplantation are significantly different, determined, inter alia, by the effect of ischaemia in the organs, and are regulated in a dedicated legal framework, set out in Directive 2010/53/EU of the European Parliament and of the Council. Composite vascular allografts, such as hands or faces, should be considered as falling within the definition of organs, as indicated in that Directive. Nonetheless, when organs are removed from a SoHO donor for the purpose of separating tissues or cells for human application, for example heart valves from a heart or pancreatic islets from a pancreas, this Regulation should apply."

> "a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularization."[45]

From a technical standpoint, current organoids are far from reproducing the cellular, structural and functional complexity of whole organs. However, with more fine-tuned and sophisticated culture protocols, the question of whether organoids could one day be considered as *organs* naturally arises. From a legal standpoint, one could make the case that sufficiently complex organoids could indeed fulfil the definition of organs. If future organoids are vascularised, maintain their structure, and develop physiological functions with a significant level of autonomy, then the question of their classification as organs or parts of organs would arise. However, the sole fulfilment of the directive's definition should not be the deciding factor in applying its provisions. Indeed, the scope and objectives of the directive does not necessarily align with organoid therapeutic uses. For one thing, organs are obtained from donors, while organoids are grown in vitro. Thus, both processes come with very distinct requirements when it comes to quality and security for instance. The question of whether organoids can be classified as organs under EU law is still yet a theoretical question, but which might need to be clarified in the near future.

Moving on now to embryoids, it is important to state again that they are quite different from other organoids, as they do not model a given organ, but instead model the embryonic development.

3) Are Embryoids Embryos?

One main area of debate in the literature on organoids relates to the possible definitions of embryoid models.[46] While it is generally agreed in the scientific literature that current models are not fully equivalent to embryos,[47] it will become necessary, as they become more faithful, to clarify their definition in relation to embryos. In most jurisdictions, France included,[48] the legal framework covering

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[45] Art. 2, ibid.

[46] A. S. Iltis, G. Koster, E. Reeves, and K. R. W. Matthews, "Ethical, Legal, Regulatory, and Policy Issues Concerning Embryoids: A Systematic Review of the Literature," *Stem Cell Research & Therapy* 14, n° 1, 2023; E. Posfai, F. Lanner, C. Mulas, and H. G. Leitch, "All models are wrong, but some are useful: Establishing standards for stem cell-based embryo models," *Stem Cell Reports* 16, n° 5, 2021; Hyun I., M. Munsie, M. F. Pera, N. C. Rivron, and J. Rossant, "Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells," *Stem Cell Reports* 14, n° 2, 2020.

[47] The current consensus is that embryo models cannot develop into foetuses and neonates (yet). N. Rivron, A. Martinez Arias, M. F. Pera, N. Moris, and H. I. M'hamdi, "An Ethical Framework for Human Embryology with Embryo Models," *Cell*, 186, n° 17, 2023.

[48] J. Granat, "Recherche sur des embryons: obligation d'une double autorisation," *Actualité Juridique Droit Administratif*, 2024, p. 1520. However, there is a clear trend of liberalising embryo research in the last decade: G. Rousset, "La libéralisation continue du régime juridique des recherches sur l'embryon et sur les cellules souches," *Droit de la famille*, n° 10 (1 October 2021) ; P. Égéa, *op. cit.*

embryo research is more stringent than the framework of stem cell research.[49] Against this backdrop, it is then important to carefully examine definitional criteria of embryos provided in law and compare them to current embryoid models. Indeed, if embryoids were classified as embryos in these jurisdictions, they would trigger a more stringent regime.[50]

From a legal point of view, the European Court of Justice provided what is generally accepted as the legal definition of the human embryo. In the *Brüstle* case,[51] the Court had to interpret the term "human embryo" as provided by the Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions.[52] Doing so, it stated that its autonomous interpretation of the term had to "be understood in a wide sense".[53] Thus:

> "[. . .] any human ovum must, as soon as fertilised, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive, since that fertilisation is such as to commence the process of development of a human being."[54]

This led the Court to "assimilate human embryos and other human organisms created by scientific and technological means with the same capacity of development as human embryos",[55] such as parthenotes.[56] Subsequently, in the *International Stem Cell Corporation* case,[57] the Court established a "capacity" criterion:

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[49] A. M. Daoud Pereira, M. Popovic, W. J. Dondorp, M. T. Bustos, A. L. Bredenoord, S. M. Chuva de Sousa Lopes, S. C. van den Brink, B. A. J. Roelen, G. M. W. R. de Wert, and B. Heindryckx, "Modelling Human Embryogenesis: Embryo-like Structures Spark Ethical and Policy Debate," *Human Reproduction Update* 26, n° 6, 2020.

[50] For instance, the Australian Embryo Research Licensing Committee (ERLC) of the National Health and Medical Research Council made a decision that blastoid models come within the definition of a human embryo under the Research Involving Human Embryos Act 2002. Consequently, research on blastoid models has to comply to the strict ethical and legislative requirements applicable to embryo research. See, National Health and Medical Research Council, "NHMRC Statement on iBlastoids," 18 March 2021.

[51] European Court of Justice (GC), 18 October 2011, *Oliver Brüstle v Greenpeace eV.*, C-34/10, ECLI:EU:C:2011:669.

[52] See art. 6(2)(c) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, *OJ* 1998 L 213, 30.7.1998, p. 13–21.

[53] Ibid., §§26 and 34.

[54] European Court of Justice, Brüstle, *op. cit.*, §35.

[55] P. Cruz Villalón, opinion delivered on 17 July 2014 in *International Stem Cell v Comptroller General of Patents*, C-364/13, ECLI:EU:C:2014:2104, §47.

[56] Parthenotes are non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis using an electrical or chemical stimulus.

[57] European Court of Justice, 18 December 2014, *International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks*, C-364/13, ECLI:EU:C:2014:2451.

"[the term "human embryo"] must be understood as meaning that, in order to be classified as a 'human embryo', a non-fertilised human ovum must necessarily have the inherent capacity of developing into a human being.

Consequently, where a non-fertilised human ovum does not fulfil that condition, the mere fact that that organism commences a process of development is not sufficient for it to be regarded as a 'human embryo', within the meaning and for the purposes of the application of Directive 98/44."[58]

While these decisions were influential, it is also important to note that this criterion has been the focus of many bioethical discussions much older than these cases.[59] Therefore, in the context of EU law, to know whether an embryoid model could be assimilated to an embryo would depend on their developmental capacity.[60]

In contrast, there is no explicit definition of the embryo provided in French statutory law or case law. However, the emergence of embryoid models inevitably led to discussions on their definition and status. Firstly, the 2021 revision of the bioethics law introduced the term of "*modèle de développement embryonnaire*" (embryonic developmental model) in the title covering stem cell research in the PHC.[61] Opting to include embryonic developmental models (or embryoids) under the regime of stem cell research instead of embryo research, lawmakers clearly decided that, for now at least, embryoids and embryos shall not be assimilated. Secondly, the French biomedicine agency[62] also contributed its definition to the debate. Its orientation council[63] delivered an opinion on embryoids,[64] establishing two criteria that differentiate embryoids from embryos. The first relates to their origin as embryoids are not made from the fusion of two gametes.[65] The second relates to an external subjective element since embryoids are not created in the context of a

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58 Ibid., §§28-29.

59 Denker, Hans-Werner, "Human Embryonic Stem Cells: The Real Challenge for Research as Well as for Bioethics Is Still Ahead of Us," *Cells, Tissues, Organs* 187, n° 4, 2008; M. Reichlin, "The Argument from Potential: A Reappraisal," *Bioethics* 11, n° 1, 1997; S. Buckle, "Arguing from Potential," *Bioethics* 2, n° 3, 1988.

60 For a discussion on important "tipping points" for the developmental capacity, see N. C. Rivron, A. Martinez Arias, M. F. Pera, et al., "An ethical framework for human embryology with embryo models," *Cell*, 186, august 2023, n° 17, p. 3548–3557.

61 Arts. L2151-6 and L2151-7 PHC.

62 The agency is notably responsible for delivering authorisation of embryo research protocols and receiving declaration of research protocols on stem cells.

63 The biomedicine agency relies on its orientation council to ensure that patients, donors and ethical principles are respected in the activities within its remit. It provides reasoned opinions on the quality of the Agency's medical and scientific expertise, taking into account ethical issues.

64 Ch. Bruno, H. Letur, R. Lévy, C. Therry, E. Bieth, A. de Broca, M. Delpech, and F. Guérin, "Avis du Conseil d'orientation de l'Agence de biomédecine : les modèles embryonnaires," 2023.

65 Embryos being the result of the fusion of a male gamete and a female gamete, while embryoids were made from stem cells, Ibid., p. 5.

parental project.[66] Both of these criteria are debatable as they are quite restrictive.[67] The opinion of the orientation council also endorsed the definitions suggested by the International Society for Stem Cell Research (ISSCR)[68] for "integrated" and "non-integrated embryo models".[69] This distinction somewhat mirrors the developmental potential criterion: non-integrated models are not able to undergo further development, while integrated models can be "at risk" of attaining increased developmental potential. Yet, nowhere in its opinion does the orientation council make an explicit reference to the capacity criterion itself. This is surprising as it is undeniable that it has had durable influence in doctrinal discussions and earned at least some degree of recognition with national institutions.[70] One cannot help but wonder why such an important ontological criterion has been omitted, in favour of a restrictive ontological criterion (their origin) and a questionable functional criterion (the parental project).

Debates surrounding embryoid definitions illustrate a broader feature of organoid definitions in general: they emerge from a discursive practice. When there is a clear and identified need for definitional criteria which is not filled by lawmakers, other actors contribute their expertise. Academics, courts, professional associations and administrative bodies all intervene to better define embryo models, to assess how far they are from a real embryo and to regulate them accordingly. Consequently, even if French lawmakers have been reluctant to define sensitive entities in the past, we can anticipate that definitional criteria will have to be adopted for embryoid models, if not in binding provisions, at least in soft law instruments. In the meantime, while lawmakers avoid taking position on these important questions, a consensus is slowly emerging on the definitions suggested by the professional associations[71] which

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66 Under French law, *in vitro* embryos can only be made for assisted reproduction therapies, requiring a parental project. Consequently, even embryos donated for research purposes were once subject of a parental project. In comparison, an embryoid is not subject of such a project. Ibid.

67 Firstly, because some entities are classified as embryos despite the fact they do not result from the fusion of two gametes (i.e. cloned embryos). Secondly, because even if a parental project is required for creating *in vitro* embryos in the context of assisted reproductive technologies, it is obviously not the case of *all* embryos.

68 International society for stem cell research, "ISSCR Guidelines for Stem Cell Research and Clinical Translation," 2021.

69 A dichotomy hinging on the ability of an embryo model to pursue a more complex or "integrated" development, thus being closer to the critical "ability to develop into a human being".

70 Comparing hESCs and embryos, the French Council of State realises an elegant synthesis of the French and European perspectives: "En particulier, contrairement à l'embryon, les cellules souches embryonnaires n'ont pas la capacité de se développer pour devenir un organisme viable. Elles ne disposent donc pas de la spécificité, soulignée notamment par la jurisprudence […] qui confère à l'embryon son statut particulier de '*personne humaine potentielle*'," Rapport du Conseil d'État, projet de loi relatif à la bioéthique, § 53, p. 22, 18 July 2019.

71 At the time of this writing, this consensus is not without uncertainties, as the distinction between "integrated" and "non-integrated" embryo models might not endure. A. T. Clark, H. Cook-Andersen, S. Franklin, et al., "Stem cell-based embryo models: The 2021 ISSCR stem cell guidelines revisited," *Stem Cell Reports*, 20, n° 6, Elsevier, June 2025.

are in turn adopted by national agencies. Whether these definitions emerge from expert circles or from a democratic process, they will both result from a consensus.[72] However, prioritising one type of consensus over the other will inevitably mean arbitrating important societal values.

As we have seen in these last few subsections, organoids unearth important definitional features when comparing legal regimes applying to the human body, to SoHOs and to the embryo. In summary, European union biolaw is increasingly adopting functional definitions and France is steering clear of adopting definitions of its own. Yet, it is undisputable that major considerations still have to be had for the ontology of organoids. Such enquiries often confront us with important ethical questions about the reification of biology or about the beginning of human life. These are important questions that should not be hastily set aside.[73] Functional criteria favour a utilitarian view of the human body and should thus be used responsibly. In the next sections, we will study definitions applicable to organoids which purely depend on their function.

B) Organoids and Their End Uses

There are three main clusters of activities that have comprehensive regulatory frameworks in place for organoid uses. Since these regimes deal primarily with the use made of a product, rather than its composition, the expectation here is that the definition of organoids will disappear behind other broader classifications of objects that are defined by their function rather than their ontology. The three main frameworks of interest cover basic research uses (1), preclinical uses (2) and clinical uses (3).

1) Basic Research and Sensitive Organoid Research Protocols

Basic research uses of organoids are regulated at the national level under stem cell research frameworks. In French law, a title of the PHC is dedicated research protocols on human embryos, hESCs and hIPSCs. Since 2021, the law distinguishes protocols on embryos, protocols on hESCs and protocols on hIPSCs.[74] More specifically, articles L2151-6 and L2151-7 PHC organise declaration procedures

[72] In the United-Kingdom, the Human Fertilisation and Embryology Authority and the Nuffield Council on Bioethics have endorsed the Code of practice put together by Cambridge Reproduction. See, Cambridge Reproduction and Progress Educational Trust, "Code of practice for the generation and use of human stem cell-based embryo models," July 2024; Nuffield Council on Bioethics, "Human stem cell-based embryo models: A review of ethical and governance questions," 2024.

[73] A. Le Goff, "Les organoïdes, la nouvelle frontière du vivant de laboratoire," *Revue semestrielle de droit animalier*, n° 2, 2022.

[74] A. Gilson-Maes, "La libéralisation de la recherche sur l'embryon humain et sur les cellules souches issues du corps humain dans le projet de loi relatif à la bioéthique," *Médecine & Droit* 2020, n° 162, 2020.

to the biomedicine agency for research protocols on stem cells.[75] They list types of protocols that trigger a different procedure before the biomedicine agency where the orientation council is required to deliver an opinion when such a protocol is examined. These "sensitive" cases include protocols for *differentiating stem cells in gametes*, obtaining *in vitro models of embryonic development*, or inserting *human cells in animal embryos destined to be implanted in animals*. In the case of organoid research, some protocols would indeed fall under these listed cases. For instance, embryoid models are classified as "in vitro models of embryonic development".[76] For protocols producing gonadal organoids, it is unclear whether they could be construed as "protocols for differentiating stem cells into gametes".[77] Yet, this list does not account for various types of entities currently being grown in vitro which are raising ethical questions. For instance, a large body of literature is developing on the ethics of neural organoids[78] and chimeras engrafted with neural organoids.[79] Barely enacted, this list of protocols might already be ill adapted to the fast-changing landscape of stem cell derived entities. With the future revision of the French bioethical law, other organoid models might come under scrutiny.

Again, as with substances of human origin, French law relies on a limitative list instead of trying to define broad classes of objects. Such an approach would seem effective if the list of protocols were assured to remain static in the coming years. However, by proceeding this way, any new inclusion of sensitive protocols would require a revision of the law. With a rapidly evolving research landscape, a more future-proof approach might soon be needed. A possible avenue could be instead

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75 A.-M. Leroyer, "Embryon - Recherche - Cellules souches," *Revue trimestrielle de droit civil*, n° 04, 2013.

76 At the time of this writing, it is unclear if this applies to all embryoid models or only to complex models such as blastoids.

77 This would probably depend on whether the gonadal organoid is mature enough to produce gametes itself. Even then, strictly speaking, a gonadal organoid producing gametes would not be exactly the same process as *differentiating stem cells into gametes*. However, a purposive interpretation of the term could imply otherwise, focusing on the fact that the end result is the in vitro production of gametes with stem cells as starting material.

78 See, for instance, H. T. Greely, "Human Brain Surrogates Research: The Onrushing Ethical Dilemma," *The American Journal of Bioethics*, 21, n° 1, 2021 ; M. Owen, Z. Huang, C. Duclos, A. Lavazza, M. Grasso, and A. G. Hudetz, "Theoretical Neurobiology of Consciousness Applied to Human Cerebral Organoids," *Cambridge Quarterly of Healthcare Ethics*, 2023 ; M. Kataoka, T.-L. Lee, and T. Sawai, "The Legal Personhood of Human Brain Organoids," *Journal of Law and the Biosciences*, 10, n° 1, 2023.

79 A. Erler, "Human Brain Organoid Transplantation: Testing the Foundations of Animal Research Ethics," *Neuroethics* 17, n° 2, 2024; J. J. Koplin, "Response to the ISSCR Guidelines on Human–Animal Chimera Research," *Bioethics* 37, n° 2, 2023; J. Johnston, I. Hyun, C. P. Neuhaus, K. J. Maschke, P. Marshall, K. P. Craig, M. M. Matthews, et al., "Clarifying the Ethics and Oversight of Chimeric Research," *Hastings Center Report* 52, n° S2, 2022; J. Taupitz, and M. Weschka, *CHIMBRIDS – Chimeras and Hybrids in Comparative European and International Research: Scientific, Ethical, Philosophical and Legal Aspects*, Vol. 34, Veröffentlichungen Des Instituts Für Deutsches, Europäisches Und Internationales Medizinrecht, Gesundheitsrecht Und Bioethik Der Universitäten Heidelberg Und Mannheim. Berlin, Heidelberg: Springer Berlin Heidelberg, 2009.

to establish an abstract and broad legal category of "sensitive protocols". Its scope could be defined by inclusion criteria based on ethically sensitive characteristics of the protocols. For instance, a protocol could be defined as sensitive based on the characteristics of the entity it will create.[80] Such an approach would require an in-depth consideration of the ontological features that are deemed ethically significant. Thus, contrary to the expectation formulated above, the French basic research framework does not provide functional definitions. For now, it relies on a list of sensitive protocols. However, it might well require ontological criteria in the future to cover novel types of protocols. These criteria would more closely match ethical issues raised by stem cell research but this approach would be in stark contrast with other frameworks regulating organoid uses.

2) Preclinical Research and Organoids as Replacement Models

Some of the most promising applications of organoids and OoCs concern preclinical studies.[81] The current standard to generate preclinical data in toxicology is to rely on animal experiments.[82] However, animal-based models often lack human relevance and have a low predictability rate. The ethics of animal research have increasingly been called into question due to growing pressure to move away from such practices.[83] To this end, the EU has explicitly etched into law the "3R" principles (Replacement, Reduction, and Refinement) aiming at increasing the welfare of animals used in experiments.[84] In pursuing these principles, experimenters are urged to use *alternative approaches*[85] ("*approches alternatives*" or "*méthodes alternatives*" in French)[86] that is to say technical alternatives to reduce the number of animals

[80] Potential broad inclusion criteria could be "an entity capable of gametogenesis," "an entity capable of functional neural activity," "an entity in which human biological material contributes significantly to a non-human animal biological functions". These three criteria would each cover various types of mature gonadal organoids, neural organoids and chimeras.

[81] A. L. Bredenoord, H. Clevers, and J. A. Knoblich, « Human Tissues in a Dish: The Research and Ethical Implications of Organoid Technology », *Science* 355, n° 6322, 2017.

[82] To be clear, animals are also used in basic research. Yet, most of the work to develop alternatives to animal research has been done in the field of preclinical studies (i.e. toxicology). Hartung, Thomas, "Research and Testing Without Animals: Where Are We Now and Where Are We Heading?" In *Animal Experimentation*, ed. Kathrin Herrmann and Kimberley Jayne. Working Towards a Paradigm Change, Brill, 2019.

[83] J. MacClellan, "Minding Nature: A Defense of a Sentiocentric Approach to Environmental Ethics," University of Tennessee, 2012; P. Carruthers, *The Animals Issue: Moral Theory in Practice*, Reprint, Cambridge, Cambridge Univ. Press, 1994.

[84] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, *OJ L 276*, 20 October 2010, p. 33–79.

[85] Ibid., recitals 10, 42, 46-47 and art. 47.

[86] See, for instance, art. R214-130 of the Rural and Marine Fisheries Code regarding the development, validation and promotion of alternative approaches and décret n° 2013-118 du 1er février 2013 relatif à la protection des animaux utilisés à des fins scientifiques, *JORF* n° 0032, 7 février 2013, p. 2199 for mentions of alternative methods.

used or, at least, to reduce their suffering. Additionally, the European Commission and European member states have been tasked with furthering the development and validation of alternatives.[87] Organoids and OoCs are among the best candidates for this purpose.[88] New molecules could be directly tested on organoids made of human tissues rather than on animals, thus reducing the number of animals used for toxicity assays, as well as increasing the representativeness of results. They are gaining gradual regulatory approval, appearing in several policy instruments from the EU Reference Laboratory for alternatives to animal testing (EURL-ECVAM)[89] and the European Medicines Agency (EMA).[90] This culminated in their inclusion in the proposed reform of the European pharmaceutical regime[91] as *new approach methodologies* (NAMs).[92] Thus, they could soon be used to provide non-clinical data in support clinical trials and marketing authorisation applications. This radical departure from previous practices using animal data was initiated in the United States by the Food and Drug Administration.[93]

From a definitional standpoint, the proposed reform includes organoid models in a larger list of objects rather than specifically defining them. For instance, both the proposed Directive and Regulation list organoids models among new approach

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87 Recitals 46-47 and art. 47 of Directive 2010/63/EU, *op. cit.*

88 "Over the past decade, cell culture-based toxicological testing in combination with high-content visualization techniques, complex organoid systems, omics, advanced modelling and prediction systems have updated the toxicological toolbox profoundly. These scientific advances gave rise to an increased understanding of systems biology and toxicological mechanisms, leading to the development of new conceptual approaches to chemical hazard assessment. The use of NAM approaches also provided insights into the nature of possible interactions of chemicals with regard to their biological targets," S. Schmeisser, A. Miccoli, M. von Bergen, E. Berggren, A. Braeuning, W. Busch, C. Desaintes, et al., "New Approach Methodologies in Human Regulatory Toxicology – Not If, but How and When!" *Environment International*, 178, 2023.

89 Joint Research Centre (European Commission), J. Barroso, S. Batista Leite, E. Berggren, S. Bopp, D. Carpi, S. Casati, et al., *Non-Animal Methods in Science and Regulation: EURL ECVAM Status Report 2022*, Publications Office of the European Union, 2023.

90 *3RsWP Meeting Report*, European Medicines Agency, 21 April 2023.

91 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, 26.4.2023, COM/2023/193 final; 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, 26.4.2023, COM/2023/192 final.

92 Recital 31 of the Proposal for a Directive, COM/2023/192 final, *op. cit.* and recital 46 of the Proposal for a Regulation, COM/2023/193 final, *op. cit.*

93 M. Wadman, "FDA No Longer Has to Require Animal Testing for New Drugs," *Science*, 379, n° 6628, 2023; P. Rand, FDA Modernization Act 2.0, Pub. L. No. S. 5002, 2022.

methodologies that should be favoured, where possible, over animal testing.[94] The proposed Directive also primarily focuses on the definition of non-clinical studies, where OoCs are listed among other methods that can be used aside from animal testing:

> "A non-clinical study is a study or a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test related to the investigation of the safety and efficacy of a medicinal product. Such test may include simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling, other non-human or human biology-based test methods, and animal-based tests."[95]

Here, Organoids and OoCs are not defined *per se*. Rather they are exemplary items of a broader legal category. It is their function that triggers their inclusion in that legal category. Defining each item of this list might have been deemed unnecessary, as experts of the field have been closely monitoring the development of these various alternative models. Indeed, the inclusion of organoids and OoCs as NAMs is in fact grounded on extensive European[96] and international[97] soft law guidance laying down conditions for their regulatory acceptance. Yet, without proper definitions, one has to rely on a "common sense" understanding of the terms which might hinder legal classification of borderline cases in the future. Interestingly, we can find an example of a more comprehensive approach at the French level. The position paper published

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94 "[. . .] the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D-) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models," Proposal for a Directive relating to medicinal products for human use, *op. cit*., recital 31. See recital 46 of the Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, *op. cit.*

95 Art. 4, Proposal for a Directive relating to medicinal products for human use, *op. cit.*

96 Committee for Human Medicinal Products, "Mandate, objective and rules of procedure for the Non-Clinical and New Approach Methodologies European Specialised Expert Community," European Medicines Agency, 14 March 2023; S. Batista Leite, M. Cipriano, D. Carpi, S. Coecke, M. Holloway, R. Corvi, A. Worth, J. Barroso, M. Whelan, "Establishing the scientific validity of complex in vitro models.: Results of a EURL ECVAM survey," Publications Office of the European Union, Luxembourg, 2021; EURL ECVAM, "EURL ECVAM Status Report on the Development, Validation and Regulatory Acceptance of Alternative Methods and Approaches (2019)," EURL ECVAM, 9 March 2020; EMA, "First EMA Workshop on Non-Animal Approaches in Support of Medicinal Product Development – Challenges and Opportunities for Use of Micro-Physiological Systems (EMA/CHMP/SWP/250438/2018)," 2018. See, most recently, this meeting report: M. Piergiovanni, M. Mennecozzi, S. Stavroula, et al., "Heads on! Designing a qualification framework for organ-on-chip," *ALTEX – Alternatives to animal experimentation*, 41, April 2024, n° 2, p. 320-323.

97 OECD, Guidance Document on Good In Vitro Method Practices (GIVIMP). OECD Series on Testing and Assessment, 2018; OECD, Guidance Document for Describing Non-Guideline In Vitro Test Methods. OECD Series on Testing and Assessment, 2017.

by the French National Agency for Medicines and Health products safety (ANSM) offers both a definition of OoCs as well as potential regulatory requirements.[98] This definition is an interesting combination of ontological criteria (*what it is made of*) and functional criteria (*what it aims at accomplishing*):

> "An organ-on-a-chip is a microphysiological system combining tissue engineering and microfluidics, composed of one or more types of cells cultivated in vitro, in 3D, and perfused continuously. The organ-on-a-chip aims to reproduce an architecture close to in vivo physiology, by recreating an organ-specific microenvironment through different stimuli (mechanical, electrical or biochemical)."[99]

The functional criteria are broad enough to not point to one specific use of OoCs, which is often the case with functional definitions provided in legal frameworks. This can be explained by the fact that this position paper's definition is rather an attempt at providing a consensual *scientific* definition rather than a positive *legal* definition for the purpose of a given legal regime.

All in all, such definitional work relies heavily on the close collaboration of stakeholders from institutional bodies, the academia, private research centres and the industry.[100] It is made publicly available in soft law instruments in various form (meeting reports, guidance documents, position papers). As with embryoids, it is grounded on iterative and discursive processes. They gradually reach consensual definitions and regulatory requirements which in turn helps reaching standards that are acceptable and applicable by all stakeholders. A striking feature of organoids and OoCs as NAMs is that their definition is intrinsically linked to what a "good" NAM is. Indeed, to be considered a NAM, models have to follow validation, standardisation and qualification requirements. Yet, neither their definition nor their regulatory requirements are found in hard law instruments. Consequently, organoids and OoCs find themselves in a strange limbo state (even in the current state in the pharmaceutical reform) where they are given an increasingly important role to pursue regulatory objectives such as the 3Rs principles, while lacking clear definitions and regulatory requirements in hard law.

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[98] Suggested regulatory requirements include justification of the concentration of tested molecule, choice of the microfluidic chip, justification of the experimental protocol (and compatibility with physiological phenomena), choice of measured parameters, choice of analytical and quantification methods, model validation and duration of the study. S. G. Teixeira, P. Houeto, F. Gattacceca, N. Petitcollot, D. Debruyne, M. Guerbet, J. Guillemain, I. Fabre, G. Louin, and V. Salomon, "National reflection on organs-on-chip for drug development: New regulatory challenges," *Toxicology Letters*, 388, 2023, p. 9–11.

[99] Ibid., p. 3.

[100] For an example of such work done in France, see G. Mottet, A. Grassart , P. Barthélémy, et al., "Organoïdes, organes sur puce, complex in vitro model: définitions, applications, validation, éthique," *Therapies*, 80, n° 1, January 2025, p. 1-16.

Therefore, hesitations remain on the definition of organoids and OoCs. They are only listed in the pharmaceutical reform but are given ontological and functional definitions in soft law instruments. This clearly shows that this regulatory pathway is still being shaped. It is also possible that the final version of the reform of the EU pharmaceutical legislation might take a different stance on their definitions, similarly to what happened with the SoHO Regulation.

Turning now to clinical applications, it will become apparent that medicinal products and medical devices are greatly shaped by functional considerations, while not entirely dismissing biological criteria.

3) Clinical Applications of Organoids for Human Health

Clinical applications of organoids will be categorised as medicinal products in the case of regenerative medicines (1) and OoCs will be classified as in vitro diagnostic medical devices when used for diagnostic purposes and treatment response prediction (2).

a) Medicinal Products

Organoids could be used for therapeutic purposes to restore diseased tissues in patients. As cell therapies, they can be derived either from patients themselves (autologous uses) or from donors (allogenic uses). Starting cells can even be genetically modified when the pathological trait is caused by a genetic mutation. Therapeutic organoids will be regulated as *medicinal products* (MPs) under Directive 2001/83/EC on the Community code relating to medicinal products for human use (MP Directive).[101] A medicinal product is:

> "(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis", and are products "for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process."[102]

More specifically, therapeutic organoids will be regulated as *advanced therapy medicinal products* (ATMPs) under Regulation No 1394/2007 on advanced therapy medicinal products (ATMP Regulation).[103] In turn, the ATMP regulation offers

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[101] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, *OJ L 311*, 28 November 2001, p. 67–128.

[102] Art. 1 (2) and art. 2 respectively, Directive 2001/83/EC, *op. cit.*

[103] The ATMP Regulation is a *lex specialis* of the MP Directive. To be classified as an ATMP, a product also has to fulfil the criteria of MPs.

an even finer grained categorisation. Organoid based therapies would most likely fall under the category of *tissue engineered products* (TEPs)[104] since the starting cells undergo substantial manipulation to develop into organoids and they are not intended to be used for the same essential functions in the recipient as in the donor.[105] For organoids that are genetically modified, they could be categorised as *gene therapy medicinal products* (GTMPs).[106] Organoids that are ATMPs integrating medical devices[107] would be classified as *combined advanced therapy medicinal products* (CATMPs),[108] a category especially designed to reduce uncertainty for these borderline products.[109] Finally, the ATMP regulation also carves a "hospital exemption" which leaves room for smaller-scale productions to be regulated at the national level. Accordingly, in French law, depending on the type of establishment producing these therapies and their scale of production, organoids will either be

[104] A tissue engineered product is a product that "contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition," art. 2 (b), Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, *OJ L 324*, 10 December 2007, p. 121–137.

[105] By engineered, it is meant that "the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annexe I, in particular, shall not be considered as substantial manipulations, [and that] the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor," art. 2 (c), ibid.

[106] A gene therapy medicinal product is "a biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence," Part IV of Annex I to Directive 2001/83/EC, *op. cit*.

[107] A medical device is "any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more [. . .] specific medical purposes [. . .] and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means," art. 2 (1), Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, *OJ L 117*, 05 May 2017, p. 1–175.

[108] A combined advanced therapy medicinal product "must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1 (2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1 (2)(c) of Directive 90/385/EEC, and its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to," art. 2 (d), Regulation (EC) No 1394/2007, *op. cit*.

[109] Recital 4 and art. 2 (1)(d), ibid.

regulated under the general regime of the ATMP regulation as "*médicaments de thérapie innovante*" (MTI, which is the French translation of ATMP) or be regulated under the hospital exemption and be called "*médicaments de thérapie innovante préparés ponctuellement*" (MTI-PP).[110]

The MP and ATMP regimes exhibit a complex interplay of functional and biological criteria. Definitions often include a functional criterion such as the expected effect on human health, followed by the precise biological mechanism used to reach that purpose. For instance, the important criterion of "substantial manipulation" used to classify a tissue as "engineered" hinges on ontological changes—to its biological characteristics, physiological functions or structural properties—. This interesting interplay between function and ontology can be explained by the fact that medicinal products interact with the biology of the human body. Thus, important classifications have to be made on the level of biology. To capture the specificities of each of these products, the MP and ATMP frameworks rely on many criteria that are either cumulative or alternative. This creates a complex regulatory framework which aims at regulating medicinal products that all serve a similar health purpose but do so through very different modes of action.

Organoids have just recently emerged as potential candidates for cell therapies. Thus, it is not surprising that they are not mentioned in the ATMP Regulation. Moreover, they do not seem distinct enough from other cell therapies to deserve a category of their own in hard law. Different types of organoid therapies would instead be classified among the existing categories of the ATMP Regulation. Therefore, even if the MP and ATMP frameworks extensively rely on biological criteria, they would still classify organoid therapies under broader categories of medicinal products.

For medical devices, the emphasis on their functions is even more pronounced in their definition.

b) In Vitro Diagnostic Medical Devices

Still in a clinical context, organoids could be cultured and analysed by an in vitro diagnostic medical device (IVDMD) to diagnose illnesses or predict treatment response in a patient.[111] They are covered by Regulation 2017/746 on in vitro diagnostic medical devices[112] which defines an IVDMD as:

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[110] Art. L5121-1, 17° PHC makes explicit reference to the definition provided by the ATMP Regulation.

[111] As they require viable biological materials, organoids and OoCs are exempt from the scope of the Regulation 2017/745 on medical devices. See, art. 1(6) of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, *OJ L 117*, 05 May 2017, p. 1–175.

[112] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices, *OJ L 117*, 05 May 2017, p. 176–332.

> "Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state; (b) concerning congenital physical or mental impairments; (c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients; (e) to predict treatment response or reactions; (f) to define or monitoring therapeutic measures."[113]

The organoid would then be the *specimen* that is being analysed by the IVDMD. At the national level, article L5221-1 PHC simply reproduces the European definition of IVDMDs. Organoids would then be "*échantillons*" (which is the French translation of specimens). The IVDMD definition relies on broad criteria targeting all kinds of devices, serving various types of clinical functions. Despite being used in a clinical context, IVDMDs are not so closely connected to the human body than other medicinal products,[114] which is reflected in its definition. In the IVDMD Regulation, the specimen from the human body is mostly contingent.

Consequently, organoids by themselves would not be categorised as IVDMDs. Instead, it is the microfluidic device necessary for OoCs that would be an IVDMD when it is used in a clinical setting for the examination of specimens. Among the legal frameworks considered, this is probably where organoids are furthest away from the regulatory focus.

In conclusion of this section, it appears that both ATMP and MD/IVDMD frameworks will be immensely relevant to mature therapeutic uses of organoids. Yet, organoids find themselves entirely subsumed in broader categories of products. They also do not appear to raise immediate issues regarding their classification, which signals that these legal regimes are quite resilient. Even if questions might be raised regarding the finer classification of organoids among the different types of ATMPs, this is an issue faced by all ATMPs in general.[115] Consequently, organoids used in a clinical context do not appear particularly distinct from other types of products in that category, making it less likely to see a definition emerge in these frameworks.

Finally, irrespective of the stage of development of an organoid and irrespective of its end use, it will be applied the GMO frameworks if it is genetically modified.

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[113] Art. 2 (2), Ibid.

[114] For MDs that do end up in the human body, see the combined advanced therapy medicinal products in the previous section.

[115] Correct classification of ATMPs is so complex that is it ultimately a matter of case-by-case analysis. See, A. Mahalatchimy, *L'impact du droit de l'Union européenne sur la règlementation des médicaments de thérapie innovante en France et au Royaume-Uni*. PhD Thesis, Université Toulouse 1 Capitole, 2015, p. 647.

C) The Transversal Frameworks of GMOs

Finally, irrespective of their uses, the GMO framework will apply to any organoids that have been genetically modified at any point in their production. The European framework provides two transversal regimes, distinguishing contained uses[116] from deliberate releases[117] of genetically modified organisms. From a definitional standpoint, organoids will be defined as *genetically modified (micro-)organisms* when such processes are applied to them.[118] French law reproduces and combines the definitions provided by both Directives.[119] Their classification between the two Directives does not hinge on the definitions of an organism or micro-organism (which also happen to be purely biological definitions). Rather, their application will be decided by two main criteria. Firstly, there is the question of their classification as "genetically modified" organisms. Even if this classification relies on a biological criterion (whether "genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination"), the criterion is in fact intertwined with techniques that are listed in the annexe of the Directives. Secondly, the application of one Directive or the other depends on the context of use of the GMO: whether it is being contained or released. So, even if these Directives contain ontological definitions, classification will ultimately rely on the technique used (and whether it is included in the list in annex) as well as the broader context of use.

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[116] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, *OJ L* 125, 21.5.2009, p. 75–97, CELEX number: 32009L0041.

[117] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, *OJ L* 106, 17.4.2001, p. 1–39, CELEX number: 32001L0018.

[118] A micro-organism is "any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture" and a genetically modified micro-organism is "a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination; within the terms of this definition: (i) genetic modification occurs at least through the use of the techniques listed in Annexe I, Part A; (ii) the techniques listed in Annexe I, Part B, are not considered to result in genetic modification," respectively point a and b, art. 2, Directive 2009/41/EC on the contained use of genetically modified micro-organisms. An organism is "any biological entity capable of replication or of transferring genetic material" and a genetically modified organism an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination; Within the terms of this definition: (a) genetic modification occurs at least through the use of the techniques listed in Annexe I A, part 1; (b) the techniques listed in Annexe I A, part 2, are not considered to result in genetic modification" , respectively point 1 and 2, art. 2, Directive 2001/18/EC, *op. cit.*

[119] Organisms and genetically modified organisms are defined in art. L531-1 of the Environmental Code: "*Au sens du présent titre, on entend par : 1° Organisme : toute entité biologique non cellulaire, cellulaire ou multicellulaire, capable de se reproduire ou de transférer du matériel génétique ; cette définition englobe les micro-organismes, y compris les virus, les viroïdes et les cultures de cellules végétales et animales ; 2° Organisme génétiquement modifié : organisme dont le matériel génétique a été modifié autrement que par multiplication ou recombinaison naturelles.*"

However, classification of newer gene editing techniques is not straightforward precisely because of this interplay between ontological and functional approaches.[120] In the debates over the inclusion of newer gene editing process, discussions will dive into questions of ontology and notably the naturalness or artificiality of a process.[121] Even if biological criteria are not centre stage in hard law, biological arguments will be leveraged by interested stakeholders. Again, there is a clear trend of using ontological or functional criteria for strategic purposes.

This last subsection concludes this panorama of the organoid regulatory landscape, which covered organoid production from the collection of the starting material to their end uses, including the transversal regimes of GMOs. On the one hand, the specificity of organoids is quite apparent regarding certain ethical issues they raise (as with embryoids and neural organoids). There, ontological uncertainties are often indicative of ethical and legal issues yet unresolved. On the other hand, for most legal regimes that rely on functional criteria, the regulatory pathway for organoid applications is quite clear. Regarding the third option of using lists instead of definitions, their main drawback is that they make it harder to know whether a novel object should be interpreted as fitting that list. In comparison, ontological and functional criteria at least provide better starting points for legal interpretation.

Having presented the main legal regimes applicable to organoid technologies, we shall now examine further the definitional features that have been identified.

II. Identifying Common Definitional Features in the Complex Regulatory Landscape of Organoids

When taking a step back, a broader picture of the regulation ecosystem emerges. In it, definitions are shaped by their interaction with other nearby definitions, as well as by policy objectives pursued by the legislation they find themselves in. Ultimately, laborious definitional work had to be done by European lawmakers to go beyond a mere chaotic web of definitions and approach a coherent whole (A). Any unified definition of organoids in law would have to find its place in that ecosystem. To do so, we will undertake to elucidate core features of the legal notion of organoids that we have observed in the various legal regimes analysed (B).

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[120] "It is doubtful, for instance, whether the CRISPR/Cas method, which can change the genetic information of a cell through self-repair mechanisms, creates a gene-therapeutical medicinal product," S. Deuring, "The Legal Requirements for—and Limits to—the Donor's and the Patient's Consent," In *Brain Organoids in Research and Therapy: Fundamental Ethical and Legal Aspects*, edited par H.-G. Dederer and D. Hamburger, *Advances in Neuroethics*, Springer International Publishing, 2022, p. 172.

[121] See, on this topic, the contribution of Pr. Estelle Brosset in this issue.

A) The Interplay Between Definitional Approaches and Policy Objectives

We will now take a closer look at the definitions identified so far and suggest a typology of definitional styles adopted by French and European lawmakers (1). Definitions often emerge from a process of interactions between multiple stakeholders which can best be described in terms of network dynamics (2). With this understanding of how definitions interact and emerge from the involvement of multiple stakeholders, we will examine how coherence can be reached even in this highly fragmented regulatory landscape (3).

1) An Interwoven Network of Definitions

Firstly, looking at the semiotics of the definitions gathered, it is notable that the way in which criteria are laid down vary greatly. That is to say, without considering the broader legislative context, there are already differences in the way criteria can be selected and assembled to form the definition of a concept. For instance, some definitions are simply *absent* and thus do not provide any criteria, as seen in French law in the case of organs and embryos.[122] This is usually associated with a desire from lawmakers to avoid ethical conundrums when defining such sensitive entities.[123] This evidently hinders the clarity of the law when dealing with borderline cases such as organoids and embryoids. Curiously, definitions can also be *negative* when they state what they are not. Such is the case with hiPSCs in French law which are explicitly said to not be obtained from embryos, as for dissipating any controversy about their origins.[124] However, other definitions, especially in EU law, provide much more straightforward criteria. Among them, two main trends have been analysed above following Marie Glinel's dichotomy.[125] Several of them can be said to be *ontological* (or *bioveridical*)[126] when the legal definitional criteria of an object match their biological definition. Alternatively, definitions can be *functional* when they emphasise the place and function of the product in a broader regulatory regime, with definitional criteria related to the manufacturing process or the end uses. For substances of human origin, European definitions have followed

[122] Aside from the definitions provided by EU law that have been transposed in French law or that are found in European case law on patents.

[123] See, for instance, the intervention of the French Minister of Health from 2002 to 2004, J.-F. Mattei, about the bioethical law project n° 189 of 2004. The French attitude regarding the status of the embryo is not to define it (*what it is*), but instead to define our acceptable conduct towards it (*what ought to be done with it*).

[124] This choice was not explained in the explanatory memorandum to the Act.

[125] M. Glinel, *op. cit.*, p. 388.

[126] Ibid., p. 414.

inconsistent trajectories in the last decades[127] before the recent SoHO Regulation finally established an almost hegemonic approach. Now, even SoHOs—substances most closely related to human biology—are defined by their end use.

Secondly, definitions could be said to be *systemic* when they are designed to clarify interactions between nearby legal regimes. This is done for instance to favour the application of a more stringent legal regime to a product to ensure a high level of health protection to EU citizens. This is part of the reason why medicinal products have a *dual* definition which ensures a broad application of its protective provisions.[128] Other definitions are said to be *attracting* and will favour a broad interpretation of the scope of the corresponding legislation. In the SoHO Regulation for instance, definitions are designed to apply to any substance of human origin intended to be applied to humans or used in products.[129] This follows two objectives. It includes in the scope of the Regulation substances for which classification long remained unclear, leading to inappropriate protection of donors and recipients (such as breast milk or intestinal microbiota).[130] It also ensures that all steps in the developments of a SoHO based product are covered, either by specific legislation, or by provisions in the SoHO Regulation.[131] This way, the SoHO Regulation acts as a net for any SoHO products

[127] For an illustration, compare the evolution of the definition of blood between the Directive 2002/98/EC of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, *OJ L 33*, 8 February 2003, p. 30–40 (Blood Directive) and the proposal for a SoHO Regulation. In the Blood Directive, blood is defined as "whole blood collected from a donor and processed either for transfusion or for further manufacturing," art. 3 (a). In the SoHO proposal, blood was defined as "the liquid that circulates in arteries and veins carrying oxygen to and carbon dioxide from the tissues of the body," art. 3(1). In the final SoHO Regulation, blood is not defined and is simply classified as a SoHO, art.3(1). Blood went from an ontological definition, to a functional one, before finally disappearing under the wider functional definition of SoHOs.

[128] A dual definition which is also influenced by national traditions, since the definition by presentation was historically inspired by the French approach while the functional definition originated in German law. See, A. Leca, *Traité de droit pharmaceutique*, 10th ed., Intempora. Bordeaux: LEH édition, 2020, p. 189.

[129] "All SoHO that are intended to be applied to humans fall within the scope of this Regulation," recital 9 of the SoHO Regulation, *op. cit.*

[130] "[. . .] Since donation and human application of SoHO other than those regulated by Directives 2002/98/EC and 2004/23/EC are increasingly common, it is necessary to extend the scope of this Regulation to any SoHO, in order to prevent a situation in which certain groups of SoHO donors or SoHO recipients and offspring from medically assisted reproduction are not protected by an appropriate Union level quality and safety framework. This will, for example, ensure the protection of SoHO donors and SoHO recipients of human breast milk, intestinal microbiota, blood preparations that are not used for transfusion, and any other SoHO that might be applied to humans in the future," recital 7 of the SoHO Regulation, *op. cit.*

[131] "Where SoHO are collected for the purpose of manufacturing products regulated by other Union legislation, the provisions laid down in this Regulation that aim to protect SoHO recipients should contribute also to the objectives of the legislative measures adopted in those other frameworks to ensure a high level of protection of recipients of those products manufactured from SoHO. Therefore, without prejudice to Directive 2001/83/EC and Regulations (EC) No 1394/2007, (EU) No 536/2014 and (EU) 2017/745, this Regulation should always apply to the registration, evaluation and testing of SoHO donors, as well as to SoHO collection and release. This Regulation should also apply to the storage, import and export of SoHO up to and including their distribution to a manufacturer regulated by other Union legislation" recital 32 of the SoHO Regulation, *op. cit*.

that may not fit existing legal regimes and is thus supposed to close any regulatory gaps that might linger at the interface between regimes.[132] Sometimes, *intersectional* definitions are provided when legislations overlap. For instance, CADTMPs and GTMPs are two types of ATMPs for which other regimes also apply (CADTMPs contain MDs and GTMPs intervene at the level of recombinant nucleic acid). Dual, attracting and intersectional definitions illustrate how systemic considerations can shape definitions to reinforce the coherence of a fragmented regulatory ecosystem.

Thirdly, definitions can be *incomplete* when they can only be interpreted with reference to other provisions found elsewhere in the instrument itself or in soft law instruments. For instance, criteria provided by functional definitions are often not sufficient to determine the applicability of a legal regime. Complementary criteria will be found in other parts of the legislation, such as in its scope article or its annexes.[133] Sometimes, interpreting criteria will necessitate reference to soft law instruments. Such is the case with the criterion of "industrial scale of production" for MPs or of "substantial manipulation" for ATMPs.[134] Indeed, these criteria are so technical that even an exegetical analysis of the legislation will not yield a definitive answer. In the case of ATMPs, the EMA expressly recognises that the correct classification of these products ultimately depends on a case-by-case assessment.[135]

Having drawn up a typology of the definitions we encountered, we can anticipate a few developments regarding the definition of organoids. First of all, we identified a large number of definitional approaches in our sample of study. If organoids are indeed given a definition one day, it would most likely be either ontological (sticking to the biological definition) or functional (where the criteria would depend on the context of the instrument). Considering the interconnectedness of definitions in European biolaw, the definition of organoids could also contain "systemic" criteria (which is mostly a feature of functional definitions) to clarify interactions with neighbouring legal regimes. However, EU law does seem to favour a degree of abstraction in the type of products it regulates, and it is not clear what kind of future instrument could be expected to specifically define organoids *per se*. This is why it is most likely that organoids will remain subsumed under broader class of objects

[132] "[…] close interaction between this regulatory framework and other related frameworks is essential to ensure coherence between relevant legal frameworks, without gaps or overlaps," ibid.

[133] Functional definitions often necessitate a more systematic interpretation than ontological definitions which can be taken at face-value.

[134] For clarifications on the criteria of "placing on the market" and "industrial scale," see European Commission, *Staff working document – Annexe to the proposal for a regulation on advanced therapy medicinal products impact assessment*, COM(2005) 567 final, 2005.

[135] According to art. 17 of the ATMP Regulation, the Committee on Advanced Therapies must provide a scientific recommendation on advanced therapy classification which is delivered under 60 days by the Agency. See, also EMA, and CAT, *Scientific recommendation on classification of advanced therapy medicinal products*, 17 October 2012, EMA/498937/2012.

(such as ATMPs or NAMs). As for a French law, it seems unlikely that organoids will change the decade-long trend of avoiding defining biological entities. In conclusion, it is difficult to anticipate a definition of organoids that would fit in that complex regulatory landscape and its internal logic. In the end, it is perhaps more helpful to study actors, aside from the lawmakers, that are active in developing definitions for organoids or that might be more compelled to produce a definition in the future, even if those definitions are not binding.

2) An Interwoven Network of Stakeholders

To understand the dynamics driving norm-making (and definition setting) in the field of organoids, one should consider the impact of a variety of regulatory actors. Without discarding the traditional Kelsenian view of the pyramid of norms, we can usefully mobilise network theories for their explanatory power of complex regulatory environments.[136] Indeed, describing legal norms as imperative statements placed in hierarchical relations of conformity in regard to one another does not fully account for the complexities of contemporary norm-making. Today, there are a number of contextual elements that are necessary to interpret a norm. It becomes almost impossible to circumscribe the precise scope and content of an Act without having regard to *a priori* processes (such as impact studies, public consultations or engagement with interested stakeholders), as well as *a posteriori* processes (such as constitutional reviews or soft law interpretations by independent administrative bodies). This complexity is obviously compounded by the fact that the European integration has given a supranational dimension to these processes. In fact, decision powers were transferred to the European executive and legislative branches, but even farther, to independent agencies or expert bodies that have a range of normative powers. Their legitimacy is supposed to be grounded in their expertise, their independence and the various procedural control mechanisms imposed on them.[137] As they are closer to the developments in their field, they are deemed better suited to oversee it. They can even stir legislative changes by suggesting new concepts, as illustrated by the concept of NAMs. This concept was used by the EURL-ECVAM in soft law documents years before making its way in the proposals for a reform of the EU pharmaceutical legislation. In this field, supranational influences go even beyond the European level and reach a global scope. Indeed, standards for defining and validating NAMs is part of global cooperation efforts carried between Europe, the United States, Canada, Japan, Korea, Brazil, China, etc.[138] More generally, private

[136] F. Ost, and M. van de Kerchove, "De la pyramide au réseau ? Vers un nouveau mode de production du droit ?," *Revue interdisciplinaire d'études juridiques*, 44, n° 1, 2000.

[137] Ibid., p. 34.

[138] A. O. Stucki, T. S. Barton-Maclaren, Y. Bhuller, J. E. Henriquez, T. R. Henry, C. Hirn, J. Miller-Holt, et al., "Use of New Approach Methodologies (NAMs) to Meet Regulatory Requirements for the Assessment of Industrial Chemicals and Pesticides for Effects on Human Health," *Frontiers in Toxicology*, 4, 2022.

actors often participate in the norm-making process and go as far as developing forms of self-regulation of their field.[139] They anticipate national legislations and offer their own guidelines as alternatives to hard-and-fast rules. For instance, the definition of integrated and non-integrated embryo models was first suggested by the ISSCR and was later endorsed by the orientation council of the French biomedicine agency in its opinion on embryo models. To anticipate the evolution of the legal concept of organoids, legal scholars should thus stay alert to soft law guidance from private and public bodies which often prefigure changes in hard law.

As definitions leave expert circles, decision-makers should remain critical of the vested interests of the communities offering their definition before adopting them in hard law. Indeed, definitional choices can conceal deeper sensitive issues. International associations of scientists as well as European and French administrative agencies tremendously shape the future regulation of these technologies. In the last decades, efforts have been made to include civil society stakeholders such as patients' associations or NGOs in decision-making processes related to public health matters.[140] Yet public awareness and democratic discussion are lagging for some topics related to organoids and especially in the field of basic research on neural organoids, embryoids and chimeras. This is particularly problematic as these expert conversations are not representative of broader societal sensibilities. In a pluralistic society, definitions (and substantive provisions) should not be blindly adopted from private actors and should be openly discussed in order to reach an agreement on their regulatory purpose. Consequently, a legal definition of organoids is not only a technical question, it also carries important ethical and societal considerations, in particular for sensitive types of organoids.

3) Reaching Coherence in a Fragmented System

Approaching the organoid regulatory ecosystem through the concepts of fragmentation and defragmentation helps clarify the processes at work.[141] There are several ways in which that environment can be said to be fragmented or defragmented. It is first territorially fragmented as legislative competences are shared between the EU and member states. It is also fragmented in the types of instruments used, ranging from European Regulations and Directives, national legislations and decrees, to soft law instruments and professional guidelines. These instruments emanate from different types of actors whose legitimacy is grounded in different bases, most often in their democratic mandate or their technical expertise. These actors are

[139] F. Ost and M. van de Kerchove, *op. cit.*, p. 67.

[140] There are an increasing number of multistakeholder consultations at the European level, with inclusion of representative of civil society in working groups (such as the 3RsWP for NAMs) or through public consultations before legislative proposals from the Commission (such as the SoHO Regulation).

[141] A. Mahalatchimy, and E. Rial-Sebbag, "Deciphering the Fragmentation of the Human Genome Editing Regulatory Landscape," In *Frontiers in Political Science*, 2022.

embedded in a multi-level regulatory structure where one level can influence the other, as exemplified by the harmonising effect of EU law on French law or by the way regulatory agencies coordinate at the European and international levels.

We observed earlier that definitions relevant to the legal concept of organoids are found across multiple instruments, emanating from various actors, with criteria that are not always straightforward to identify and apply. These elements have concrete consequences on the ability of stakeholders to navigate the regulatory framework of organoid technologies and adapt their behaviour accordingly.[142] If producers of organoids cannot identify how their product should be classified due to the fragmentation of the field, it evidently hampers their ability to conform to the substantive obligations that apply to them. However, a few definitions are starting to emerge internationally which could avoid excessive fragmentation of organoid regulation.

Consequently, defragmenting the framework of organoid technologies through harmonisation and globalisation of legal norms allows for clearer regulation. This can be supported by increasing cooperation between administrative bodies of different legal systems to establish common definitions. Additionally, reducing gaps between legal regimes and reducing the number of instruments applying simultaneously to a given matter can also lead to greater coherence of the framework domestically.[143]

However, fragmentation of a regulatory framework does not mean that it is necessarily incoherent. Fragmentation is often the result of opening new loci of expression. If fragmentation dilutes the role of traditional state powers and their centralised authorities in the decision-making process, it also evidently allows for a number of new actors to provide inputs through public consultations and working parties for instance. Ideally, with an increased number of open forums to contribute to the making of the norm, it opens up the possibility of a process more in touch with the reality of its final recipients. From an academic perspective, this also allows us to study norms in the making and to follow the genealogy of new concepts and definitions. It could also be argued that territorial fragmentation provides structural coherence to the multi-level repartition of competences. Indeed, some matters are more efficiently dealt with at the European or international level while some matters should remain in the purview of the state. On ethical issues related to organoids, member states are better suited to pass legislation that is coherent with national sensibilities.

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[142] Interviewed stakeholders expressed "concerns regarding the level of regulatory scrutiny, the burdens placed on applicants regarding the clinical testing of ATMPs, and the problems applicants may face in evidencing how they have met regulatory standards for marketing authorization," J. Lewis, and S. Holm, "D6.1: Regulating Organoid and Organoid-Related Activities: An Analysis of the Regulatory Gaps and Areas of over-Regulation," *Hybrida Project*, 2022, p. 58.

[143] As we have seen with systematic definitions.

Thus, coherence in a fragmented regulatory framework can mean respecting the purview of expertise and action of each actor. However, a reduced clarity of the regulation is probably the cost to be paid to achieve this increased involvement of varied stakeholders. All in all, these issues of legitimacy, normativity, clarity of law and regulatory globalisation must all coalesce to achieve a coherent regulatory framework of organoid technologies. All of these factors will play out in an eventual definition of organoids in law.

B) Unveiling the Core Features of the Legal Notion of Organoids

Having examined the larger normative landscape of organoids, it is time to circle back to our specific object of study. From the complex picture we drew, what are the core elements that would define organoids in law? If providing a truly innovative legal definition of organoids is probably out of the question for the moment (1), there are still several legal definitional challenges that must be resolved by legal scholars (2) and for which we wish to offer a few insights (3).

1) The Arduous Task of Defining Organoids

Organoids cannot yet be said to be a fully-fledged legal concept. At best they are a concept of legal science in the making. They are a strictly biological concept that is captured under different legal regimes that do not yet recognise them as *organoids*. In these regimes, they are never singled out and framed as legal concepts in the abstract. There are several reasons why organoids have not yet been defined in any hard law instruments.

The Hybrida Project formulates three hypotheses on the lack of explicit mention of organoids and OoCs in legally binding regulations.[144] Firstly, procurement of SoHOs and SoHO products have been regulated for years before the popularisation of organoid models. Since organoids are novel techniques, collaborations between stakeholders and lawmakers have only started. This could explain the lack of specific provisions and definitions. As we have seen, organoids have just started to appear in reforms put forth by the Commission following extensive work conducted by the EURL-ECVAM with stakeholders. Secondly, it is also possible that organoid technologies are not sufficiently different from previous technologies (in particular 2D cell cultures) to justify specific policy measures. Contrary to the first hypothesis, some organoid technologies could very well be not novel enough for lawmakers to consider adopting new legislation. This hypothesis should be seriously considered for applications where robust regulatory frameworks are already in place such as the ATMP and IVDMD regulations. Thirdly, organoids might not have tailor-made

[144] Ibid., pp. 31–32.

regulations because it is unclear what specific normative issues they raise and whether these issues would be important enough to be dealt with by specific instruments. As an example, ethical and legal issues raised by neural organoids cultured at scale for biocomputing have not yet been adequately explored in the literature at the time of this writing. Lacking a precise assessment of these challenges, it is in turn difficult to evaluate the necessity for a specific legal regime covering these products.

Ultimately, these doubts directly tie back to the typicality of organoids. Are they novel and distinct enough from other objects to warrant a specific conceptualisation and a dedicated framework? The answer to this question depends on the field of application considered. In the ATMP framework, organoids are clearly not distinct enough from other products. For NAMs, their typicality is unclear, and conceptualisation is more advanced for the "organ-on-chip" subtype. Finally, the typicality of some subtypes of organoids is clear: embryoids are distinct enough from other types of stem cell research protocols to have warranted extensive conceptualisation in the last few years.

All in all, it is not surprising that no statutory or case law definition of organoids exists at the moment considering the number of unknown factors. Most likely, some organoids subtypes will progressively be defined in binding instruments when pressing regulation is required (perhaps for OoCs or embryoids), while other established frameworks will probably address organoid applications only through soft law documents (in the case of ATMPs possibly). Even if a clear *concept* of organoids in law seems unlikely, early policy instruments still contribute to developing a *notional* understanding of organoids and organoid subtypes.

2) In Defence of Trying Anyway

Even if the possibility to define a legal concept of *organoids* remains uncertain, there are still definitional difficulties related to organoid subtypes that are worth overcoming. Borderline cases raise important definitional challenges such as knowing whether organoids are organs and whether embryoids are embryos. They exemplify the "open texture" of legal concepts as theorised by Hart. Legal concepts are usually made of discernible typical cases that are easy to classify under a general rule while limit cases lie in the penumbra of our concepts which challenge the application of the general rule. When applying a general rule, we are sometimes faced with "open alternatives"[145] where interpretative choices are necessary. Hart himself stated that "uncertainty at the borderline is the price to be paid for the use of general classifying terms in any form of communication concerning matters of fact".[146] Deciding whether to apply a rule to a limit case cannot be reduced to

[145] H. L. A. Hart, *The Concept of Law*, 3rd ed., Clarendon law series, 2012, p. 127.

[146] Ibid., p. 128.

a self-evident syllogism. Rather, interpreting the legal rule will depend on "many complex factors running through the legal system and on the aims or purpose which may be attributed to the rule".[147] This is why these "complex factors" have been extensively studied above. Whether organoids therapies can be defined as organs in the sense of the Organ Directive for instance is an interesting legal exercise in the abstract. However, this thought experiment can only be truly fruitful if conducted with the broader regulatory context in mind with its rationale, its aims, its substantive measures and the practical consequences of applying a given regime to a given subtype of organoids. Consequently, better definitions of organoids subtypes also imply deciding which regulatory frameworks ought to apply to them. Doing so will provide in return greater clarity on existing criteria, which offers two innovative outcomes.

Firstly, it can lead to a revivification or a recalibration of existing legal concepts. Confronting borderline cases allows us to not only clarify the definition of our object of interest but sometimes inform us back on the undisclosed aims of a rule. Indeed, "when the unenvisaged case does arise, we confront between the competing interests in the way which best satisfies us. In doing so we shall have rendered more determinate our initial aim".[148] Doing so puts us in an interesting dialectical position. By deciding when organoids can be more than mere *models* and be equivalent to the *real thing*, be it an organ or an embryo for instance, then we will have gained knowledge on the nature of that real thing. From a teleological perspective, organoids should be defined as organs only if it makes sense to apply to them the legal regime of organs. Thus, it would not be sufficient to demonstrate that a case could be made that organoids could be covered by the definition of an organ, it should be demonstrated that the organ framework is better suited to organoid transplants. As it stands, the ATMP Regulation is indeed more appropriate to future organoids therapies than the organ framework since organoids share many production steps with other cell therapies that organs do not have to go through.[149] However, as we get closer to a point where organoids could be assimilated to organs on the basis of their definitions, it encourages us to revisit and confront these definitions.

Secondly, borderline cases can highlight the need for a new legal concept with its own scope and identifying criteria. When venturing far into the penumbra, we might reach a point where our object is too far removed from the typical cases to be considered similar. In such cases, new categories must be theorised, with their own typical cases and identifying criteria. Is there a need for a new category between ATMPs and organs to deal with organoids therapies? What about a new category between stem cells and embryos for embryoids? Beyond merely creating a

147 Ibid., p. 127.

148 Ibid., p. 129.

149 There are also issues of graft allocation with organs that are not relevant for cell therapies.

"third way" between two alternatives, it could also lead us to reconceptualise even broader categories of law in general. Such work has been undertaken in several contemporary discourses in fields of law that are dealing with living matter in a form or the other. We are seeing such attempts in biolaw regarding the status of the human body,[150] as well as in environmental[151] or animals' rights law[152] regarding potential new types of legal personhood.[153] Hoppe et al., emphasises how organoid models lead us to similar enquiries, considering that "we need to contemplate innovative legal approaches to categorising entities that are deserving of legal protection. Not everything will always be a thing, an animal, or a human".[154] Consequently, gathering evidence on the essence and functions of organoids might lead us to novel ways of conceptualising living matter in law altogether.[155] Consequently, working on the legal definition of organoids is a proxy for more fundamental enquiries on the way our legislation names and frames uses of living matter.

In conclusion, uncertainty about definitions are often more temporary embarrassments than insurmountable obstacles. Sometimes, uncertainty has to be embraced as transformative force: "Exceptional new challenges produced by scientific progress are therefore not confounders of law, but desirable antagonists, leading to an evolution of norms in technology regulation".[156] The absence of definitions is the

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150 G. Farjat, "Entre les personnes et les choses, les centres d'intérêts," *Revue trimestrielle de droit civil*, n° 02 (14 June 2002): 221-47. ; J.-Chr. Galloux, "L'utilisation des matériels biologiques humains : vers un droit de destination ? " *Recueil Dalloz*, n° 2, 1999; N. Reboul, "Pour une rénovation de la summa divisio des personnes," *Petites Affiches*, n° 259, 2016; H. Popu, "La dépouille mortelle, chose sacrée: à la redécouverte d'une catégorie juridique oubliée," *Logiques juridiques*, L'Harmattan, 2009, p. 64.

151 A. Zabalza, "Les droits de la nature à la boussole des communs. Premiers jalons pour une théorie du sujet de droit sans personnalité juridique," *Revue juridique de l'environnement*, n° 2, 2024; Vanuxem, Sarah. *Des choses de la nature et de leurs droits*. Sciences en questions, Quae, 2020.

152 N. Reboul-Maupin, "Droit des animaux : opérer une distinction fondamentale entre biens vivants et biens inertes (biens organiques et bien inorganiques)," *Les Petites Affiches*, 4, 2023; M. Bouteille-Brigant, "La qualification juridique de l'animal au regard de la distinction des personnes et des choses," *Revue de Droit rural* 3, n° 489, 2021; G. Arnason, "The Moral Status of Cognitively Enhanced Monkeys and Other Novel Beings," *Cambridge Quarterly of Healthcare Ethics* 30, n° 3, 2021.

153 J. Jowitt, "The Desirability of Legal Rights for Novel Beings," *Cambridge Quarterly of Healthcare Ethics* 30, n° 3 (July 2021): 504-16; D. Landivar, and É. Ramillien, "Du sujet de droit à l'hyper-sujet du droit : Une analyse anthropologique comparée du droit des entités de la nature en Bolivie et en Équateur," *Revue juridique de l'Environnement* 43, n° 1, 2018.

154 N. Hoppe, M. Lorenz, and J. Teller, "Transplantation of Human Brain Organoids into Animals: The Legal Issues," In *Brain Organoids in Research and Therapy: Fundamental Ethical and Legal Aspects*, edited by H.-G. Dederer and D. Hamburger, 205-19, *Advances in Neuroethics*, Springer International Publishing, 2022, p. 218.

155 Kataoka M., Lee T.-L., and Sawai T., "The Legal Personhood of Human Brain Organoids," *Journal of Law and the Biosciences* 10, n° 1 (1 January 2023); J. Jowitt, "On the Legal Status of Human Cerebral Organoids: Lessons from Animal Law," *Cambridge Quarterly of Healthcare Ethics*, 17 February 2023, 1-10; T. Pietrzykowski, *Personhood beyond Humanism: Animals, Chimeras, Autonomous Agents and the Law*, New York, NY: Springer Berlin Heidelberg, 2018.

156 Ibid., p. 217.

indication of a way less travelled that it is in need of serious legal consideration. Other times, uncertainty is precisely a feature of ethically sensitive legal frameworks. For instance, when answering definitional questions that would entail taking a symbolic moral stance, French lawmakers were historically cautious:[157] they favoured discussing what ought to be done with an entity rather than discussing what that entity is.[158] As lawyers, however, it falls on us to explore how far exactly we can push back the veil of ignorance; to identify which definitional questions we can tackle with definite certitude and which issues have to be dealt with a trembling hand.

3) Sketching the broad strokes of a legal definition of organoids

Having explored the value of this definitional work, we will highlight in the following paragraphs broad strokes that characterise all organoid subtypes.

Firstly, defining organoids will not be value neutral. These cutting-edge products find themselves in a regulatory environment that attempts to balance important policy objectives such as supporting public health, ensuring responsible research and commercial practices, as well as fostering innovation. We have seen how definitions can be decisive in pursuing broader legislative objectives or ensuring the coherence of a regulatory ecosystem. Definitions can attest of a stabilised status quo. They can be preventively designed to accommodate or anticipate future technological developments. They can signal social change passed into law. Sometimes, they participate themselves in accelerating the adoption of a new regulatory paradigm. All of these traits ultimately stem from choices made more or less explicitly by lawmakers, which are themselves involved in a broader network of actors responsible for norm-making.

Secondly, organoid technologies highlight the ambivalent role of novelty. On the one hand, novelty can be synonymous of innovation which has to be caught up to,[159] rewarded[160] and facilitated for the benefit of public health.[161] Novelty even influences the naming of concepts themselves, as with *new* approach methodologies.[162] Novelty

[157] As we mentioned, French law never had definitions for organs and embryos aside from those provided by EU law.

[158] "For while we cannot settle the question of the nature of the embryo, in practical terms we can, and indeed must, define how we should behave towards it; and it is the role of the legislature to lay down this law. The legislator's position is therefore one of duty towards the embryo, and not one of being" [author's translation], J.-F. Mattei, *op. cit.*

[159] Recital 4 of the explanatory memorandum of the proposal for a SoHO Regulation, *op. cit.*

[160] Recital 11 of proposal for a Directive on the Union code relating to medicinal products for human use, *op. cit.* See the incentive system put in place in Chapter VII to encourage innovative research and in particular for unmet medical needs.

[161] Recital 5 of the SoHO Regulation, *op. cit.*

[162] One might wonder for how long these approach methodologies will remain *novel* if they become truly normalised. Will they still be novel in ten years?

as innovation is a promise that should be fostered and cared for. On the other hand, novelty is also the harbinger of unknown risks which have to be duly managed. In the face of uncertainty, GMO technologies were subjected to an *ex ante* suspicion. What matters in the European GMO framework is not the final characteristics of a GMO product, but the processes it has been subjected to. That product might be indiscernible from another product obtained through naturally occurring processes[163] but in virtue of the precautionary principle more stringent measures are required when gene editing processes are applied.[164] Thus, organoids find themselves at a crossroad of contradictory stances towards novelty that have to be reconciled. They are both a promise that lawmakers should help bearing to fruition and a risk that has to be managed.

Thirdly, organoids showcase the degree of autonomy inherent in biological matter. The self-organising properties of organoids are exploited precisely because they allow complex structures and functions to be recapitulated through autonomous processes.[165] Autonomy is thus not a mere property of humans; it is baked into the very fabric of biology. The latent autonomy of biology is even explicitly recognised in the definition of the organ[166] and the definition of the embryo could be construed in terms of autonomy.[167] This vast reconfigurable potential of biology is in fact discernible in the various legal regimes studied. Since biological matter does not work in a clockwork manner, it has to be managed somehow. The unpredictability of biology justifies the risk-based approach to GMOs or the risk/benefit assessments applied to ATMPs. It is laboriously being tamed to reduce variability and prepare future standardised practices for NAMs. As we increase our ability to leverage autonomous biological processes, we should expect future legal regimes to increasingly have to contend with that potential.

Ultimately, with standardisation of practices as well as increased consensus on the definitional criteria of organoids and organoid subtypes, it will become easier to bridge the gap between scientific and legal discourses. To elucidate legal criteria to be applied to organoid applications, it will be necessary to maintain a dialogue between law and biosciences to culminate in an evidence-based and coherent regulatory framework.

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163 T. Sprink, D. Eriksson, J. Schiemann, and F. Hartung, "Regulatory Hurdles for Genome Editing: Process- vs. Product-Based Approaches in Different Regulatory Contexts," *Plant Cell Reports*, 35, n° 7, 2016.

164 M. Herdegen, *The International Law of Biotechnology: Human Rights, Trade, Patents, Health and the Environment*, 2nd ed., Principles of International Law, Cheltenham, Edward Elgar Publishing, 2023, p. 42.

165 Even if organoid cultures obviously require great care from technicians, they exhibit spontaneous and emergent features that are lacking from 2D cell cultures.

166 As we saw, under the Organ Directive, an organ is "a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy" (emphasis added).

167 The capacity criterion could be used to distinguish embryos, which have enough "biological" autonomy to fully develop into a human being, from current embryoids that do not.

Conclusion

Organoids are regulated by a large number of legal regimes where their application will depend on the composition of the organoid as well as its context of use. All of these regimes provide their own definitions and classification criteria. Thus, it is doubtful that a unified definition of organoids in hard law could find its place in that complex ecosystem. A functional definition of organoids would have to take that complexity into account and anticipate interactions with nearby regimes by making explicit reference to the relevant legal regimes that apply to the various uses of organoids. Conversely, an ontological definition of organoids would probably just mirror their scientific definition. Such a definition would probably be limited in scope to a specific legal regime, with limited influence on other legal frameworks. So, while a unified definition of organoids in law would seem to increase coherence of the organoid regulatory landscape, especially if this definition is found at the EU level, the ecosystem is simply so vast that such attempt might prove unfeasible or ineffective. At the soft law level, however, we saw that multiple stakeholders (governmental agencies and professional associations mainly) are actively engaging in definitional work. They are slowly defining the contours and content of "embryoids" and "organs-on-chip" as their own categories. As for the field of legal studies, it appears currently difficult to elaborate a unified concept of organoids. There is, however, a lot of work yet to be done at the notional level, to elucidate what might be exactly the typicality of organoids. Perhaps the term "organoids" is too vast a category and contains too many different entities to reach a meaningful level of conceptual thinking. Narrower categories of entities, such as embryoids, therapeutic organoids or OoCs, cover much more delimited domains of application, with clearer ontological and functional boundaries. With further work, it might be possible to find necessary and sufficient criteria that precisely delineate the typicality of each one of these concepts. Doing so, we can expect to find the same tensions that we found in substantive law: definitions are the result of balance of interests. Notably, using ontological or functional criteria in definitions inevitably reflect deeper strategical choices made by their authors. Functional definitions appear more efficient in their interpretation, but ontological definition confronts us with difficult questions about the precise nature of what exactly we are creating. Ultimately, we highlighted that the legal notion of organoids cannot be value neutral, that it upholds an ambivalent relationship to novelty and that it showcases the autonomous nature of biological processes.