

# Regulatory Challenges at the Intersection of Cellular and Medical Device Therapies in Europe: The Case of the Bioartificial Pancreas

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## Abstract

Regenerative medicine solutions for type 1 diabetes are a rapidly developing field of medical technology. So far, these solutions have been principally cell-based treatments and, at present, in Europe, are regulated under the European Union regulations for Advanced Therapy Medicinal Products (ATMPs). But now, new, emerging technology combining cellular therapy with medical devices is under development. The potential of this novel hybrid model to create a bioartificial pancreas is tantalising. However, incorporating medical devices creates a further layer of complexity to an already challenging product development process. Moreover, it raises important questions about how bioartificial organs should be regulated.

This article seeks to expose the complexity of the legal and regulatory landscape relating to such products, focusing on the laws of the European Union and, where appropriate, bringing in examples from other jurisdictions. We set out the role of the European Medicines Agency (EMA) and review the classification of existing ATMPs and those proposed for type 1 diabetes to highlight the potential consequences and effects of nomenclature and classifications. We argue that emerging hybrid regenerative medicine solutions at the intersection of cellular and medical device therapies, in which medical devices are integral to and facilitate the cell therapy mechanism of action, are not satisfactorily accounted for in the existing legal paradigm regulating regenerative medical therapies. We suggest that these functional hybrid products, currently in their infancy, may yet have far-reaching implications for the interface of law, regulation and technology. For example, they are likely to challenge the conventional discourse related to a market in (bioartificial) organs. We recommend that the EMA, national competent authorities for medical devices, national transplantation authorities and those responsible for overseeing translational clinical research respond to this by developing the existing regulatory framework in such a way that captures the essence of these hybrid products as a single entity. Issuing guidance on updated regulations to researchers engaged in this emerging technology will be key to the success of its translation into human therapies.

**Keywords:** Regenerative medicine; bioartificial organs; advanced therapy medicinal products; medical devices.

## 1. Introduction

Type 1 diabetes (T1D) affects approximately 8.75 million people globally,<sup>1</sup> with incidence increasing year on year. In the last century, the treatment and prognosis of this condition have evolved considerably, with many advances linked to the manufacture of synthetic analogue insulin and innovations in medical devices, such as continuous glucose monitors (CGMs) and insulin pumps. But now, new technologies that combine medical devices with cells are in development, aimed at replicating the insulin-

<sup>1</sup> Ogle, IDF Atlas Reports.



producing islet cell function of the native pancreas. This type of regenerative medicine solution could represent a long-sought-after cure for T1D.<sup>2</sup> However, these products at the intersection of cellular and medical device therapies are a step up in complexity compared to existing conventional cell therapies and, as such, present new challenges to existing legal and regulatory frameworks. Products in development include Viacyte's Encaptra device<sup>3</sup> and the VANGUARD product.<sup>4</sup> All of these products differ in the precise details of their components but broadly contain both cellular and non-cellular components. We will discuss these components—and the relevant law and regulation—in due course. For now, all we need to note is that these engage different regulatory frameworks, and it is here that the uncertainty and complexity lie with respect to the law for what we will argue are 'hybrid' products.

To demonstrate the complexities that these hybrid products present, we start in section one by setting out the current challenges in diabetes care, including those posed by the commonly used device- and cell-based treatments. In section two, we introduce the possible solutions offered by regenerative medicine. There, we discuss the current classification of Advanced Therapy Medicinal Products (ATMPs), including those incorporating medical devices, as well as the role of the European Medicines Agency (EMA) in regulating such therapies in Europe.<sup>5</sup> Comparisons are drawn between characteristics of currently authorised products and those that have been previously proposed for T1D. In section three, we expose the new challenges faced in regulating a bioartificial pancreas and consider the regulatory burden that accompanies such complex products. In section four, we demonstrate the impact of classification on clinical utility and consider how a bioartificial pancreas should be classified. We argue that emerging hybrid regenerative medicine solutions at the intersection of cellular and medical device therapies, in which medical devices are integral to and facilitate the cell therapy mechanism of action, are not satisfactorily accounted for in the existing legal paradigm regulating regenerative medical therapies. Finally, we consider how these functional hybrid products may have far-reaching implications for the interface of law, regulation and technology. We use the example of a market in (bioartificial) organs to demonstrate how a hybrid bioartificial pancreas could represent a paradigm-shifting technology.

As we will demonstrate, the complexities—practical and regulatory—involved in developing and bringing to market a hybrid bioartificial pancreas are manifold. However, to properly appreciate these, we need to understand why this solution is needed in the first place. As such, before examining the cutting-edge cellular therapies—which serve as the foundations for even more advanced ones combining cellular and medical device components—we begin the next section by setting out some of the background and current development state of the treatment of T1D.

## 2. Devices and Cells: Current Therapies for Type 1 Diabetes

T1D is characterised by the destruction of insulin-producing cells, also known as islet cells, in the pancreas. The hormone insulin controls blood sugar (glucose) levels. As a result of islet cell destruction, blood glucose levels rise. The administration of exogenous insulin restores some degree of control but with less precision and responsiveness than the native pancreas. Consequently, people living with diabetes (PwDs) frequently experience periods of both low (hypo-) and high (hyper-) glucose levels (glycaemia). Over time, they develop complications due to abnormal blood glucose levels in the heart, eyes, nerves, brain and kidneys, the severity of which has been shown to be directly related to the degree of blood glucose control.<sup>6</sup> Therefore, many innovations in diabetes treatment are focused on achieving as close to a 'normal' physiological blood glucose (euglycaemia) profile as possible. There has been significant progress, and the outlook for PwDs has dramatically improved. For example, it was once thought that 20–30% of those living with T1D would develop kidney failure during their (limited) lifetime; however, although rates of improvement appear to vary, more recent studies have shown the overall incidence of this has fallen to 2–14.5%.<sup>7</sup> This decrease in one of the most serious complications of diabetes reflects the significant improvements that have taken place in treatment strategies over the last 50 years—almost all of which incorporate, in some way, medical devices. However, as we are about to see, despite the technological advances made with these, current medical device therapies for T1D still come with some significant drawbacks for PwDs.

Devices for the treatment of diabetes are frequently divided into two principal groups: those used to record and monitor blood glucose levels and those used to administer insulin. Historically, PwDs aiming to maintain their glucose in an 'optimal' range

<sup>2</sup> Examples in development include but are not limited to the 'VX-880 by VERTEX', a product being developed by the Horizon 2020-funded VANGUARD consortium and 'ViaCyte'.

<sup>3</sup> ViaCyte Inc., San Diego, California and Vertex Pharmaceuticals.

<sup>4</sup> VANGUARD, "New Generation Cell Therapy."

<sup>5</sup> In this article we focus on EU regulation of ATMPs and medical devices as they might apply to a bioartificial pancreas. For a detailed look at the medical device regulation in the UK post Brexit, see Quigley, "Shape of Medical Devices Regulation."

<sup>6</sup> Nathan, "Diabetes Control and Complications Trial."

<sup>7</sup> Bakris, "Are All Patients With Type 1."

would have to take blood glucose measurements by finger prick testing multiple times a day.<sup>8</sup> This practice is progressively being overtaken by the use of CGM devices, where a sensor placed under the skin can give continuous readings of blood glucose in near real-time. The most technologically advanced devices connect to an application on the user's phone and may even send data to their medical team. The use of CGMs has been shown to improve long-term blood glucose control,<sup>9</sup> with encouraging signs that this also translates to reduced complications.<sup>10</sup> Increasingly, those with T1D are using CGMs in combination with insulin pumps. While some systems require users to input their glucose readings manually, others aim to bridge this gap with software. This creates a 'closed-loop system', or what is sometimes described as an 'artificial pancreas'.<sup>11</sup> PwDs have strongly advocated for this technology to be developed in the hope that it will not only improve key medical outcomes—improved blood sugar control, reduced complications and, ultimately, reduced mortality—but also reduce the burden associated with measuring glucose, along with calculating and administering insulin doses. However, although both CGM and pump technology have been available separately for several decades, as with all new medical devices and treatments, there has been a delay in moving technology from theory to the clinic. For example, only a few hybrid closed-loop systems have received regulatory approval across the European Union (EU).<sup>12</sup>

However, the challenges and disadvantages of current device-based therapies are not limited to regional differences in funding. There are practical issues, such as glucose sensors or infusion sets detaching, leaking or causing skin irritation.<sup>13</sup> Given the large amount of consumables needed for these devices—such as infusion sets for insulin pumps—waste and environmental impact have been highlighted as a source of concern.<sup>14</sup> Further, 'unexpected tasks for the user [and] difficulties wearing the system'<sup>15</sup> mean that despite the reduction in blood testing and injections, users may find even closed-loop devices burdensome. Indeed, participants in one study, for example, reported that they felt 'misled by terms such as "closed loop" and "artificial pancreas", which seemed to imply a more "hands-off" experience'.<sup>16</sup>

There are also issues of equality of access. For example, it is estimated that less than 0.5% of the global diabetic population currently uses CGM.<sup>17</sup> Globally, barriers to accessing technological solutions include costs, reimbursement arrangements and socio-economic factors. The use of diabetes technology is often highest among those in the least deprived socio-economic groups.<sup>18</sup> The issue of inequitable access is brought into sharp focus in low-income countries, where accessing even basic treatment is problematic. As a result, while device-based therapies are being presented by some as the ideal solution, they are only actively being used by a minority of PwDs. According to the World Health Organization's (WHO) latest report on diabetes, improving access to even the most basic diabetes technology is essential to reduce the significant inequalities currently observed globally in patient outcomes.<sup>19</sup> As we will see when we return to the issue of access in section five, advanced therapies, such as the bioartificial pancreas, have the potential to compound inequalities, leading to an even larger gap between those with access to the latest technologies and those without access to even the most basic supplies. We do not deny this, but we do suggest some ways in which equality of access needs to be considered.

However, arguably, the biggest drawback of device-based therapies for T1D is that they have not been able to precisely replicate the function of the native pancreas. Given this, and in light of the non-clinical limitations of device-based therapies, an intuitive solution could be to replace the damaged pancreatic cells and tissues. An assortment of sources for these replacement cells have been investigated,<sup>20</sup> and a variety of techniques have been proposed. However, at present, the only established cell-based therapies for diabetes are those that fall under the auspices of deceased donor organ transplantation. Whole pancreas transplantation from deceased donors has been used in selected PwDs since the 1960s. With modern techniques, independence

<sup>8</sup> Precisely what 'optimal' consists of is a matter of debate and is also, to some extent, value laden.

<sup>9</sup> Teo, "Effectiveness of Continuous Glucose Monitoring."

<sup>10</sup> Beck, "Advances in Technology for Management."

<sup>11</sup> Beck, "Advances in Technology for Management."

<sup>12</sup> Beck, "Advances in Technology for Management." We acknowledge that there are also open source automated insulin delivery systems or 'DIY' artificial pancreas systems available. These preceded the availability of any commercial systems and were developed by PwDs frustrated with the lack of technological solutions for better managing their diabetes. However, apart from one system, Tidepool Loop, these systems have not received regulatory approval. Moreover, while there is a growing community of PwDs who use them, and although their development is what prompted the development of the commercially available systems, they are not the mainstay of treatment for most PwDs. See Downey, "European Regulatory Pathway Tidepool Loop."

<sup>13</sup> Kesavadev, "Evolution of Insulin Delivery Devices"; Heinemann, "Insulin Infusion Sets."

<sup>14</sup> Heinemann, "Diabetes Technology and Waste."

<sup>15</sup> Iturralde, "Expectations and Attitudes of Individuals."

<sup>16</sup> Iturralde, "Expectations and Attitudes of Individuals."

<sup>17</sup> Heinemann, "Self-Measurement of Blood Glucose."

<sup>18</sup> Addala, "Decade of Disparities in Diabetes."

<sup>19</sup> World Health Organization, Global Report on Diabetes.

<sup>20</sup> Including human and non-human animal donors, such as pigs.

from insulin is achieved in 80–90% of recipients for five years.<sup>21</sup> Nevertheless, pancreas transplantation requires a highly invasive operation; 5–10% of recipients suffer early graft failure<sup>22</sup> and up to 30% experience serious complications, such as the need for further surgery.<sup>23</sup> An alternative is an islet cell transplant, where just the insulin-producing cells of the pancreas are injected into a vein near the liver.<sup>24</sup> However, without the mechanical protection and blood supply offered by the tissues of a whole pancreas, transplanted islet cells can be attacked by the recipient's immune system or fail to 'engraft' effectively. Correspondingly, insulin independence rates are inferior at 25–50% at five years.<sup>25</sup> However, the procedure is less invasive, and its reported complication rate is lower (10–14%).<sup>26</sup> In both cases, though, long-term treatment with immune suppression is required to prevent the recipient's immune system from rejecting the donor cells, which increases their risk of developing malignancies and infections. Possibly, the greatest limitation to either of these transplantation techniques is the international shortage of deceased donor pancreases. As a result, whole pancreas or islet cell transplantation are treatments currently reserved for only those who already have the most severe diabetic complications.

To summarise, while significant advances have been made in both the fields of medical device- and cell-based therapies for diabetes, neither strategy has accomplished the key clinical goal of restoring euglycaemia. Consequently, researchers have turned their focus to even more cutting-edge science to provide possible solutions. It is to this we now turn. We first examine the potential offered by what are known as ATMPs—that is, medicinal products that utilise cells, tissues or gene therapies. We then focus on one sub-category of these that combines ATMPs with a medical device, examining some of the legal and regulatory challenges that these bring in the context of developing a bioartificial pancreas.

### 3. The Bioartificial Pancreas: A Regenerative Medicine Therapy for Type 1 Diabetes

Regenerative medicine is an emerging area of science that uses advanced biotechnologies, such as tissue engineering, 3D bioprinting and gene editing, to 'replace or regenerate human cells, tissue or organs to restore or establish normal function'.<sup>27</sup> So far, these industrially prepared or manufactured regenerative medicine products have been classified as ATMPs.<sup>28</sup> As these technologies are still experimental, describing what future therapies may look like in clinical practice involves a measure of speculation. However, there is a growing pool of literature describing key preclinical and clinical advances in bioengineering, through which it is possible to begin sketching out the likely core characteristics of a regenerative medicine therapy for T1D.

Let us begin by noting that all regenerative medicine therapies for T1D require securing a safe and reliable source of insulin-producing cells—allogeneic<sup>29</sup> deceased human donor islet cells, stem cells<sup>30</sup> and xenogeneic<sup>31</sup> cells have all been proposed.<sup>32</sup> In addition, other cell types may also be included to provide immune protection or to create a new vascular supply to the product to improve its function.<sup>33</sup> One of the key lessons from the experience of human allogeneic islet cell transplantation is that islet cells are very susceptible to destruction if implanted directly into the body. For this reason, many groups are also looking to enclose or 'encapsulate' cellular components or to provide a supporting 'scaffold' onto which cells can be distributed.<sup>34</sup> The aim is to provide protection to delicate cells, aid implantation and retrieval of the product and support the production of a hospitable microenvironment without which the cellular components will not optimally function or survive. Materials that are being investigated include synthetic materials—such as polytetrafluoroethylene (PTFE), cyclic olefin copolymer (COC),

<sup>21</sup> Gruessner, "2022 International Pancreas Transplant Registry."

<sup>22</sup> Gruessner, "2022 International Pancreas Transplant Registry."

<sup>23</sup> Manrique, "Relaparotomy After Pancreas Transplantation."

<sup>24</sup> Insulin-producing cells are found in a structure called the 'islets of Langerhans', hence 'islet cell' transplant.

<sup>25</sup> Collaborative Islet Transplant Registry, Eleventh Allograft Report.

<sup>26</sup> Collaborative Islet Transplant Registry, Eleventh Allograft Report.

<sup>27</sup> Mason, "Brief Definition of Regenerative Medicine."

<sup>28</sup> Li, "3D Bioprinting 2D Regulatory Landscape."

<sup>29</sup> Allogeneic cells are those derived from individuals of the same species but that are genetically different.

<sup>30</sup> Stem cells may come from a variety of human donor sources. Common sources include embryonic cells from aborted tissue, amniotic stem cells retrieved from the amniotic membranes of live births and adult tissues that have been genetically altered or 'induced' to become stem cells.

<sup>31</sup> Xenogeneic cells are those derived from a different species.

<sup>32</sup> Berney, "From Islet of Langerhans Transplantation"; Hanna, "Advances and Challenges of Endocrine"; Photiadis, "Current Status Bioartificial Pancreas Devices"; Wassmer, "Generation of Insulin-Secreting Organoids."

<sup>33</sup> See Berney, "From Islet of Langerhans Transplantation"; Hanna, "Advances and Challenges of Endocrine"; Photiadis, "Current Status Bioartificial Pancreas Devices"; and Wassmer, "Generation of Insulin-Secreting Organoids" for a summarising composition of a proposed bioartificial pancreas.

<sup>34</sup> See Berney for articles summarising the composition of a proposed bioartificial pancreas, "From Islet of Langerhans Transplantation"; Hanna, "Advances and Challenges of Endocrine"; Photiadis, "Current Status Bioartificial Pancreas Devices."

silicone or metals like titanium—and decellularised biological materials—such as alginate, collagen or hydrogel membranes—which may be from human or animal sources.

However, regardless of which material is used, encapsulation apparatus or scaffolds are highly likely to fall under the definition of a medical device (more on this shortly). This novel approach of using both cells and devices in one product is distinct from all current treatment options available and is becoming increasingly referred to by its proponents as a ‘bioartificial pancreas’. One example is the proposed VANGUARD product. This product has both non-cellular and cellular components.

There are two principal non-cellular components:

1. The KGM Sphericalplate 5D®—this is a proprietary laboratory platform that will be used to generate uniform, size-controlled clusters of the various cellular components at high numbers.<sup>35</sup>
2. Hydrogel matrix from human amniotic membrane (HAM)—this is stripped from a human placenta at the time of elective caesarean section and then decellularised. It will provide structure to the assembled cellular components once implanted into the recipient.

Meanwhile, there are three types of cellular components:

1. Gene-edited Human Amniotic Epithelial Cells (hAECs)—these cells are derived from the same human placental source as HAM. Cells are gene-edited using CRISPR-Cas9 gene-editing technique and provide immune protection and anti-inflammatory properties.
2. Blood Outgrowth Endothelial Cells (BOECs)—these cells will be isolated from the peripheral bloodstream of the proposed recipient to promote angiogenesis (the development of new blood vessels) and vascularisation (the development of blood vessels in an organ or body part) that will not induce an immune response in the recipient.
3. Insulin-Secreting Cells—these cells could be sourced in a variety of ways.
  - a. They can be relatively unmodified insulin-secreting cells from deceased human donors.
  - b. They could be islet cells retrieved from transgenic pigs.
  - c. They could be created from pluripotent embryonic stem cells that have been induced to become insulin-producing cells.

While there is much promise regarding therapies that combine cellular and synthetic components in this manner, as we are about to see, regulating their development and use is mired in uncertainty. To see why this is so, we first examine the use and regulation of ATMPs; then, we contextualise the place of medical devices when it comes to so-called combined ATMPs (cATMPs).

### 3.1 The Use and Regulation of Advanced Therapy Medicinal Products

In Europe, any products that use viable cells<sup>36</sup> are classified and regulated under the provisions of Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (ATMPs Regulation).<sup>37</sup> The ATMPs Regulation was devised in response to advances in cellular and molecular biotechnology in the early part of the new millennium. Specifically, there were concerns that while existing medicinal product regulations had attempted to define cellular and gene therapies, these did not encompass the complex array of treatments starting to be offered. New classifications and provisions were required. The Regulation divides ATMPs into four principal groups:

1. **Gene therapy medicinal products (GTMPs)** are products that contain ‘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’.<sup>38</sup> Additionally, the therapeutic effect of the product must be directly related to the altered sequence or the results of its expression.

<sup>35</sup> SPHERICALPLATE 5D - Ecosystem for Regenerative Medicine. The Sphericalplate 5D is a 3D cell culture plate for the formation of uniform and size-controlled spheroids in high quality and yield. The platform material is COC. The fifth dimension is defined as the communication of the cells with each other; the critically determined shape and size of the microwells in the spherical plate create an environment that is as physiological as possible. Plus, a special nanocoating hinders cells from attaching to the surface. This results in the formation of uniform spheroids with an undisturbed cell communication, preventing wrong signals that would induce unwanted gene expression/differentiation.

<sup>36</sup> Products containing exclusively non-viable human or animal cells and/or tissues are excluded.

<sup>37</sup> Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [2007] OJ L 324/121. We focus on the EU regulations, but for an account of the situation for medical devices in the UK post Brexit, see Quigley, “Shape of Medical Devices Regulation.”

<sup>38</sup> Directive 2001/83/EC, annex I, part IV. 2.1.

2. **Somatic cell therapy products** (sCTMPs) are products that are presented as preventing, treating or diagnosing a disease that ‘contains or consists of cells or tissues that have been subject to *substantial manipulation* so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor’.<sup>39</sup>
3. **Tissue engineered products** (TEPs) are products that contain ‘engineered tissues or cells and [are] presented as having properties for, or [are] used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue’.<sup>40</sup>
4. **Combined ATMPs** are products that meet the definition of any ATMP but also contain one or more medical devices or active implantable medical devices as defined by Article 1(2)(a) of Directive 93/42/EEC Concerning Medical Devices<sup>41</sup> and Article 1(2)(c) of Directive 90/385/EEC Concerning Active Implantable Medical Devices.<sup>42</sup>

The first thing to say here is that accurate early categorisation of ATMPs is essential in efforts to streamline the ‘bench to bedside’ product development process. To this end, in the EU, the EMA established the Committee for Advanced Therapies (CAT) to provide feedback to researchers as to which category their proposed product would fall under. Advice can be sought from the CAT at any time during the development process, including during preclinical research. In the United Kingdom (UK), developers of regenerative medicine products can access similar support through the Medicines and Human Products Regulatory Agency (MHRA) Innovation Office. However, despite the wealth of support available regarding these types of products, including, for instance, summaries of the scientific opinions that the CAT has published concerning proposed products,<sup>43</sup> there is no clear guidance as to how a product that falls within the definition of all these classifications will be categorised.

This gap, faced when classifying a bioartificial pancreas, poses challenges to the whole system of ATMP classification. Cellular components originating from a variety of sources may also be subject to differing degrees and types of modification. It has been suggested that cells that have been gene-edited *and* substantially manipulated to change their physiological properties or functions *and* have been engineered to replace the functions of the pancreas could all be included.<sup>44</sup> Moreover, as components such as scaffolds or encapsulation materials fall under the definition of medical devices, a bioartificial pancreas, as described, may include components that fulfil criteria for all ATMP classifications within a single product. The existing ATMPs Regulation does attempt to bridge the gap created by products that are on the borderline between classifications. Regulation 1394/2007, Article 2(3–5) states:

- (3) An advanced therapy medicinal product containing both autologous and allogeneic cells or tissues is to be treated as being for allogeneic use.
- (4) A product that falls within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product is to be treated as a tissue engineered product.
- (5) A product that falls within the definition of:
  - (a) a somatic cell therapy medicinal product or a tissue engineered product; and
  - (b) a gene therapy medicinal product,
 - is to be treated as a gene therapy medicinal product.<sup>45</sup>

However, there is no clear guidance on how a product that falls within the definition of all these classifications should be treated.

Secondly, and significantly, the ATMPs Regulation seems to envisage medical devices used in cATMPs as always being secondary to the cellular components. They state, ‘these products, *whatever* the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered the principal mode of action of the combination product’.<sup>46</sup> Crucially, however, as we will argue in more depth below, in the case of the bioartificial pancreas, medical devices are not simply combined with cells as passive ancillary bystanders. Rather, they are integral to and facilitate the cell survival and cell therapy mechanism of action. This, as we will also argue, makes a considerable difference to how we should conceive

<sup>39</sup> Directive 2001/83/EC, annex I, part IV. 2.2 (emphasis supplied).

<sup>40</sup> Regulation (EC) No 1394/2007, chapter 1, art 2(1)(b).

<sup>41</sup> Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices [1993] OJ L 169/1, art 1(2)(a), 93.

<sup>42</sup> Council Directive 90/385/EEC of 20 June 1990 on the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices (90/385/EEC) [1990] OJ L 189/17, art 1(2)(c).

<sup>43</sup> In the UK, developers of regenerative medicine products can access similar support through the Medicines and Human Products Regulatory Agency (MHRA) Innovation Office.

<sup>44</sup> An example of this would be the product proposed by the VANGUARD consortium as set out above.

<sup>45</sup> Regulation (EC) No 1394/2007, art 2(3–5).

<sup>46</sup> Regulation (EC) No 1394/2007, para 4. Author’s emphasis.

of these combined products within the regulatory system. However, before examining the medical devices component of cATMPs, it is worth briefly noting some points regarding the current situation of (the market authorisation of) ATMPs. This is because the history of what has happened since the ATMPs Regulation was passed is revealing in terms of the difficulties that beset both the science and regulation in the area within which the bioartificial pancreas is located.

The first ATMP granted market authorisation under the ATMPs Regulation was in 2009, just a few months after the Regulation came into force, but it was a further three years before there was another. Since 2009, just 25 ATMPs have been granted market authorisation, with almost half of these being granted in the last three years alone.<sup>47</sup> Of the ATMPs that have completed this process, the majority are GTMPs (17/25 or 68%) rather than sCTMPs (4/25 or 16%) or TEPs (3/25 or 12%). Tellingly, since the Regulation's inception, just one cATMP has received market authorisation.<sup>48</sup> Further, in this time, six products have also left the market (including the single combined product), either due to the developers' having their market authorisation removed or due to their failing to renew it once it had lapsed. This leaves only 19 cell or gene therapies currently authorised on the European market. Of these, it is particularly noticeable that most of the products concerned are targeted at rare<sup>49</sup> rather than common conditions, with 19 of the 25 having secured 'orphan drug status'<sup>50</sup> (a scheme incentivising and protecting the development of drugs targeted at rare diseases). In comparison, with over 30,000 newly diagnosed cases of T1D each year in Europe alone,<sup>51</sup> no ATMP on the market has ever targeted such a large group of potential recipients.

Relatedly, while no previous ATMP for T1D has ever been authorised, between 2010 and 2021, the CAT issued published scientific opinions on 11 proposed ATMPs for T1D.<sup>52</sup> These are likely to be of interest to developers of a bioartificial pancreas.<sup>53</sup> Two products were deemed not to come under the auspices of the ATMPs Regulation, as the cells they used (allogeneic deceased donor islet cells in both cases) had undergone processing that fell short of the 'substantial manipulation' threshold. However, the remaining nine proposed ATMPs in the published CAT opinions do exhibit some of the characteristics that a bioartificial pancreas may contain. For example, almost half (5/11) contained allogeneic (rather than autologous)<sup>54</sup> sourced cells, two contained xenogeneic cells and one contained genetically modified bacterial cells. This is in contrast to authorised ATMPs, of which 15/25 (60%) use autologous cells, 6/25 (24%) contain no viable cells at all and only 3/25 (12%) use allogeneic cells.<sup>55</sup> This is important because where autologous cells are used, the donor and recipient are the same person, and some risks, such as transmitting infection, are considerably lower. Also, in contrast to the 25 authorised ATMPs, which, as seen above, are mostly categorised as GTMPs, over half (6/11 or 55%) of the proposed ATMPs for T1D were designated as sCTMPs, and just one was considered a GTMP. Of the remaining four proposed ATMPs for T1D, two<sup>56</sup> were designated as combined products, one of which used alginate microcapsules for encapsulation.<sup>57</sup>

What this illustrates is that at least some of the authorised and proposed ATMPs do share characteristics or components with proposed regenerative medicine therapy solutions for T1D; for example, the use of xenogeneic or genetically modified cells, the inclusion of devices and so on. However, none approach the complexity of what is proposed in a bioartificial pancreas. This is because the bioartificial pancreas is a cATMP, combining both cellular and medical device components. As such, it engages not only with the ATMPs Regulation but also those governing medical devices. Given this, we conclude this section by setting out some of the pertinent context relating to medical device regulation before examining the regulatory challenges of products that engage multiple regulatory regimes in section four.

### 3.2. *Bioartificial Pancreases and Medical Device Regulation*

In addition to being subject to the ATMPs Regulation, bioartificial pancreases would also likely be subject to the medical device regulations. In particular, the synthetic structural components—for example, the COC Sphericalplate 5D (SP5D) in the proposed VANGUARD product—of these hybrid devices would have to comply with medical device regulations. In the EU,

<sup>47</sup> European Medicines Agency, CAT Quarterly Highlights Approved ATMPs.

<sup>48</sup> European Medicines Agency, MACI Article 20 Procedure Assessment. MACI is a product used for the repair of knee cartilage that uses autologous cells and a porcine collagen membrane; it is classified as a type I/III medical device.

<sup>49</sup> Rare conditions are defined as affecting fewer than 1 in 2,000 people.

<sup>50</sup> European Medicines Agency, CAT Quarterly Highlights Approved ATMPs.

<sup>51</sup> International Diabetes Federation, Atlas-Factsheet Europe 2021.

<sup>52</sup> Full reports are available on their website archive for products assessed prior to 2019; however, products assessed after 2019 merely have summary characteristics.

<sup>53</sup> ViaCyte Inc., San Diego, California and Vertex Pharmaceuticals; VANGUARD, "New Generation Cell Therapy."

<sup>54</sup> Autologous cells come from the recipient themselves, whereas allogeneic cells come from a separate human donor.

<sup>55</sup> All of which are gene therapies.

<sup>56</sup> The single authorised cATMP represents just 4% of that group.

<sup>57</sup> European Medicines Agency, Alginate Encapsulated Porcine Pancreatic Islet.

this means compliance with the new Medical Device Regulation 2017/745 (EU MDR), which came into force later than intended as a result of the COVID-19 pandemic in 2021.<sup>58</sup>

Medical devices are classified as either class I, IIa, IIb or III and are subject to 22 classification rules, within each of which there are several subclassification rules.<sup>59</sup> This classification takes into account the intended purpose of the devices and their inherent risks.<sup>60</sup> In the case that several rules—or if within the same classification rule, several sub-rules—apply to the same device based on the device’s intended purpose, the strictest rule and sub-rule resulting in higher classification (class III being the highest) will apply. Broadly speaking, relevant definitions for the classification of medical devices include but are not limited to consideration of their (i) specific medical purpose, (ii) duration of use (either transient, short- or long-term) and (iii) invasiveness (in which a device, either wholly or in part, penetrates inside the body, either through a body orifice or through the surface of the body, including surgically implanted devices).

In addition to the general requirement of risk classification, all medical devices must have a conformity assessment that determines whether the requirements of the regulations relating to a device have been fulfilled prior to the device being placed on the market. In the EU, this is a Conformité Européenne (CE) mark. Conformity assessments are carried out by notified bodies—private entities regulated by the medical device regulations—and manufacturers may choose which of the many bodies across the EU they apply to. This regulatory oversight at the national level is in contrast to the regulation of pharmaceutical medicines, which in the EU is centralised and, as we have already observed when examining ATMPs, is entirely overseen by the EMA.

Precisely which device classification rules would apply to the bioartificial pancreas is not immediately clear. Under classification rule 8 of the EU MDR, all implantable devices and long-term surgically invasive devices (more than 30 days) are classified as class IIb unless they have a biological effect or are wholly or mainly absorbed, in which case they are classified as class III.<sup>61</sup> Under classification rule 14:

all devices incorporating, as an integral part, a substance which, if used separately, can be considered a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, *including a medicinal product* derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and *that has an action ancillary to that of the devices*, are classified as class III.<sup>62</sup>

Other classification rules may apply.

What is particularly interesting about the bioartificial pancreas is that although we might all agree that, for now at least, in terms of meeting medical device regulation requirements, it would probably be classified as a class III invasive long-term use and surgically implantable device product used in combination with cells to treat (T1D) disease, this does not capture the true extent of the role of its synthetic structural components. For example, consider the COC SP5D component in the proposed VANGUARD product. The fifth dimension of this device has been defined as the communication of the cells with each other. The critically determined shape and size of the microwells in this synthetic culture plate create an environment that is as physiological as possible. In addition, a special nanocoating hinders cells from attaching to the surface of the culture plate. This results in the formation of uniform spheroids with undisturbed communication of the cells with each other, thereby preventing the induction of unwanted gene expression/differentiation and facilitating cell therapy. This kind of interaction between the culture plate and cell lines is a game changer. In this setting, neither the device nor the cell takes on an ancillary role. Rather, the device is integral to facilitating the cell survival and cell therapy mechanism of action. The potential of this kind of hybrid model product to act as a springboard to the development of new and yet more complex implantable, multi-functional bioartificial organs, which no doubt will eventually interact with software and smart technology, is immense and knows no bounds.

Medical Device Regulations and the ATMPs Regulation are mutually exclusive. However, both should be applicable in the case of combination/hybrid products that comprise both a medical device and a medicinal substance, including a human blood

<sup>58</sup> 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 117/1 (Medical Device Regulation, MDR), art 2. ‘Medical device’ is defined as ‘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 medicinal purposes.

<sup>59</sup> Medical Device Regulation, “ANNEX VIII.”

<sup>60</sup> Medical Device Coordination Group, Guidance on Classification of Medical Devices.

<sup>61</sup> Medical Device Coordination Group, Guidance on Classification of Medical Devices.

<sup>62</sup> Medical Device Coordination Group, Guidance on Classification of Medical Devices, emphasis added.



or plasma derivative or tissues or cells of human origin (Reg 722/2012). But, as seen in the case of the bioartificial pancreas, at present, neither set of regulations takes proper account and accurately captures its truly hybrid nature, in which the intended purpose and function of the hybrid product is only made possible by the combination of its constituent parts, with no particular part (device or cellular) playing an ancillary role. In this way, bioartificial pancreases pose problems for existing regulatory regimes. Unlike other ATMPs, the medical device components of a bioartificial pancreas are likely to play an active role in the proper functioning of the therapy. Consequently, these innovative medical technologies will likely be subject to both regulations governing cATMPs and those governing medical device regulations. This poses a potential problem for the development of a bioartificial pancreas and the transition of the therapy from the lab to the clinic. Although there are technical and scientific challenges surrounding working with delicate human cells, as well as challenges commercialising these products and negotiating reimbursement arrangements with health bodies and insurers,<sup>63</sup> the complexity of the regulatory regime developers have to work within is also an independent factor slowing down development. This was suggested in a recent survey of European ATMP developers, which found that regulatory challenges were cited more commonly (34%) than technical (30%) or scientific challenges (14%) in the development of ATMPs.<sup>64</sup> Given that bioartificial pancreases would also likely have to comply with medical device regulations, the regulatory challenges facing these therapies would be magnified even further.

#### 4. Developing a Bioartificial Pancreas: The Challenge of Engaging Multiple Regulatory Regimes

At each stage of its development—preclinical research, clinical trials, market approval and post-market surveillance—the complexity in the composition of a proposed bioartificial pancreas will pose new regulatory challenges. At the preclinical stage, each of the proposed cell types and their source, which have advantages and disadvantages from a scientific perspective, also engage multiple different regulations. For example, the procurement of deceased donor islet cells would, first and foremost, be governed by the laws of organ donation from the jurisdiction in which the donor cells were procured. Across Europe, there are both ‘opt-in’ and ‘opt-out’ models for deceased donor consent in operation,<sup>65</sup> but in either case, the use of cells in research or for inclusion in a cellular product would require specific permission from the donor or an appropriate proxy.<sup>66</sup> As a consequence, supply is likely to be limited. Organs and tissues intended for use in transplantation must meet quality and safety requirements set out in EU Directive 2004/23/EC,<sup>67</sup> and stem cells, depending on their provenance, would be subject to the European tissues and cells directives.<sup>68</sup> Additionally, if they have been genetically manipulated, directives on genetically modified organisms (GMOs) will be relevant.<sup>69</sup> In the case of cells used for purposes such as immune protection or vascularisation, much like insulin-producing cells, these would be subject either to the ‘tissues and cells’ directive or ‘the blood directive’ 2002/98/EC,<sup>70</sup> depending on provenance, and to genetic modification restrictions if any have been made.

If, instead, islets originating from xenogeneic sources are used, these present even greater difficulties. Proponents argue that using animal sources could provide a relatively unlimited supply of cells and so make a bioartificial pancreas available to a much larger group of PwDs. However, the acceptability of non-human animal cells remains an area where there is little consensus, and despite several decades of research and debate, important ethical and legal issues remain unresolved.<sup>71</sup> To discuss these in depth is beyond the scope of this article, but on the simple question of the permissibility and regulation of xenogeneic cells in an ATMP, we will highlight our concerns. Xenogeneic islets as a treatment for diabetes have been under investigation since the 1990s, with the production of transgenic animals being governed by regulations for the treatment of

<sup>63</sup> Cornwall, “Advanced Therapies”; Ronco, “Price and Reimbursement of Advanced”; Ten Ham, “Challenges in Advanced Therapy Medicinal.”

<sup>64</sup> Ten Ham, “Challenges in Advanced Therapy Medicinal.”

<sup>65</sup> An ‘opt-in’ model is where individuals must have expressed in life their desire to donate organs after death, while ‘opt-out’ assumes that everybody would like to be considered a donor unless they have registered their dissent.

<sup>66</sup> For example, in the UK, use of pancreatic cells for inclusion in an ATMP is specifically excluded from the procedures covered by ‘deemed consent’ regulations by The Human Tissue (Permitted Material: Exceptions) (England) Regulations 2020 Section 2(5)(d).

<sup>67</sup> 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 [2010] OJ L 207/14.

<sup>68</sup> 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 [2004] OJ L 102/48.

<sup>69</sup> 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 [2009] OJ L 125/75.

<sup>70</sup> Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 Setting Standards of Quality and Safety for the Collection, Testing, Processing, Storage and Distribution of Human Blood and Blood Components and Amending Directive 2001/83/EC [2002] OJ L 33/30.

<sup>71</sup> Nairne, Animal-to-Human Transplants; Fovargue, Xenotransplantation and Risk.

non-human animals for scientific purposes<sup>72</sup> and those for GMOs.<sup>73</sup> However, while the 2007 regulations anticipate the use of non-human animal cells in ATMPs, they do not explicitly authorise their use or provide a comprehensive regulatory framework. In fact, much like the use of other ethically contentious cell sources, their permissibility is left firmly as a matter devolved to Member States. The preamble to the regulations states:

The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of, or derived from these cells.<sup>74</sup>

In the years following, differing regulatory approaches have indeed been taken. For example, the Netherlands has had a ban on xenotransplantation and the use of xenogeneic cells in place since 2002.<sup>75</sup> In 2014, the Italian Government approved an animal welfare bill that would effectively ban xenotransplantation research, although not animal-to-human transplants themselves.<sup>76</sup> The UK holds an equally confusing position. There is no legislative prohibition on xenogeneic organ transplantation or the use of xenogeneic cells; however, the official interim regulatory authority assigned to oversee such work—the UK Xenotransplantation Interim Regulatory Authority (UKXIRA)—was disbanded in 2006 and has not been replaced.<sup>77</sup> So, while there may arguably be advantages to using xenogeneic cells, the absence of guidance or a legal framework means it is not clear if researching or marketing a xenogeneic cell product would be permissible in all (or any) European jurisdictions.

When translating from preclinical to clinical work, many regulatory challenges also become practical. In manufacturing products for human use, good manufacturing practice (GMP) must be adhered to.<sup>78</sup> GMP is a set of standardised, internationally accepted rules for the quality and standards used in the manufacturing of medical products. It covers aspects such as materials, premises and staff training. At the earliest stages of preclinical development, many non-commercial laboratories do not conform to these stringent requirements or consistently use expensive GMP-compliant materials. However, as a product approaches the clinical testing stage, it is necessary that all processes and materials are of a GMP standard and manufactured in GMP-compliant labs. While, ideally, all laboratories would be applying these standards from the earliest possible phase, the requirements are such that many smaller or academic laboratories are often unable to meet them. In the translation to clinical trials, therefore, smaller players (academic institutions, etc.) often give way to larger commercial pharmaceutical organisations.

As we saw in the previous section, the ATMPs Regulation comes into effect at the market authorisation stage. In this respect, a bioartificial pancreas is likely to test the expertise of even the CAT when it comes to the classification question. The variety and complexity of the cell sources proposed in a bioartificial pancreas are significantly greater than that observed in any established ATMPs. In addition, as noted previously, just one cATMP has previously received market authorisation, which was subsequently withdrawn. A bioartificial pancreas comprising multiple cell sources and a medical device could potentially represent the most complex product to have been assessed yet. Finally, even if a bioartificial pancreas were to successfully navigate all these regulatory requirements and come to market, developers would then be required to undertake post-market authorisation pharmacovigilance studies to monitor the safety of such novel products. In the case of a product using xenogeneic cells, this could include lifelong surveillance for xenogeneic infections.<sup>79</sup>

The addition of medical devices adds further challenges on top of this already complex regulatory matrix. For instance, it is presently unclear if all approved or notified bodies have the specialist experience necessary to assess the safety and efficacy of devices as part of the conformity assessment process in the context of a cATMP. Scaffolds and matrices could be authorised for one medical purpose but undertake a whole new purpose within a cATMP. The ATMPs Regulation acknowledges in its forward matter that the complexity presented by cATMPs requires a specific approach.<sup>80</sup> Further, according to Article 9(1), overall responsibility for the final evaluation of a cATMP should be retained by the EMA.<sup>81</sup> As a result, for a cATMP, multiple legal instruments and agencies are, in effect, engaged concurrently. The medical device component continues to be defined by

<sup>72</sup> 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 [2010] OJ L 276/33.

<sup>73</sup> Directive 2001/18/EC; Directive 2009/41/EC.

<sup>74</sup> Regulation (EC) No 1394/2007, section (7)

<sup>75</sup> Special Medical Procedures Act 2021 (Netherlands) art 6a 173.

<sup>76</sup> Legislative Decree 26/2014 (Italy) art 3(1) 1(q)

<sup>77</sup> McLean, “Demise of UKXIRA.”

<sup>78</sup> Commission Directive 2003/94/EC of 8 October 2003 Laying Down the Principles and Guidelines of Good Manufacturing Practice in Respect of Medicinal Products for Human Use and Investigational Medicinal Products for Human Use [2003] OJ L 262/22.

<sup>79</sup> European Medicines Agency, Guideline on Xenogeneic Cell-based Medicinal.

<sup>80</sup> Regulation (EC) No 1394/2007, para 4.

<sup>81</sup> Regulation (EC) No 1394/2007, art 9(1).

and must meet the essential requirements for design and construction, microbial contamination, labelling and so forth in Annex I of the EU MDR,<sup>82</sup> but the definition and safety requirements for the overall product are under the ATMPs Regulation. Further, an approved or notified body may conduct the conformity assessment. Or, if one has not been undertaken, the EMA may seek one from an appropriate approved or notified body,<sup>83</sup> but the overall assessment of the product and market authorisation of a cATMP is granted by the EMA. This devolved and isolated approach to medical device regulation and assessment leaves the door open to heterogeneous interpretation and application of standards between approved and notified bodies and the EMA regarding device components. Ultimately, the EMA will have access to the necessary expertise and act as the final arbiter, so a significant safety issue seems unlikely to arise, but it does further complicate the market authorisation process and potentially add additional burdens on developers and slow progress even further.

This brings us to one of the principal concerns when considering the regulation of a bioartificial pancreas. From lab to market, there are more than 20 European regulations or directives (these are set out in Table 1) that could apply to a bioartificial pancreas before any requirements specific to particular countries are even considered.<sup>84</sup> These are overseen by an abundance of regulatory authorities—the EMA, national competent authorities for medical devices, national transplantation authorities and those responsible for overseeing clinical research. To ensure adherence to all the applicable statutes requires highly specialist resources and a detailed understanding of the law. While it is undoubtedly important that these complex treatments using cell and gene therapies are highly regulated to prevent harm to patients and donors alike, the burden this creates may discourage smaller organisations or academic institutions from even entering the sector and stifle innovation.

The analysis in this article explicitly focuses on the complexity of regulation at the level of application. Nevertheless, we acknowledge that there are broader issues of regulatory principle that have a bearing on any normative questions in this area. In particular, in suggesting, as we have just done, that a high degree of regulatory complexity can create burdens that are in tension with innovation, it might prove useful to further explore the ‘why’ of regulation in this area. This may be needed to better explore how hybrid devices, such as bioartificial pancreases, can be regulated more coherently and how we could better strike a balance between, for instance, innovation and considerations of risk. Additionally, our analysis would likely also be bolstered by further consideration of the consequences of both over- and under-regulation.<sup>85</sup> However, due to limitations of space and to mitigate the risk of moving too far from the focus of the current article on practical application, this is a task for another day.

In this vein, therefore, we should note that it is not just the regulatory burden that may cause difficulties for those keen to realise the benefits of a bioartificial pancreas; the classification a therapy receives can significantly affect its clinical availability. Let us see why this is the case.

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<sup>82</sup> Regulation (EU) 2017/745.

<sup>83</sup> Regulation (EC) No 1394/2007, article 9(3).

<sup>84</sup> These have been flagged by ATMP developers as a further stumbling block; see Ten Ham, “Challenges in Advanced Therapy Medicinal.”

<sup>85</sup> Our thanks to the reviewers who made these points to us. For a discussion on these wider issues of regulatory principles and theory, see Baldwin, “Driving Priorities Risk Based Regulation”; Braithwaite, “Types of Responsiveness”; Carpenter, Preventing Regulatory Capture.

**Table 1. Summary of European Union Regulations and Directives that may be applicable to a bioartificial product and its components**

	<b>EU Regulations and Directives</b>
<b>Tissues and cells</b>	Directive 2004/23/EC, also known as the European Tissues and Cells Directive, covering standards for donation, procurement and testing, processing, preservation, storage and distribution of human tissues and cells Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells
<b>Blood components</b>	Directive 2002/98/EC (amending Directive 2001/83/EC) of January 2003 sets standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components
<b>Genetically modified organisms</b>	Directive 2009/41/EC of the European Parliament on the contained use of genetically modified micro-organisms Directive 2001/18/EC of the European Parliament on the deliberate release into the environment of genetically modified organisms
<b>Use of animals</b>	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
<b>Transplantation</b>	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
<b>Clinical Trials</b>	Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Directive 2001/20/EC of April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicines for human use Directive 2003/94/EC of October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
<b>Good Manufacturing Practice</b>	Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use Directive 2003/94/EC of October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
<b>Good Clinical Practice</b>	Directive 2001/20/EC of April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicines for human use Directive 2005/28/EC of April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
<b>Advanced Therapy Medicinal Products</b>	Regulation (EC) No 1394/2007 EC on advanced therapy medicinal products and amending Directive 2001/83/EC (medicinal products for human use) and Regulation (EC) No 726/2004 (on procedures for the authorisation and supervision of medicines for human and veterinary use and establishing the European Medicines Agency) Directive 2009/120/EC relating to medicinal products for human use as regards advanced therapy medicinal products
<b>Medicines for human use</b>	Directive 2001/83/EC relating to medicinal products for human use
<b>Medical devices</b>	Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices 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 (2017)

<b>Pharmacovigilance</b>	Regulation (EU) No 1235/2010 of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products Directive 2010/84/EU of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use
<b>Paediatric use</b>	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use
<b>Data protection</b>	Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data

## 5. Consequences and Implications of the Classification Problem

In section three, we outlined the classification system utilised in the ATMPs Regulation. We also argued that the classifications contained therein are inadequate and a poor fit for cATMPs combining cellular and medical device components, such as the bioartificial pancreas. In this section, we demonstrate the potential consequences and implications of this. First, we draw on examples related to transplantation to show why classification in this realm matters. Second, we argue that the bioartificial pancreas ought to be conceptualised as a hybrid product and, as such, there is a pressing need for further guidance on this and similar cATMPs.

### 5.1 Lessons from Transplantation

A prime example of the importance of classification is found in deceased donor islet cell transplantation. Over the course of the last 20 years, European centres have formed the largest global transplantation program, providing 2,608 transplants to 1,295 recipients.<sup>86</sup> In the EU and UK, islet cell transplantation from allogenic deceased donors is regulated under organ transplantation. This practice is based on the assessment of the CAT in 2010, which confirmed that the cells used for islet cell transplantation were minimally manipulated and ‘intended to be used for the same essential function in the recipient and the donor, i.e. pancreatic function’, and so did not fall into the category of an ATMP.<sup>87</sup> Similarly, the separation of cells from the pancreas of those undergoing a pancreatectomy and their subsequent reimplantation (an autologous islet cell transplant)<sup>88</sup> has also been assessed as not falling under the ATMPs Regulation. In contrast, in the United States in 2015, the processing of cells involved in preparing them for islet cell transplantation was determined to render them a ‘cell therapy’.<sup>89</sup> As a result, they are regulated under laws for biologic drugs and cell and gene therapies. This has led to ‘the demise of islet allotransplantation in the US’,<sup>90</sup> with only 11 recipients receiving islet allotransplantation between 2016 and 2019, all under the auspices of a clinical trial as an investigational product. This demonstrates the importance of classification in the availability of even well-established treatments—let alone novel and innovative ones—and raises important questions about which approach we should adopt. Should we adopt the ‘transplant approach’ (which leads to more implantation) or a ‘cell-therapy approach’ (which leads to greater caution)? The classification of ‘bioartificial organs’ for transplant will inevitably impact their availability and how they are allocated. But if, as we argue in section 5.2, it is possible for bioartificial organs to be classified as a single entity rather than the sum of each of its constituent parts, this may help improve accessibility.

We can also see the potentially far-reaching implications of how technologies are classified if we consider the issue of the commercialisation of bioartificial organs. Although many jurisdictions have long held that human tissues and organs cannot be bought and sold, it is also usually accepted that the modifications and manipulations by skilled scientists render cell-based therapies outside the realm of this prohibition. The case of the bioartificial pancreas, and indeed any novel hybrid regenerative medicine therapies, may challenge this accepted paradigm and demand a new approach from legislators.

<sup>86</sup> Berney, “Worldwide Survey of Activities and Practices.”

<sup>87</sup> European Medicines Agency, Suspension Containing Human Islets.

<sup>88</sup> For example, for pancreatic cancer.

<sup>89</sup> Piemonti, “US Food and Drug Administration”; Witkowski, “Demise of Islet Allotransplantation.”

<sup>90</sup> Witkowski, “Demise of Islet Allotransplantation.” pp.1365-1375.

It is important to acknowledge that the enterprise of organ donation and transplantation has been largely built upon a foundation of altruism. The exchange between donor and recipient is often conceptualised and referred to as a ‘gift relationship’.<sup>91</sup> Regulations for organ transplantation seek to protect this spirit of altruism so integral to the practice of transplantation by mandating that organs are allocated by clinical need on a strict, not-for-profit basis.<sup>92</sup> The use of language such as ‘bioartificial organ’, therefore, brings with it this history of altruism and fair distribution. In stark contrast, cell-based therapies are medicinal products that can, quite legitimately (at least legally speaking), be marketed for profit.<sup>93</sup> Access to new, expensive and scarce technology is frequently limited, sometimes being only available to those able to pay for it. If a regenerative medicine ATMP for T1D is considered a ‘bioartificial pancreas’, it begs the question of what sort of approach to its allocation and distribution should be adopted. If they are principally regarded as products, then this discourse may be the same as for any commercial endeavour. However, if we are to regard them truly as ‘bioartificial organs’ for transplantation, then an entirely new discourse influenced by the history and ethos of altruistic transplantation may be necessary.

When bioartificial pancreases (or any bioartificial organs) first become available, it is highly likely that, as with organs used for allogeneic transplants, they will be a scarce resource. If, for instance, deceased donor cells are to be used, there remains a shortage of donors. Stem cell lines are sometimes difficult to proliferate and have been known to fail unexpectedly. If xenogeneic cells are used, few countries have access to certified premises for the breeding and rearing of transgenic animals. Likewise, the current manufacturing infrastructure for cell-based therapies is relatively limited, based as it is on a market of a small number of ATMPs aimed principally at rare diseases. Together, these limitations mean that, at least initially, it is unlikely that a bioartificial pancreas will be readily available to all those who could potentially benefit. Decisions, therefore, will need to be made regarding what criteria may be used to decide how this scarce resource is allocated.

At present, the regulations for cellular therapies and ATMPs are primarily concerned with ensuring the quality and safety of the proposed treatment. However, proper regulations for bioartificial organs will need to consider additional issues, such as whether there would need to be a waiting list to determine those in most urgent need.<sup>94</sup> If so, who would administer it? Should this differ depending on whether the cells are from living or deceased human donors or from xenogeneic sources? Organs for transplant have axiomatically been assumed to be a part of the recipient, but should this be equally true of a bioartificial pancreas? Quigley asked, ‘Should internal medical devices that keep the person alive be viewed as part of the person or mere objects (or something else)?’<sup>95</sup> This question seems just as apt for a bioartificial pancreas as it does for a pacemaker.

All these questions and more are currently unanswered. But what can be observed is that the nomenclature we use to describe these therapies seems to form part of an inexorable link between their composition, classification and clinical utility. This raises the question of whether the current nomenclature and classification system is fit for purpose when considering regenerative medicine products or whether new classifications are needed that acknowledge that bioartificial organs represent a paradigm-shifting technology. However, one thing is already clear: disparities in the availability and uptake of existing cell- and device-based treatments for T1D perpetuate differential outcomes for PwDs.<sup>96</sup> If we are to make progress in narrowing these divisions, it is vital that we learn from the twentieth-century experiences of medical device innovation for T1D we described in section 2 and that developers and regulators alike ensure that novel and emerging therapies do not continue these trends.

### ***5.2 Complex cATMPs and the Bioartificial Pancreas as Hybrid Products***

As we saw in section three, when it comes to a bioartificial pancreas, one of the main challenges regarding classification is that the devices are integral to the survival and functioning of the cellular components. The different components are not, as seems to be implicit in the ATMPs Regulation and various pieces of guidance, simply combined in a manner such that they merely sit in comfortable proximity to each other. As the relentless pace of scientific development moves forward, it has become apparent that, in the same way that early cell therapies were insufficiently covered by definitions in medicinal product regulations, products like a bioartificial pancreas may not fit neatly into existing classifications. They are not, as we have shown throughout this article, satisfactorily accounted for in the existing legal paradigm regulating regenerative medical therapies. This includes both the ATMPs Regulation and medical device regulations. Given this, what is to be done?

We suggest that, for these regenerative medicine therapies where devices perform an integral function in protecting, supporting and maintaining cellular components, a new classification of ‘hybrid’ product could be adopted and should either replace

<sup>91</sup> Titmuss, “Gift Relationship.”

<sup>92</sup> For a discussion, see Cronin, “Directed and Conditional Deceased Donor.”

<sup>93</sup> We acknowledge the potential divergence in terms of moral legitimacy for cells for profit. See, for example, Oza, “Ground-breaking Henrietta Lacks Settlement.”

<sup>94</sup> As there is for both whole pancreas and islet transplantation.

<sup>95</sup> Quigley, “Everyday Cyborgs.” pp. 278-306.

<sup>96</sup> Auzanneau, “Heterogeneity of Access to Diabetes Technology”; Addala, “Decade of Disparities in Diabetes.”

‘combined’ product or be added as an additional classification. For a number of reasons, this would better capture the permutations and complexity of products, such as the bioartificial pancreas, that sit at the intersection of cellular therapy and medical devices.

In this vein, we propose that hybrid ATMPs (hATMPs) are products in which any ATMP is combined with one or more medical devices (including implantable devices) as defined by Article 2 of EU MDR concerning medical devices<sup>97</sup> and Article 2(5) concerning implantable medical devices,<sup>98</sup> and in which:

1. The pharmacological, immunological or metabolic action of the cellular components that is considered the principal mode of action of the combination product is not possible without the integration of at least one of the medical devices; and
2. At least one of the medical devices (in combination with the cellular components) is integral to the protection, support, survival, maintenance and functioning of the cellular components; and
3. At least one of the medical devices (in combination with the cellular components) is integral to, and not ancillary to, the principal mode of action of the combination product.

Moreover, we suggest that the EMA, national regulators and competent authorities for medical devices, national transplantation authorities and those responsible for overseeing translational clinical research respond to this by developing the existing regulatory framework in such a way that captures the essence of these hybrid products as a single (organ) entity and issuing guidance for researchers engaged in this emerging technology. Further, due consideration of the status of hATMPs as ‘bioartificial organs’, as well as what form operational oversight of their (organ) allocation should take, must be part of that deliberation and framework guidance.

## 6. Concluding Remarks

In this article, we have examined regenerative medicine solutions for T1D, including novel hybrid models aimed at creating a bioartificial pancreas. We have also exposed the complexities of the legal and regulatory landscape governing their use, particularly the regulatory challenges at the intersection of cellular and medical device therapies. We have demonstrated that a bioartificial pancreas would incorporate multiple features that have few precedents in the existing field of ATMPs and, as such, is a game changer in technology, regulation and the law. Current regulations generate a highly complex and burdensome matrix of regulatory oversight but fail to address important issues raised by bioartificial organs. In particular, as observed in the case of the bioartificial pancreas, medical devices are not simply combined with cells; rather, they are integral to and facilitate the cell therapy mechanism of action. Together, these issues indicate that changes in the regulatory paradigm are required to better reflect the truly hybrid nature of these products. We have proposed that a new classification of ‘hybrid’ product could be adopted and should either replace ‘combined’ product or be added as an additional classification. We urge national regulators and competent authorities to respond by developing the existing framework and issuing guidance for researchers. We also suggest serious consideration is given to the status of ‘bioartificial organs’ as this technology evolves. In addition, we have highlighted that issues concerning equality of access, commercialisation and profitability of bioartificial organs, among others, will need to be considered. We recommend that multinational discussions are needed now on how to regulate novel regenerative medicine products, such as bioartificial pancreases, before these products come to market. There should be a focus on safety, regulatory harmonisation and ensuring equality of access to not further entrench disparities based on socio-economic advantage.

Innovation requires regulation, but it should be acknowledged that overly stringent and complex regulatory frameworks can stifle progress. A failure to strike this balance could lead to some seeking to circumvent regulatory protections where possible. Outside the EU, autologous stem cell therapy for type 2 diabetes is already being offered in the absence of formal positive clinical trials ‘in exchange for considerable sums of money’.<sup>99</sup> This has led to unease not only regarding inequality of access to new therapies but also the safety of products that have not been subject to the same rigorous assessments. In 2020, the EMA released a stark warning against accepting unproven stem cell treatments, reporting ‘serious, sometimes fatal, side effects including infections, unwanted immune reactions, [and] tumour formation’.<sup>100</sup> It is vital that, moving forward, the need to regulate regenerative medicine products is balanced with the need to explore improved treatments for patients.

<sup>97</sup> Medical Device Regulation, “MDR - Article 2 - Definitions.”

<sup>98</sup> Medical Device Regulation, “MDR - Article 2 - Definitions,” art 2(5).

<sup>99</sup> Diabetes UK, “Stem Cell Research and Diabetes.”

<sup>100</sup> Medicines Agency, “EMA Warns Against Using Unproven.” EMA/CAT/94295/2020 28 April 2020

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## Bibliography

- Addala, Ananta, Marie Auzanneau, Kellee Miller, Werner Maier, Nicole Foster, Thomas Kapellen, Ashby Walker, Joachim Rosenbauer, David M. Maahs, and Reinhard W. Holl. "A Decade of Disparities in Diabetes Technology Use and HbA1c in Pediatric Type 1 Diabetes: A Transatlantic Comparison." *Diabetes Care* 44, no 1 (2021): 133–140. <https://doi.org/10.2337/dc20-0257>.
- Auzanneau, Marie, Joachim Rosenbauer, Werner Maier, Simone von Sengbusch, Johannes Hamann, Thomas Kapellen, Guido Freckmann, Silke Schmidt, Eggert Lilienthal, and Reinhard W. Holl. "Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany." *Journal of Diabetes Science and Technology* 15, no 5 (2021): 1059–1068. <https://doi.org/10.1177/19322968211028608>.
- Bakris, George L. and Mark Molitch. "Are All Patients With Type 1 Diabetes Destined for Dialysis If They Live Long Enough? Probably Not." *Diabetes Care* 41, no 3 (2018): 389–390. <https://doi.org/10.2337/dci17-0047>.
- Baldwin, R. and J. Black. "Driving Priorities in Risk Based Regulation: What's the Problem?" *Journal of Law and Society* 43, no 4 (2016): 565–595. <https://doi.org/10.1111/jols.12003>.
- Beck, Roy W., Richard M. Bergenstal, Lori M. Laffel, and John C. Pickup. "Advances in Technology for Management of Type 1 Diabetes." *The Lancet* 394, no 10205 (2019): 1265–1273. [https://doi.org/10.1016/S0140-6736\(19\)31142-0](https://doi.org/10.1016/S0140-6736(19)31142-0).
- Berney, Thierry, Axel Andres, Melena D. Bellin, Eelco J. P. de Koning, Paul R. V. Johnson, Thomas W. H. Kay, Torbjörn Lundgren, Michael R. Ricketts, Hanne Scholz, Peter G. Stock, Steve White, and the International Islet Transplant Centers. "A Worldwide Survey of Activities and Practices in Clinical Islet of Langerhans Transplantation." *Transplant International* 106, no 9S (2022): S126. <https://doi.org/10.1097/01.tp.0000885932.10579.59>.
- Berney, Thierry, Charles H. Wassmer, Fanny Lebreton, Kevin Bellofatto, Laura Mar Fonseca, Juliette Bignard, Reine Hanna, Andrea Peloso, and Ekaterine Berishvili. "From Islet of Langerhans Transplantation to the Bioartificial Pancreas." *La Presse Médicale* 51, no 4 (2022): 104139. <https://doi.org/10.1016/j.lpm.2022.104139>.
- Boscari, Federico and Angelo Avogaro. "Current Treatment Options and Challenges in Patients with Type 1 Diabetes: Pharmacological, Technical Advances and Future Perspectives." *Reviews in Endocrine and Metabolic Disorders* 22, no 2 (2021): 217–240. <https://doi.org/10.1007/s11154-021-09635-3>.
- Braithwaite, J. "Types of Responsiveness." In *Regulatory Theory: Foundations and Applications*, edited by Peter Drahos, 117–132. Australia: ANU Press, 2017. <http://doi.org/10.22459/RT.02.2017>.
- Carpenter, D. and D. Moss, eds. *Preventing Regulatory Capture*. United Kingdom: Cambridge University Press, 2013. <https://doi.org/10.1017/CBO9781139565875>
- Collaborative Islet Transplant Registry (CITR). *Eleventh Allograft Report*. (Collaborative Islet Transplant Registry, 2022).
- Commission Directive 2003/94/EC of 8 October 2003 Laying Down the Principles and Guidelines of Good Manufacturing Practice in Respect of Medicinal Products for Human Use and Investigational Medicinal Products for Human Use [2003] OJ L 262/22.
- Committee for Advanced Therapies. *Scientific Recommendations on Classification of Advanced Therapy Medicinal Products*. (European Medicines Agency Committee for Advanced Therapies, 2022). [https://www.ema.europa.eu/documents/other/scientific-recommendations-classification-advanced-therapy-medicinal-products\\_en.xlsx](https://www.ema.europa.eu/documents/other/scientific-recommendations-classification-advanced-therapy-medicinal-products_en.xlsx).
- Cornwall, Tamsin, Sarah Taylor, Emily Williams, and Kiah York. "Advanced Therapies: Innovation, Regulation and Patentability in the UK." *Bio-Science Law Review* 18, no 3 (2021): 11.
- Cronin, Antonia J. and James F. Douglas. "Directed and Conditional Deceased Donor Organ Donations: Laws and Misconceptions." *Medical Law Review* 18, no 3 (2010): 275–301. <https://doi.org/10.1093/medlaw/fwq019>.
- Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices [1993] OJ L 169/1 art 1(2)(a).
- Council Directive of 20 June 1990 on the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices (90/385/EEC) [1990] OJ L 189/17, art 1(2)(c).
- Diabetes UK. "Stem Cell Research and Diabetes (Oct 2011)." [https://www.diabetes.org.uk/research/our-approach-to-research/research-position-statements/stem\\_cell\\_research\\_and\\_diabetes](https://www.diabetes.org.uk/research/our-approach-to-research/research-position-statements/stem_cell_research_and_diabetes).
- Dickson, Rachael, Jessica Bell, Amber Dar, Laura Downey, Victoria Moore, and Muireann Quigley. "#WeAreNotWaiting DIY Artificial Pancreas Systems and Challenges for the Law." *Diabetic Medicine* 39, no 5 (2022). <https://doi.org/10.1111/dme.14715>.
- 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 [2001] OJ L 106/1.
- Directive 2001/83/EC of the European Parliament and of the Council of 06 November 2001 on the community code relating to medicinal products for human use. 2001/83/EC [2001] OJ L 311, 28/11/2004
- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 Setting Standards of Quality and Safety for the Collection, Testing, Processing, Storage and Distribution of Human Blood and Blood Components and Amending Directive 2001/83/EC [2002] OJ L 33/30.

- 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 [2004] OJ L 102/48.
- 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 [2009] OJ L 125/75.
- 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 [2010] OJ L 207/14.
- 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 [2010] OJ L 276/33.
- Downey L, O'Donnell, Melvin T, Quigley M, "European Regulatory Pathway Tidepool Loop Following Clearance in the United States?" 24 October 2023 *Diabetic Medicine* <https://doi.org/10.1111/dme.15246>
- European Medicines Agency. *Guideline on Xenogeneic Cell-Based Medicinal Products*. (Committee for Medicinal Products for Human Use, 2009).
- . *Scientific Recommendation on Classification of Advanced Therapy Medicinal Products- Suspension Containing Human Islets of Langerhans, Autologous or Allogeneic*. (2011).
- . *MACI Article 20 Procedure Assessment Report*. (2014).
- . *Scientific Recommendation on Classification of Advanced Therapy Medicinal Products- Alginate Encapsulated Porcine Pancreatic Islet Cells*. (2013).
- . *EMA Warns against Using Unproven Cell-Based Therapies*. (2020).
- . *CAT Quarterly Highlights and Approved ATMPs*. (2023).
- Fovargue, Sara. *Xenotransplantation and Risk: Regulating a Developing Biotechnology*. Cambridge Law, Medicine and Ethics. Cambridge: Cambridge University Press, 2012.
- GOV.UK. "Regulating Medical Devices in the UK." Last modified December 31, 2020. <https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk>.
- Gruessner, Angelika C. and Rainer W. G. Gruessner. "The 2022 International Pancreas Transplant Registry Report—A Review." *Transplantation Proceedings* 54, no 7 (2022): 1918–1943. <https://doi.org/10.1016/j.transproceed.2022.03.059>.
- Hanna, Reine and Ekaterine Berishvili. "Advances and Challenges of Endocrine Pancreas Bioengineering." *Current Opinion in Endocrine and Metabolic Research* 23, (2022): 100320. <https://doi.org/10.1016/j.coemr.2022.100320>.
- Heinemann, Lutz. "Insulin Infusion Sets: A Critical Reappraisal." *Diabetes Technology & Therapeutics* 18, no 5 (2016): 327–333. <https://doi.org/10.1089/dia.2016.0013>.
- Heinemann, Lutz and David C. Klonoff. "Diabetes Technology and Waste: A Complex Story." *Journal of Diabetes Science and Technology* 16, no 6 (2022): 1381–1384. <https://doi.org/10.1177/19322968211022321>.
- Heinemann, Lutz and Andreas Stuhr. "Self-Measurement of Blood Glucose and Continuous Glucose Monitoring – Is There Only One Future?" *European Endocrinology* 14, no 2 (2018): 24–29. <https://doi.org/10.17925/EE.2018.14.2.24>.
- International Coalition of Medicines Regulatory Authorities. *Horizon Scanning Assessment Report – Artificial Intelligence*. (International Coalition of Medicines Regulatory Authorities, 2021). [https://www.icmra.info/drupal/sites/default/files/2021-08/horizon\\_scanning\\_report\\_artificial\\_intelligence.pdf](https://www.icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf).
- International Diabetes Federation. *International Diabetes Federation Atlas-Factsheet Europe 2021*. (International Diabetes Federation, 2021). [https://www.mepinterestgroupdiabetes.eu/wp-content/uploads/2021/11/IDF-Atlas-Factsheet-2021\\_EUR.pdf](https://www.mepinterestgroupdiabetes.eu/wp-content/uploads/2021/11/IDF-Atlas-Factsheet-2021_EUR.pdf).
- Iturralde, Esti, Molly L. Tanenbaum, Sarah J. Hanes, Sakinah C. Suttiratana, Jodie M. Ambrosino, Trang T. Ly, David M. Maahs, Diana Naranjo, Natalie Walders-Abramson, Stuart A. Weinzimer, Bruce A. Buckingham, and Korey K. Hood. "Expectations and Attitudes of Individuals With Type 1 Diabetes After Using a Hybrid Closed Loop System." *The Diabetes Educator* 43, no 2 (2017): 223–232. <https://doi.org/10.1177/0145721717697244>.
- Kesavadev, Jothydev, Banshi Saboo, Meera B. Krishna, and Gopika Krishnan. "Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas." *Diabetes Therapy* 11, no 6 (2020): 1251–1269. <https://doi.org/10.1007/s13300-020-00831-z>.
- Li, Phoebe, Alex Faulkner, and Nicholas Medcalf. "3D Bioprinting in a 2D Regulatory Landscape: Gaps, Uncertainties, and Problems." *Law Innovation and Technology* 12, no 1 (2020): 1–29. <https://doi.org/10.1080/17579961.2020.1727054>.
- Manrique, A., C. Jiménez, R. M. López, F. Cambra, J. M. Morales, A. Andrés, E. Gutiérrez, T. Ortuño, J. Calvo, A. G. Sesma, and E. Moreno. "Relaparotomy After Pancreas Transplantation: Causes and Outcomes." *Transplantation Proceedings* 41, no 6 (2009): 2472–2474. <https://doi.org/10.1016/j.transproceed.2009.06.165>.
- Mason, Chris, and Peter Dunnill. "A Brief Definition of Regenerative Medicine." *Regenerative Medicine* 3, no1 (2008): 1–5. <https://doi.org/10.2217/17460751.3.1.1>.
- McLean, S. and L. Williamson. "The Demise of UKXIRA and the Regulation of Solid-Organ Xenotransplantation in the UK." *Journal of Medical Ethics* 33, no 7 (2007): 373–375. <https://doi.org/10.1136/jme.2007.020768>.
- [Medical Device Regulation \(medical-device-regulation.eu\)](https://www.medical-device-regulation.eu) Annex VIII

- Nairne, Patrick and Nuffield Council on Bioethics, eds. *Animal-to-Human Transplants: The Ethics of Xenotransplantation*. London: Nuffield Council on Bioethics, 1996.
- Nathan, David M. “The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview.” *Diabetes Care* 37, no 1 (2014): 9–16. <https://doi.org/10.2337/dc13-2112>.
- Ogle, Graham D., Fei Wang, Gabriel A. Gregory, and Jayanthi Maniam. *IDF Atlas Reports—Type 1 Diabetes Estimates in Children and Adults*. (International Diabetes Federation, 2022). <https://diabetesatlas.org/idfawp/resource-files/2022/12/IDF-T1D-Index-Report.pdf>.
- Oza, Anil and Mariana Lenharo. “How the Ground-breaking Henrietta Lacks Settlement Could Change Research.” *Nature*, August 4, 2023. <https://www.nature.com/articles/d41586-023-02479-8>.
- Photiadis, Sara J., Rebecca C. Gologorsky, and Deepika Sarode. “The Current Status of Bioartificial Pancreas Devices.” *ASAIO Journal* 67, no 4 (2021): 370–381. <https://doi.org/10.1097/MAT.0000000000001252>.
- Piemonti, Lorenzo, Axel Andres, John Casey, Eelco de Koning, Marten Engelse, Robert Hilbrands, Paul Johnson, Bart Keymeulen, Julie Kerr-Conte, Olle Korsgren, Roger Lehmann, Torbjörn Lundgren, Paola Maffi, Francois Pattou, Frantisek Saudek, James Shaw, Hanne Scholz, Steve White, and Thierry Berney. “US Food and Drug Administration (FDA) Panel Endorses Islet Cell Treatment for Type 1 Diabetes: A Pyrrhic Victory?” *Transplant International* 34, no 7 (2021): 1182–1186. <https://doi.org/10.1111/tri.13930>.
- Quigley, Muireann, Laura Downey, and Jean McHale. “Future of Medical Devices Regulation.” *Law, Technology and Humans* 5, no 2 (2023). 21–42. <https://doi.org/10.5204/lthj.3102>.
- Quigley, Muireann, and Semande Ayihongbe. “Everyday Cyborgs: On Integrated Persons and Integrated Goods.” *Medical Law Review* 26, no 2 (2018): 276–308. <https://doi.org/10.1093/medlaw/fwy003>.
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [2007] OJ L 324/121
- 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 [2017] OJ L 117/1.
- REPOSE Study Group. “Relative Effectiveness of Insulin Pump Treatment over Multiple Daily Injections and Structured Education during Flexible Intensive Insulin Treatment for Type 1 Diabetes: Cluster Randomised Trial (REPOSE).” *BMJ*. (2017): j1285. <https://doi.org/10.1136/bmj.j1285>.
- Roberts, Joseph T. F., Victoria Moore, and Muireann Quigley. “Prescribing Unapproved Medical Devices? The Case of DIY Artificial Pancreas Systems”. *Medical Law International* 21, no 1 (2021): 42–68. <https://doi.org/10.1177/0968533221997510>.
- Ronco, Virginia, Myriam Dilecce, Elena Lanati, Pier Luigi Canonico, and Claudio Jommi. “Price and Reimbursement of Advanced Therapeutic Medicinal Products in Europe: Are Assessment and Appraisal Diverging from Expert Recommendations?” *Journal of Pharmaceutical Policy and Practice* 14, no 1 (2021): 30. <https://doi.org/10.1186/s40545-021-00311-0>.
- SPHERICALPLATE 5D - Ecosystem for Regenerative Medicine. <https://www.sp5d.com/>.
- Ten Ham, Renske M. T., Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G. M. Leufkens, and Olaf H. Klungel. “Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe.” *Molecular Therapy. Methods & Clinical Development* 11 (2018): 121–130. <https://doi.org/10.1016/J.OMTM.2018.10.003>.
- Teo, Evelyn, Norasyikin Hassan, Wilson Tam, and Serena Koh. “Effectiveness of Continuous Glucose Monitoring in Maintaining Glycaemic Control among People with Type 1 Diabetes Mellitus: A Systematic Review of Randomised Controlled Trials and Meta-Analysis.” *Diabetologia* 65, no 4 (2022): 604–19. <https://doi.org/10.1007/s00125-021-05648-4>.
- The Human Tissue (Permitted Material: Exceptions) (England) Regulations 2020
- Titmuss, R. *The Gift Relationship: From Human Blood to Social Policy*. London: LSE Press, 1970.
- VANGUARD. “New Generation Cell Therapy: Bioartificial Pancreas to Cure Type 1 Diabetes.” <https://vanguard-project.eu/>. ViaCyte. <https://www.vrtx.com/>.
- Vertex. “VX-880 by VERTEX.” <https://www.vrtx.com/our-science/pipeline/>.
- Wassmer, Charles Henri, Fanny Lebreton, Kevin Bellofatto, Domenico Bosco, Thierry Berney, and Ekaterine Berishvili. “Generation of Insulin-Secreting Organoids: A Step toward Engineering and Transplanting the Bioartificial Pancreas.” *Transplant International* 33, no 12 (2020): 1577–1588. <https://doi.org/10.1111/tri.13721>.
- Witkowski, Piotr, Louis H. Philipson, Dixon B. Kaufman, Lloyd E. Ratner, Marwan S. Abouljoud, Melena D. Bellin, John B. Buse, Fouad Kandeel, Peter G. Stock, David C. Mulligan, James F. Markmann, Tomasz Kozłowski, Kenneth A. Andreoni, Rodolfo Alejandro, David A. Baidal, Mark A. Hardy, Amittha Wickrema, Raghavendra G. Mirmira, John Fung, Yolanda T. Becker, Michelle A. Josephson, Piotr J. Bachul, Jordan S. Pyda, Michael Charlton, J. Michael Millis, Jason L. Gaglia, Robert J. Stratta, Jonathan A. Fridell, Silke V. Niederhaus, Rachael C. Forbes, Kumar Jayant, R. Paul Robertson, Jon S. Odorico, Marlon F. Levy, Robert C. Harland, Peter L. Abrams, Oyedolamu K. Olaitan, Raja Kandaswamy, Jason R. Wellen, Anthony J. Japour, Chirag S. Desai, Bashoo Naziruddin, Appakalai N. Balamurugan,

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World Health Organization. *Global Report on Diabetes*. Geneva: World Health Organization, 2016.  
<https://apps.who.int/iris/handle/10665/204871>.

**Primary Legal Material**

*European Union (Withdrawal Act) 2018* (UK).

*Legislative Decree 26/2014* (Italy).