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Advanced therapies and the Brexit process: emerging geographies of legal responsibilities and market opportunities

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ABSTRACT

This paper analyses how so-called Brexit, that is the United Kingdom's departure from the European Union (EU), has modified the regional geography of Advanced Therapy Medicinal Products (ATMPs). The latter are therapies deriving from cell manipulation, gene editing, tissue engineering, or a combination of these techniques. Their development and delivery have been realised through research collaborations and commercial relations of international scope. In the EU, this has happened by means of a complex distribution of commercial activities and legal responsibilities. With Brexit, three main kinds of reconfigurations have occurred: the relocation of research and manufacturing activities; the reorganisation of quality control tests aimed to manage clinical risks; and the redistribution of legal responsibilities and representatives. This technical and legal reconfiguration is captured here by means of theoretical insights from the emerging domain of legal geography. Drawing on interviews conducted with both EU and UK professionals involved in ATMP development, this paper reveals the main challenges brought by Brexit to the current and future configuration of the ATMP landscape in the EU and the UK. Furthermore, it demonstrates how shifts in legal arrangements impact on science-intensive domains.

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KEYWORDS Brexit; Advanced Therapy Medicinal Products (ATMPS); legal geography

1. Introduction: geographies of legal responsibilities and market opportunities

The European Union (EU) is underpinned by economic and political integration, in addition to implying a particular distribution of legal

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responsibilities and commercial activities. When a disruptive event takes place, such as the UK's departure from the Union – so-called Brexit – in what ways are those legal and market geographies changed? Moreover, what are the implications of such a change for activities requiring specialised skills and sophisticated infrastructure, and entailing considerable risks?

The political scale and unprecedented legal nature of Brexit have inspired studies focusing on fields as different as biotechnology,[1] the car industry,[2] software development,[3] pharmaceuticals,[4] and financial markets.[5] This paper aims to identify some pressing governance and regulatory issues deriving from Brexit by focusing on the current and possible future evolution of the development, manufacture, and commercialisation of Advanced Therapy Medicinal Products (ATMPs), as it has occurred since the 2016 Brexit referendum.

The concept of ATMP has been consolidated by the EU's regulator for medicinal products – the European Medicines Agency (EMA) – which in its Regulation 1394/2007, defined ATMPs as medicines based on genes, cells, and tissues, or any product combining these components with medical devices.[6] These medicines are frequently described as highly innovative and disruptive, as they enable personalised therapeutic approaches[7] and can potentially tackle diseases for which no treatment is available.[8]

ATMP development has been outstanding in Europe – especially in leading economies such as the UK, Italy, Germany, and France – with evidence of innovative activities in fields such as gene editing[9] and bioprinting.[10] Although such activities are not always carried out by players

[1]Tim K. Mackey and John Annaloro, '"Bioexit": navigating the policy and regulatory pathways for the biotechnology industry in a post-Brexit landscape' (2018) 23 *Drug Discovery Today* 1324.
[2]Matthew Humphreys and Doug Munro, *Brexit and the car industry* (Routledge, 2019).
[3]Crispian Fuller, 'Understanding the impact of Brexit: the case of foreign software corporations in Scotland and South East England' (2021) 28 *European Urban and Regional Studies* 173.
[4]Trivedi Ankit and others, 'Transition of pharmaceutical regulations: the new regulatory era after Brexit' (2021) 33 *Journal of Pharmaceutical Research International* 804; Anda Batraga and others, 'Possible consequences of Brexit on European pharmaceutical market' (12th International Scientific Conference on New Challenges in Economic and Business Development); Mark Dayan, 'How will Brexit affect the supply of medicines?' (2020) 371 BMJ 1.
[5]Scott James and Lucia Quaglia, 'Rule maker or rule taker? Brexit, finance and UK regulatory autonomy' (2020) online first International Political Science Review 1.
[6]European Parliament and the Council, *Regulation (EC) No 1394/2007 of the European Parliament and of the Council* (2007).
[7]Sofieke de Wilde and others, 'Clinical development of gene- and cell-based therapies: overview of the European landscape' (2016) 3 *Molecular Therapy - Methods & Clinical Development* 1; Nicholas Medcalf, 'Centralized or decentralized manufacturing? Key business model considerations for cell therapies' (2016) 2 *Cell Gene Therapy Insights* 95; Kim F. Pearce and others, 'Regulation of advanced therapy medicinal products in Europe and the role of academia' (2014) 16 *Cytotherapy* 289.
[8]Vicki Brower, 'The CAR-T cell race' (2015) 29. Available at: https://www.the-scientist.com/bio-business/the-car-t-cell-race-35701 TheScientist.
[9]Katelyn Brinegar and others, 'The commercialization of genome-editing technologies' (2017) 37 *Critical Reviews in Biotechnology* 924.
[10]Edison Bicudo, Alex Faulkner and Phoebe Li, 'Sociotechnical alignment in biomedicine: the 3D bioprinting market beyond technology convergence' (2021) 66 *Technology in Society* 1.

headquartered in Europe, some key ATMP-related companies do originate from the EU, such as Cellink (Sweden), Cellectis (France), and Sanofi Aventis (France).[11] This ATMP presence opens up new clinical pathways in Europe, but the region has also had to cope with new kinds of risks. For example, CAR-T cell products, which are gene-edited medicines for resistant cancers – one of which has recently been approved by the EMA[12] – have enabled outstanding clinical outcomes[13] but have also brought about cases of severe adverse reactions requiring intensive care.[14]

In order to oversee and minimise these risks, a regulatory system (including GMP standards and pharmacovigilance) has been put in place. In a bloc like the EU, where different jurisdictions are made to align, a certain geography must then be carefully designed, involving the creation of various markets around ATMPs and the distribution of responsibilities among various stakeholders.

In this sense, ATMPs require a complex, international distribution of legal responsibilities, a traditional challenge in international law[15] that has been faced in other, non-medical areas such as climate change,[16] global trade,[17] and global migration.[18] In these areas, as well as in ATMPs, distributing responsibilities, managing risks, and overseeing emerging markets depend on the creation of a suitable international legal framework.

This requires the formulation of legal orders deeply embedded in social and spatial systems, forming what has been described as a 'lawscape'[19] or

[11] Edison Bicudo and others, 'Patent power in biomedical innovation: technology governance in biomodifying technologies' (2022) 25 *The Journal of World Intellectual Property* 473.

[12] https://www.pharmatimes.com/news/kites_yescarta_to_receive_european_marketing_authorisation_1456927

[13] Muhammad Zaheer Abbas, 'Strategic use of patent opposition safeguard to improve equitable access to innovative health technologies: a case study of CAR T-cell therapy Kymriah' (2020) *Early access Global Public Health* 1; Brower, 'The CAR-T cell race'; Julia Thornton Snider and others, 'The potential impact of CAR T-cell treatment delays on society' (2019) 25 *The American Journal of Managed Care* 379.

[14] Anne Black, Sumantha Gabriel and David Caulfield, 'Implementing chimeric antigen receptor T-cell therapy in practice' <https://pharmaceutical-journal.com/article/ld/implementing-chimeric-antigen-receptor-t-cell-therapy-in-practice>Bianca Santomasso and others, 'The other side of CAR T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden' (2021) 39 *American Society of Clinical Oncology Educational Book* 433.

[15] André Nollkaemper and others, 'Guiding principles on shared responsibility in international law' (2020) 31 *European Journal of International Law* 15; André Nollkaemper, Dov Jacobs and Jessica N. M. Schechinger (eds), *Distribution of responsibilities in international law* (Cambridge University Press, 2015).

[16] Erik Persson, Kerstin Eriksson and Åsa Knaggård, 'A fair distribution of responsibility for climate adaptation: translating principles of distribution from an international to a local context' (2021) 6 *Philosophies* 1.

[17] Yanxin Liu and others, 'Environmental and economic-related impact assessment of iron and steel production: a call for shared responsibility in global trade' (2020) 269 *Journal of Cleaner Production* 1.

[18] Rebecca Dowd and Jane McAdam, 'International cooperation and responsibility-sharing to protect refugees: what, why and how?' (2017) 66 *International & Comparative Law Quarterly* 863.

[19] Nicole Graham, *Lawscape: property, environment, law* (Routledge, 2010).

'nomosphere'.[20] These concepts come from the emerging field of legal geography, in which interpreters frame legal frameworks as '[…] enacted encodings, which weave together spatial and legal meanings'.[21] In this paper, we draw on some insights from legal geography to analyse how, in the EU, ATMP development has been supported by a particular legal geography. Furthermore, this approach evidences the ways in which Brexit subverts some aspects of that geography. This analysis is then aimed to exemplify how science-intensive domains rely on complex political, technical, and institutional arrangements whose modification can trigger processes of lasting and uncertain results, creating a new legal geography.

The paper is organised in four sections. Initially, we outline the methods underpinning our study. We move on to describe the main features of the EU's legal geography for ATMP development and delivery. The following section focuses on the changes brought about by Brexit, highlighting three issues: regional flows of medicinal products; quality control required for risk management; and the market of legal advice and representation for ATMP manufacturers. The conclusion brings some final remarks, highlighting the challenges reviewed throughout the paper.

2. Research methods

Our study has been conducted at University College London and is part of the Future Targeted Healthcare Manufacturing Hub – a multidisciplinary research hub addressing the manufacturing, business, and regulatory challenges associated with the development of targeted biological medicines. The goal of our study is to understand the regulatory questions associated with ATMPs, in light of their specific business models and manufacturing schemes. Three main methods – reviewed and approved by the UCL's Research Ethics Committee – have been applied in this project.

First, we have conducted a literature review comprising books, papers, reports, laws, and regulatory guidance. This is aimed to map the scientific challenges, technical alternatives, and social concerns around ATMPs, as well as scrutinise possible regulatory solutions to deal with these issues.

Second, quantitative data has been collected to capture some of the initial trends entailed by Brexit. Four sources have been used: 1. The European Union Drug Regulating Authorities Clinical Trials Database (EudraCT)[22]; 2. The Refinitiv database, with specialised financial market data[23]; 3. Data

[20] David Delaney, *The spatial, the legal and the pragmatics of world-making: nomospheric investigations* (Routledge, 2010).
[21] Luke Bennett and Antonia Layard, 'Legal geography: becoming spatial detectives' (2015) 9 *Geography Compass* 406, at 410.
[22] https://eudract.ema.europa.eu/
[23] https://www.refinitiv.com/en?utm_content=Refinitiv%20Brand%20Core-UKI-EMEA-G-EN-Exact&utm_medium=cpc&utm_source=google&utm_campaign=596234_

Table 1. Professionals interviewed.

	Interviewees		
Institution where the interviewee is based	UK	Europe*	TOTAL
Hospital	7	2	9
ATMP-related company	5	3	8
ATMP-related regulatory advice firm	5	4	9
Regulatory agency	2	1	3
Industry or GMP associations	1	1	2
TOTAL	20	11	**31**

* EU (Belgium, Ireland, and Spain) + Switzerland

published by the UK's regulator about institutions operating in the UK and licensed to import and export medicines[24]; and 4. The registers of the Royal Society of Chemistry[25] and the Royal Society of Biology,[26] with information on UK professionals accredited to act as Qualified Persons certifying and releasing batches of medicinal products. To process data and apply descriptive statistics techniques, the R programming language was used.[27]

Third, in-depth, qualitative interviews have been conducted with 31 professionals involved in ATMP development, delivery, and regulation, as summarised in Table 1.

As seen in Table 1, the majority of these 31 interviewees are based in the UK but we also spoke to key players in three EU countries, as well as Switzerland (not a EU member).

All interviews were recorded with consent from the interviewee. An informed consent form was signed, including a question where the interviewee chose how they would be identified in our publications. They could disclose their institutional affiliation or remain completely anonymous. This is why in this paper, we do not specify some interviewees' affiliation. Below, in quoting parts of interviews, we specify [within square brackets] the moment at which the interview took place, as this information can help readers to make sense of some of the issues discussed.

Interviews explored various aspects of ATMP development and delivery, including technical challenges, research collaborations, and regulatory gaps/uncertainties in current regulatory frameworks for ATMPs. All interviewees were also given the opportunity to talk about the ways in which Brexit has modified – or not – the operations of their institutions, as well as talk

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[24] https://cms.mhra.gov.uk/mhra/wda

[25] Royal Society of Chemistry, 'Register of eligible Qualified Persons' <https://www.rsc.org/careers/cpd/practising-scientists/qp-pharmaceutical/> accessed October 2022.

[26] Royal Society of Biology, 'Register of Eligible Qualified Persons' <https://www.rsb.org.uk/careers-and-cpd/registers/qualified-person> accessed October 2022.

[27] R Core Team, 'R: a Language and Environment for Statistical Computing' <https://www.R-project.org/>.

about their concerns and prospects for the political and regulatory situation emerging from Brexit.

For analysis, we worked on interview transcripts and applied codes to different parts of the conversation. The same codes were used in our quantitative analyses and the literature review, so it was possible to make different pieces of information converge in a final interpretation. The latter begins to be exposed in the next section where we describe the main features of the ATMP legal geography that existed before Brexit.

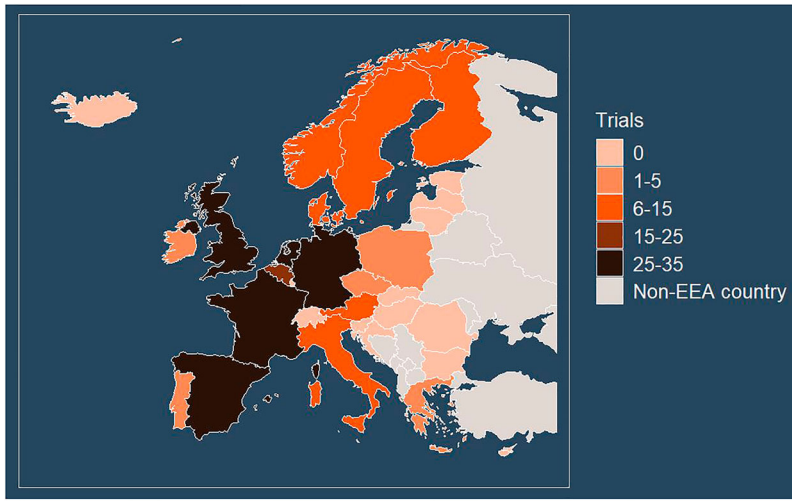
3. ATMPs in the European Union: the formation of a legal geography

According to Santos,[28] geographical space is shaped by, but is also a source of, rules, as the infrastructures and relations it holds constrain or potentialise human activities. In this sense, one can indeed identify an 'imbrication of the legal, the social and the spatial'.[29]

In the EU, the governance of biomedical technologies, including the riskiest ones, has been subject to a system formed of agencies and committees that seeks to combine political flexibility and adaptiveness with the rigidity of traditional regulations. There is then a blend of centralised and decentralised schemes, which eventually amounts to a 'networked deliberative decision making'.[30] In the ATMP domain, this resulted in a regulatory landscape with clear signs of adaptive regulation, as has been argued elsewhere.[31]

On the one hand, the European Medicines Agency (EMA), under the auspices of its ATMP Regulation (EC 1394/2007), established a centralised procedure whereby applications for marketing authorisation are submitted to the agency and, if accepted, entail access to all the national markets within the EU.[32] At least in part, this centralisation was encouraged by the industry, as this would promote the harmonisation sought by market players, in addition to creating a central point to be targeted by the lobbying initiatives described by Pirnay.[33] On the other hand, member states have kept their regulatory autonomy in critical aspects of therapy development, as is the case for clinical trials, with the

[28]Milton Santos, *The nature of space* (Duke University Press, 2021).
[29]Nicholas Blomley, *Law, space, and the geographies of power* (Guilford Press, 1994) at 63.
[30]Charles F. Sabel and Jonathan Zeitlin, 'Learning from difference: the new architecture of experimentalist governance in the EU' (2008) 14 *European Law Journal* 271, at 273.
[31]Giovanni De Grandis and Irina Brass, 'Is regulatory innovation fit for purpose? A case study of adaptive regulation for advanced biotherapeutics' (2022) *Early view Regulation & Governance* 1.
[32]Cell and Gene Therapy Catapult, 'Guidance on the development and marketing of ATMPs in the UK and EU at this position post-BREXIT' <https://ct.catapult.org.uk/sites/default/files/publication/CGT%20Catapult%20Guidance%20for%20ATMP_26.01.22_0.pdf> accessed July 2022.
[33]Jean-Paul Pirnay and others, 'Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems' (2013) 14 *Cell Tissue Bank* 525.



Map 1. CAR-T cell related clinical trials in the European Economic Area: 2011–2020.

maintenance of different systems for ethics oversight, research contracts management, certification of investigational products, and institutional arrangements in the different EU countries.[34]

For clinical trials, this decentralised regulatory and governance arrangement has enabled, for example, a geographical segmentation of research activities. This is exemplified by Map 1, elaborated with data collected in April 2021 on the EudraCT database, which registers trials conducted in the European Economic Area (that is, EU countries plus Iceland, Liechtenstein, and Norway). The Map corresponds to the period from 2011 to 2020 – the final year of the UK within the EU. It focuses on trials investigating CAR-T cell products, a kind of ATMP which derives from gene editing techniques and targets resistant cancers.

Map 1 shows the geographical segmentation of clinical trials in Europe, with a leading role being played by the UK, Spain, and others; a group of intermediate countries, including Italy and Sweden; and some emerging trial hubs, such as Poland, providing the trials industry with relatively low costs and a 'treatment-naïve' population of research participants.[35]

Therefore, in terms of clinical trials and other phases of ATMP development, a legal geography has been designed around the EMA since its creation in 1995. If the agency has amassed much expertise and centralised powers, it has also guaranteed a space within which the different national agencies can exercise influence and express regulatory creativity. As pointed out by many

[34]See, Edison Bicudo, *Pharmaceutical research, democracy and conspiracy: international clinical trials in local medical institutions* (Routledge, 2014).
[35]Adriana Petryna, *When experiments travel: clinical trials and the global search for human subjects* (Princeton University Press, 2009).

of our interviewees, the Medicines and Healthcare products Regulatory Agency (MHRA), the UK regulator for medicines and medical devices, used to be a very active player in the scope of the EMA, leading key regulatory initiatives. Interviewee 1 [a EU-based regulator / interview in November 2021], speaking of the MHRA's participation in the EMA, claimed: 'The MHRA was a big, big contributor. They were very much on the driving seat.'

The MHRA was indeed a pivotal participant in the EU's legal geography related to ATMPs. This interplay between geographic relations, social dynamics and regulatory frameworks is complex, but, as a summary, it can be described as having four main pillars. First, as an obvious consequence of the EU single market, there is the free flow of products, including that of final medicines, reagents, and starting materials. Second, the free circulation of professionals within the Union has proved most beneficial for the ATMP domain where the availability of skilled staff is rather limited, as noted by some analysts.[36] Third, the EU has elaborated original solutions to control the quality of therapies and manage risks, including the mandatory presence, at manufacturing sites, of a so-called Qualified Person, responsible for certifying medicines' attributes.[37] Finally, this ATMP legal geography has been underpinned by a robust pharmacovigilance system that includes Qualified Persons for Pharmacovigilance[38] and EudraVigilance, an electronic system for data sharing.[39]

In this therapeutic and medical domain, as in other specialised economic domains, one can identify this complex legal geography formed of hubs, specialised players, consolidated and emerging companies, and a vast landscape of regulations, guidance, and data systems. This is the construction that Brexit has come to shake, bringing about the need for new arrangements, as we analyse in the next section.

4. Brexit and the search for a new ATMP legal geography

In the approach proposed by the legal geography literature, great emphasis is given to the combined evolution of legal systems, social arrangements, and territories.[40] On the one hand, it is claimed: 'Legal provisions […] can

[36]Alexey Bersenev and Andrew Fesnak, 'Place of academic GMP facilities in modern cell therapy' in Samuel G. Katz and Peter M. Rabinovich (eds), *Cell reprogramming for immunotherapy: methods and protocols* (Humana Press, 2020); David L. DiGiusto and others, 'Proceedings of the first academic symposium on developing, qualifying and operating a cell and gene therapy manufacturing facility' (2018) 20 *Cytotherapy* 1486; Emanuela M. Iancu and Lana E. Kandalaft, 'Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting' (2020) 65 *Current Opinion in Biotechnology* 233.

[37]Emanuela Iancu and Landa Kandalaft (n 36); Pearce and others, 'Regulation of advanced therapy medicinal products in Europe and the role of academia' (n 7).

[38]*Cell and Gene Therapy Catapult* (n 32).

[39]Mark Dayan (n 4).

[40]Robyn Bartel and others, 'Legal geography: an Australian perspective' (2013) 51 *Geographical Research* 339.

move between a static moment (which might be centuries long) and relatively sudden cycles of legal change.'[41] On the other hand, there is the interest to understand how legal changes are coupled with changes in social and spatial dynamics.

In speaking of the changes provoked by Brexit in therapy production, our interviewees voiced a concern that is also present in the literature[42]: it is difficult to disentangle Brexit from other processes that happened simultaneously, especially the Covid-19 pandemic and the world economic slowdown. Nevertheless, this concern should not be too intense for social scientists who do not wish to design a model where Brexit would be an independent variable. In social sciences, every phenomenon is always looked at in its complexity, that is in its interaction with other phenomena. In this way, the pandemic and other events are not seen here as factors blurring the analysis of the 'pure effects' of Brexit but as part of the 'real world' where Brexit takes shape.

The main interpretive challenge seems to be the recency of the process examined here. As claimed by interviewee 25 [London School of Economics and Political Science / interview in July 2022], '[…] with all the delays, trade policy didn't change until the start of 2021. So we've only got one year into that new period.' Internally, the UK is still experiencing a transition period that will end in 2023, and therefore still recognising EU regulations and decisions in terms of marketing authorisations,[43] standards for quality and safety,[44] Good Manufacturing Practices for ATMPs,[45] pharmacovigilance,[46] and other matters. Therefore, with key decisions yet to be made, and key changes yet to be implemented, we can at best consider here some trends which are certainly relevant but whose confirmation is uncertain.

It is sure that some key processes are already unfolding and producing their initial effects. For example, there is much concern about a possible reduction in research funding in the UK, because of a possible lack of access to some European programmes. Nevertheless, this issue goes beyond the scope of our present analysis. Here we focus on three major, although quite subtle, changes in ATMP development and commercialisation: new requirements for importation and exportation of medicines;

[41] Bennett and Layard, 'Legal geography: becoming spatial detectives' (n. 21); at 416.
[42] Mark Dayan and others, 'Understanding the impact of Brexit on health in the UK' <https://www.nuffieldtrust.org.uk/research/understanding-the-impact-of-brexit-on-health-in-the-uk> accessed September 2022.
[43] Ankit and others, 'Transition of pharmaceutical regulations: the new regulatory era after Brexit' (n 4).
[44] Cell and Gene Therapy Catapult, 'Guidance on the development and marketing of ATMPs in the UK and EU at this position post-BREXIT' (n 32).
[45] Ibid.
[46] Sarah Hall, 'Changes in pharmacovigilance following the end of the Brexit transition' (2021) 12 *Therapeutic Advances in Drug Safety* 1.

arrangements for quality control; and legal representation for ATMP manufacturers.

4.1. ATMP trade and the new regulatory borders

Leaving the EU, the UK ceased to be part of the single market. Much of the hardships encountered during the exit negotiations had to do with the nature of the new border separating the two sides.[47] Eventually, the 'hard border' solution prevailed, ending the free flows of products seen before. This is also true for medicinal products, as pointed out by Interviewee 1 [EU regulator / interview in November 2021]: 'It's like the movement of people. The movement of medicines is also impaired now, and the movement of the active principles, the starting materials.'

It is known that in the months around the UK's official departure from the EU (January 2021), companies, including large corporations headquartered in the UK – such as AstraZeneca – and outside it – such as Novartis – were stockpiling reagents and products to cope with possible supply chain disruptions.[48] Our interviewees also talked about contingency plans being adopted, and shipment delays faced, in their institutions. Interviewee 12's case [November 2021] is particularly telling because this academic is based in the National University of Ireland Galway. For historical reasons, and under the auspices of the 1998 Good Friday Agreement, there is intense commercial activity between the UK and Ireland,[49] including flows of reagents from which this research group used to benefit. However, Brexit forced the interviewee's team to cancel some purchases from the UK, as the new border controls involved fees that proved too heavy for an academic group to bear. In the interviewee's words:

> […] at the moment, we're sourcing companies in Europe. Or the US. It's cheaper. […] I think that researchers in Ireland will take the easy way out. They have to. […] I think everywhere, including Ireland, in terms of research, we probably don't know the extent of how much we will have to move from the UK in terms of purchasing, but I suspect there will be more [moving away] […] You're a researcher. You get what you can. You get the best materials for as low cost as you can.

In addition to such disruptions, the new situation introduced the need for licences for those willing to move medicines from the EU into the UK, and the other way around. In the UK, the MHRA is the agency responsible

[47] Kenneth A. Armstrong, 'Regulatory alignment and divergence after Brexit' (2018) 25 *Journal of European Public Policy* 1099.
[48] Johannes Heusler, 'Brexit and its impact on pharmaceutical law: implications for global pharma companies' in Lars Schweizer and others (eds), *Advances in pharma business management and research*, vol 1 (Springer, 2020).
[49] Armstrong, 'Regulatory alignment and divergence after Brexit' (n 47).

for issuing these licences. Over the last year, the MHRA has witnessed an explosion in the number of licences granted, as illustrated in Chart 1.

As seen in Chart 1, importation and exportation licences, before the Brexit referendum year (2016), were mainly used by specialised distributors and pharmacies liaising with distant markets. After the referendum, distributors of medicines were the first ones to mobilise themselves for the acquisition of such licences. When the UK finally left the single market, a dramatic licence rush was triggered, with an impressive rise for distributors and an even more spectacular expansion for pharmaceutical companies (including biotech companies), which became the main acquirers of WDA licences in 2021. In the following year (2022), distributors and wholesalers appeared once again in the first position, even though the number of licences obtained by pharma/biotech companies was kept at a very high level. To be noted is also the expansion, from 2021 to 2022, in licences obtained by hospitals, trusts, and medical facilities, which have also had to expand their commercial capabilities as a result of the new legal situation.

From a regulatory point of view, ATMPs are considered as medicines, and their international trade therefore now requires these licences. To obtain them, organisations need quality systems, appropriate facilities, and qualified staff, which does not diverge from the minimum standards they have to follow anyway. The process is not very costly, implying the payment of around 4,000 British pounds for application and inspection fees. In this way, the main meaning of the change reviewed here is the introduction of a border entailing new types of costs, new bureaucratic work, and a new rationale whereby all institutions performing ATMP trade, including medical institutions, need to obtain commercial licences and engage in

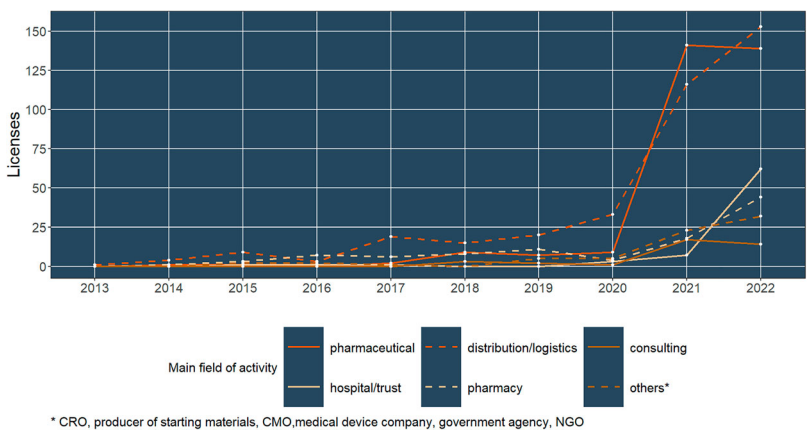


Chart 1. Holders of Wholesale Distribution Authorisations (WDA) in the UK, per type of institution: 2013–2022.

commercial relations that were previously the appanage of businesses like pharmacies and distributors.

A key effect of this new border is the slowdown in the flow of products. Because of the additional checks and border controls that are now mandatory, some organisations have faced delays that are concerning, especially for ATMPs. For example, Interviewee 15 [academic researcher based in England / interview in November 2021], explained:

> […] we have an academic [clinical] trial. We recently had to use an out-of-date antibody to manufacture a CAR-T product because we could not get a replacement from Europe in time because of this stupid thing called Brexit […] Everything went well, fortunately. The product, believe it or not, was three days out-of-date when we used it […] So ordering goods has become a complete disaster zone because of Brexit.

It is clinically and legally acceptable to approve ATMPs that fail to meet some of the required specifications, because of the particular quality attributes of these products, but also because they frequently are autologous therapies – that is, produced with starting materials collected from the patient. Therefore, in the case reported above, the researchers could carry on with manufacture without problems. However, similar delays can surely make the production of certain ATMPs completely unviable, because, as we explained before,[50] they are likely to have short, or very short, production processes and shelf lives, especially in cases where it is not possible to freeze starting materials and final medicines for transportation.

The new regulatory situation brings about, then, trade challenges that some companies may try to circumvent by establishing new units across the Brexit border. This is the approach adopted by Oxford Biomedica, a UK-based company producing viral vectors, in addition to offering ATMP-related contract manufacturing services. Considering the relevance of the EU market, and willing to understand the new regulatory situation, the company created a Brexit committee whose first decision was to install a new manufacturing unit. As explained by Interviewee 19 [Oxford Biomedica / August 2022]:

> […] we looked at the different [EU] countries, the different requirements, and we had meetings with the HPRA [Health Products Regulatory Authority] in Ireland and set up an Irish subsidiary where we have a storage industry issuing site and where we can release ATMPs for clinical trial use.

In the next years, such creation of new units, at both sides of the Brexit frontier, may be envisaged by other players. In this way, a new geography of manufacturing facilities, commercial relations, and trade licences is gradually

[50] Edison Bicudo and Irina Brass, 'Institutional and infrastructure challenges for hospitals producing advanced therapies in the UK: the concept of "point-of-care manufacturing readiness"' (2022) 17 *Regenerative Medicine* 719.

created. Besides dealing with such complex issues, organisations have to cope with the new conditions for ATMP quality control and batch certification, as analysed in the next sub-section.

4.2. ATMP control and the new certification hubs

One of the pillars of the EU's ATMP legal geography, as explained above, is the presence of so-called Qualified Persons (QPs), legally responsible for releasing medicines after certifying their attributes.[51] Furthermore, thanks to a regional agreement, products certified in a certain member state can be freely moved to another member state without having to be QP-recertified on import. This possibility has been key because QPs are highly qualified and possess specialised training and experience in manufacturing organisations, which turns them into difficult-to-find-and-hire professionals, especially for institutions with little manufacturing experience such as hospitals.[52]

Following Brexit, some agreements could be made between the EU and the UK, including the mutual recognition of GMP inspections. However, the UK was removed from the zone of QP certification, which introduced the need that the product be imported into the EU by a manufacturing authorisation holder, as well as '[…] the requirement for re-testing of the product made in the Britain on importation into the EU […].'[53] This decision taken by the EU has displeased players based in the UK, some of whom frame it as 'an EU punishment' for Brexit, as Interviewee 17 [NHS-based professional / September 2022] put it. However, the EU's decision is coherent with its guidelines, as retesting is required whenever medicines are imported into the Union from a third country – which is now the UK's status.

Some of the difficulties created by this new situation can be well illustrated by the example of Holoclar, an ATMP for treating an eye disease called limbal stem-cell deficiency. This tissue-engineered product is manufactured by Holostem, a small biotechnology company located in Italy. This therapy is being delivered in four NHS centres, being produced with stem cells collected in the UK from the patient's eyes and subsequently sent to the manufacturing site in Italy.

In order to make this ATMP available in the UK in the course of the Brexit changes, much regulatory effort was needed. This work was carried out by the pharmacists and QPs of the Newcastle Hospitals NHS Foundation Trust, an institution that has had much involvement in the development and delivery of ATMPs. The Trust obtained a variation for their Wholesale

[51] Iancu and Kandalaft, 'Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting' (n 36).
[52] Mariele Viganò, Rosaria Giordano and Lorenza Lazzari, 'Challenges of running a GMP facility for regenerative medicine in a public hospital' (2017) 12 *Regenerative Medicine* 803.
[53] Ankit and others, 'Transition of pharmaceutical regulations: the new regulatory era after Brexit' (n 4), at 805.

Dealer Authorisation, enabling them to import the product from Italy. Furthermore, in a dialogue with the MHRA, a system was agreed upon whereby the Trust's QP checks are performed remotely, based on data received from the Italian manufacturing site. This is crucial because the product has a shelf life of eighteen hours, which requires expedited procedures for processing and transportation. Some batches of Holoclar have already been manufactured but the first patient is yet to be injected with the product. It is expected that around twenty patients will be treated every year in the UK.

Interviewee 17 [NHS-based professional / September 2022], commenting on the Holoclar case, declared: 'I think that's a perfect example of what NHS Trusts can do when they have the requisite expertise in-house.' However, it is important to explain that few NHS hospitals and Trusts, as well as few companies, rely on the presence of four QPs like the Newcastle Trust. In the UK landscape, a robust QP team is rather the privilege of a handful of organisations, as illustrated in Table 2, prepared with information from the registers of the Royal Society of Chemistry[54] and the Royal Society of Biology.[55]

Table 2 brings only information related to institutions with some experience with ATMPs, and only organisations with more than one QP. It shows that organisations with two or more QPs are generally large multinational companies such as AstraZeneca, Pfizer, and Novartis. It can also be seen that most QPs have either received their accreditation or renewed their QP training in recent years. The limitation of Table 2 is the lack of information from the Royal Pharmaceutical Society, which also accredits QPs but does not publish their register, which explains, for example, the absence of the Newcastle Trust.

Therefore, the Holoclar case was possible because of this Trust's uncommon regulatory expertise, as well as a key circumstance: contrary to the EU – which now requires QP recertification for medicines imported from the UK – the UK still permits medicines to be imported from the EU without recertification, requiring only some basic QP checks. In 2023, when the Brexit transition period ends, this situation may also change, which would constitute an upheaval for ATMP development and delivery in the UK, because, as explained by Pearce and colleagues[56]: 'The need for QP release of each batch when a single batch treats a single patient is prohibitively expensive and may even be logistically impossible in some cases.' According to Interviewee 19 [Oxford Biomedica / August 2022], the final UK's decision may be distorted by strategic miscalculations:

[54]Royal Society of Chemistry, 'Register of eligible Qualified Persons' (n 25).
[55]Royal Society of Biology, 'Register of Eligible Qualified Persons' (n 26).
[56]Pearce and others, 'Regulation of advanced therapy medicinal products in Europe and the role of academia' (n 7), at 295.

Table 2. ATMP-related organisations with at least 2 QPs registered by either the Royal Society of Chemistry or the Royal Society of Biology: 2022.

Organisation	Type *	QPs	London	England (minus London)	Scotland	Earliest accreditation	Latest renewal
Astra Zeneca	pharma	**13**	0	13	0	1992	2021
GlaxoSmithKline	pharma	**11**	2	8	1	1987	2021
Pfizer	pharma	**4**	0	4	0	1999	2021
Accord Healthcare	pharma	**3**	2	1	0	2013	2021
Catalent Pharma Solutions	CMO	**3**	0	3	0	1997	2018
Eisai Manufacturing	pharma	**3**	0	3	0	1992	2021
Merck Sharp & Dohme	pharma	**3**	0	3	0	2013	2018
Novartis	pharma	**3**	0	2	1	2011	2019
Sanofi	pharma	**3**	0	3	0	1992	2014
Actavis	pharma	**2**	0	2	0	2016	2018
Fisher Clinical Services UK	consulting	**2**	0	2	0	2013	2020
Lonza	CMO	**2**	0	1	1	2001	2018
TOTAL		**52**	4	45	3	1984	2021

* 'Pharma' includes pharmaceutical companies, biotech companies, and producers of starting materials

> […] there seems to be a belief that if the UK mirrors the EU agreement and says 'Retesting has to happen,' it will encourage a lot more manufacturers to come into the UK […], but I think that people aren't thinking about how small the UK market is and how much that would cost.

Furthermore, QP recertification involves tests that destroy part of the medicine, a procedure that is frequently unviable for fragile ATMPs of very small quantities. Interviewee 5 [September 2022] is based in the Advanced Therapy Treatment Centres network, formed of public and private organisations aiming to bring ATMPs to patients. According to this professional, the practical arrangements for a possible retesting of ATMPs in the UK are far from being clear:

> […] you need to have the facilities here to do the additional testing and that's got to be up to obviously certain standards. So how do you make sure that's standardised etc? Or where would it be? Would it be in a hospital? Or would it have to go to a lab that was set up by the manufacturer?

Hence the concern voiced by Interviewee 19 [Oxford Biomedica / August 2022], considering the possibility that the UK, like the EU, would require QP recertification on import:

> […] you're […] going to get people coming out of the UK. If the UK decides to reciprocate that agreement, then that will […] restrict advanced therapies being available for UK citizens […] I know pharmaceutical companies that are already making that decision.

The processes analysed here have to do with the management of risks that may derive from ATMP use, but also with the future configuration of the relations between the EU and the UK, including marketing relations. The following section focuses on these marketing relations by highlighting the formation of new markets for regulatory services and legal representation.

4.3. ATMP ownership and the new legal networks

In the legal geography that is emerging from Brexit, market players will be crucial. Indeed, analysts have long pointed out the relevance of so-called *lex mercatoria*,[57] understood as '[…] an international legal space in which different types of economic agents operate, whose behaviour is regulated by new international rules and contractual relations […]'.[58] In the case of Brexit and ATMPs, these arrangements can derive from a mandatory redistribution of liabilities and legal representatives.

[57]Philippe Kahn, 'Droit international économique, droit du développement, "lex mercatoria": concept unique ou pluralisme des ordres juridiques?' in Philippe Fouchard (ed), *Le droit des relations économiques internationales* (Litec, 1982); Boaventura de Sousa Santos, 'Law, a map of misreading: toward a postmodern conception of law' (1987) 14 *Journal of Law and Society* 279.

[58]Sousa Santos, 'Law, a map of misreading: toward a postmodern conception of law' (n 57), at 287.

As the UK has become a third country in relation to the EU, roles and functions need to be relocated and sometimes created from scratch. For example, the UK regulator allows the QP for pharmacovigilance (QPPV) to reside either in the UK or anywhere in the EU/EEA. However: 'Where the QPPV does not reside and operate in the UK a national contact person for pharmacovigilance who does resides and operates in the UK is required'.[59] Another example pertains to clinical trials. The EU requires that the study's legal representative be located within the Union, which has made trial sponsors submit substantial amendments to competent authorities, in order to move this legal representation from the UK to the EU.

Furthermore, the new situation changes regulatory and legal networks in two substantial ways. On the hand, companies developing ATMPs outside the UK, and willing to explore the UK market, are now in need of more legal advice. This point was made by Interviewee 21 [European QP Association / October 2022]:

> I'm pretty sure Brexit has been […] beneficial for consultants in the pharmaceutical regulatory arena […] Larger organisations probably, you know, would have had the expertise on-board anyway […] I mean, the GSKs and the AtraZenecas, they usually have large regulatory departments […] Smaller companies wouldn't necessarily have the in-house expertise, so would have had to seek it elsewhere. And pay for it, usually.

On the list of regulatory services sought by companies, there is advice from professionals accredited as Qualified Persons (QPs). As explained above, it is only in large companies that QPs are found in large numbers. In this way, whenever a medium-sized company needs to implement a new procedure or manufacturing system across the Brexit border, it may need to hire a so-called Contract QP to navigate the new regulatory environment. A survey conducted by the European QP Association[60] showed that Contract QPs are used in several EU countries, being officially recognised by regulators in Czech Republic, Belgium, Denmark, Austria, and Netherlands, as well by the UK regulator. We are dealing with a small-scale service, with this report showing that the vast majority of Contract QPs are hired by only one company at a time.

As far as we could investigate, there is no study showing the number of QPs in either the EU or the UK, as a central register has not been created. In our analysis of the QP registers published by the UK's Royal Society of Chemistry[61] and the Royal Society of Biology[62] (see above), which does not include the (unpublished) register of the Royal Pharmaceutical Society,

[59]Cell and Gene Therapy Catapult, 'Guidance on the development and marketing of ATMPs in the UK and EU at this position post-BREXIT' (n 32), at 9.
[60]European QP Association, *The role of the contracted Qualified Person in Europe* (EQPA Surveys, 2022).
[61]Royal Society of Chemistry, 'Register of eligible Qualified Persons' (n 25).
[62]Royal Society of Biology, 'Register of Eligible Qualified Persons' (n 26).

Table 3. Some companies offering QP services in the four UK Nations: 2022.

Nation	Contract QP firms		Creation of the oldest firm	Creation of the youngest firm
	TOTAL	Firms with ATMP experience		
England	23	4	1979	2017
Scotland	4	2	2010	2020
Wales	1	1	1997	1997
Northern Ireland	1	0	2012	2012
TOTAL	**29**	**7**	**1979**	**2020**

we identified 29 firms offering Contract QP services. By supplementing this analysis with information collected on the websites of these QP firms, we prepared Table 3.

Table 3 shows that most QPs have not had experience with ATMPs. Therefore, this small-scale market is nevertheless likely to hold substantial flows of payments, insofar as QPs are scarce professionals with high specialisation, especially in ATMPs.

On the other hand, the ATMP legal networks are changing as a result of new needs for legal representation. EU and UK companies that develop, test, and commercialise ATMPs and have no physical presence at the other side of the Brexit frontier may need to establish a legal entity for some of their operations. This is needed, for example, for conducting clinical trials or holding marketing authorisations in the targeted jurisdiction.

With Brexit, the legal link between the EU and the UK has been broken. As a consequence, there is, once again, a growing need for services offered by legal advisors and representatives. One of such actors is Asphalion, a scientific and regulatory consultancy company with headquarters in Spain, and units in Germany and the UK. Considering the changes caused by Brexit, the company decided to create a new service for pharmacovigilance representation, as EU-based companies are now required to have a pharmacovigilance representative physically present in the UK. In addition, the company can help clients with their UK license authorisations, as explained by Interviewee 3 [Asphalion / September 2022]:

> […] what we do is we are the holders of medicines for clients in transition periods, because they're Swiss or whatever they may be. So we can be a licence holder in the UK, because we're a UK-based company, even though we don't manufacture anything. This is just an outsourced service, from a third company.

When the UK's MHRA ceases to recognise new marketing authorisations granted by the EMA, which may happen in 2023, this kind of service is likely to become even more strategic and looked for.

Therefore, the emerging ATMP legal geography leads to reconfigurations pertaining to the ways in which responsibilities are distributed and ownership managed. Currently, this process has made it possible to broaden market opportunities, with the potential increase in legal inequalities that tend to emerge when legal representation is traded on markets.[63] In gradual and subtle ways, 'liability rules' and 'negligence rules', which tended to dominate the medicines field, subside to the benefit of what Cooter called 'markets for rights.'[64] All these changes affect the role that can be played by the EU in the global scenario, and even more drastically the UK's role.

5. Discussion: the international meaning of Brexit

A drastic change such as Brexit always entails the mobilisation of different economic sectors. It is known, for example, that before the Brexit referendum, some key economic domains, such as finance, favoured full regulatory alignment with the EU if Brexit would actually take place.[65] The pharmaceutical and ATMP sector also exemplified this stance. Interviewee 21 [October 2022], now based in the European QP Association, recalls that moment:

> […] the big associations like ABPI [Association of the British Pharmaceutical Industry] and EFPIA [European Federation of Pharmaceutical Industries and Associations], representing the large pharmaceutical companies, they would … they were […] not in favour of Brexit, because […] potentially, there would be a barrier, a trade barrier of some sort, put in place where previously there was none. So that could never be in their interests.

Even though Brexit has not represented a complete upheaval for pharmaceutical and ATMP development and production, the changes reviewed in this paper are not negligible, especially for middle-sized companies. Moreover, the UK may have its position altered in the global medicines scenario.

Interviewee 20 [October 2022], who is based in a Contract QP firm in the UK, declared:

> What a lot of companies are doing is actually splitting their sites […] The GB/UK market is a big enough market to have a production here, and then they just have the production in the EU as well.

This interviewee considered a second possibility:

[63]Shai Agmon, 'Undercutting justice: why legal representation should not be allocated by the market' (2021) 20 *Politics, Philosophy & Economics* 99.
[64]Robert D. Cooter, 'Economic theories of legal liability' (1991) 5 *Journal of Economic Perspectives* 11, at 21.
[65]James and Quaglia, 'Rule maker or rule taker? Brexit, finance and UK regulatory autonomy' (n 5).

> What could happen, what I see as a potential, is anybody that thinks about it could move their supply from the UK to the EU and not have the presence in the UK.

Yet another possibility can be taken into account if one considers the evolution displayed in Chart 2, elaborated with data collected in June 2023 from the Refinitiv database.

Chart 2 focuses on mergers and acquisition (M&As) for companies involved in therapy production at large (not only production of ATMPs). It contains only deals where the UK participates as either acquirer or target, and, at the same time, an EU member state appears as either acquirer or target.

In the first years of the twenty-first century, M&As were spurred by the global financial upward movement, which could be particularly felt in the UK with its dynamic financial hub. When the bubble eventually burst, in 2008, these operations were taken to a lower, more reasonable level.

The chart shows that, from 2009 through 2017, EU-based companies always acquired less than forty UK companies. Thereafter, there was a remarkable expansion in the pace with which EU companies have acquired UK companies, with numbers crossing the threshold of forty deals after the Brexit referendum, in 2018, 2020, 2021, and 2022. In 2018, for the first time since 2008, the number of UK companies acquired by EU players (48) was bigger than that of EU companies acquired by UK players (45). In 2021 and 2022, there were again more acquisitions by the EU than acquisitions by the UK – a trend that can be difficult to reverse and could in the long term suggest a denationalisation of the UK medicines production system.

M&As are important because as shown throughout this paper, companies have now incentives for installing units across the new border designed by Brexit. EU companies interested in the UK market, and the other way around, may prefer to acquire existing companies, with their consolidated infrastructure and expertise, instead of building up a completely new unit at the other side of the border. Indeed, M&As have historically been used by pharmaceutical and biotech companies willing to explore new national markets.[66]

In spite of being a relatively small market, the UK continues to be strategic due to its expertise in clinical trials,[67] its rich innovation landscape for life sciences,[68] and its national health system of considerable purchasing power. All this can attract the interest of potential EU-based buyers,

[66]Liam Keenan, Timothy Monteath and Dariusz Wojcik, 'Patents over patients? Exploring the variegated financialization of the pharmaceuticals industry through mergers and acquisitions' (2022) *Online first Competition & Change* 1.

[67]Bicudo, *Pharmaceutical research, democracy and conspiracy: international clinical trials in local medical institutions* (n 34).

[68]Office for Life Sciences, *Life sciences industrial strategy update*, 2020.

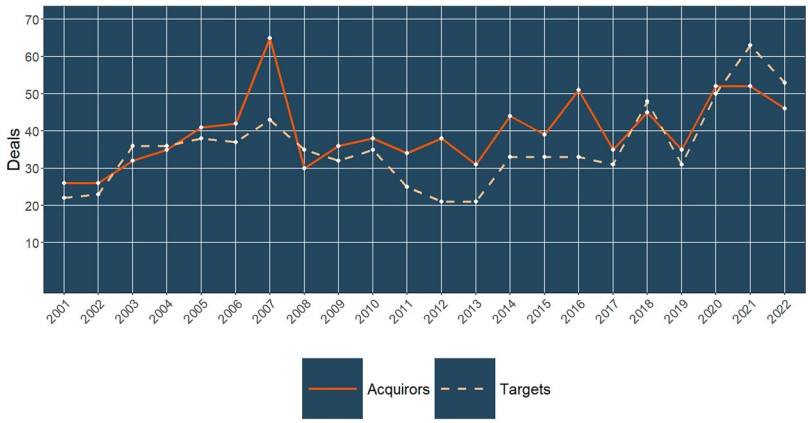


Chart 2. Mergers and acquisitions involving UK-based and EU-based pharma and biotech companies: 2001–2022.

generating predatory acquisitions. Ironically, then, the separation from the EU, which was based on a 'taking-back-control' rationale, may eventually signify a new wave of globalisation and 'Europeanisation' for the UK's ATMP landscape, with the possible disappearance of promising UK start-ups and middle-sized companies whose infrastructure and skills may be captured by players from the EU.

By invoking a legal geography approach for the appreciation of these processes, we have tried to highlight here the formation of a new legal configuration resulting from Brexit. As Massey[69] pointed out, a spatial analysis requires not only the consideration of forms and locations but also an attention to processes and relations. In terms of forms, there is an ongoing development of technologies and products whose proper distribution has been re-examined by different organisations. In terms of processes and relations, new modes of international partnerships will be generated as old modes become redundant or impracticable. Finally, the political debates around Brexit cannot be closed for good, especially because companies' and organisations' concerns will continue to be voiced, and some will possibly be reflected in new legal provisions. For we are not simply dealing with a geography but with a legal geography. In this way, the analysis of a drastic change like Brexit reveals that such events have political, technical, and institutional dimensions whose configuration impacts on the ways in which new technologies and science-intensive products can be developed, refined, and distributed.

[69]Doreen Massey, *For space* (Sage, 2005).

6. Conclusion

According to Roscoe and colleagues[70]: 'Studying Brexit permits an examination of a significant geopolitical event in real-time […].' This paper has endeavoured to analyse this ongoing geopolitical reconfiguration from the viewpoint of Advanced Therapy Medicinal Products (ATMPs). The latter are cutting edge therapies deriving from cell manipulation, gene editing, tissue engineering, or a combination of these techniques.

We have argued that the pre-Brexit context represented a regional legal arrangement, based on four agreements: the free flow of products within the single market; the circulation of professionals, who are particularly needed in fields of high specialisation; a regional system for risk management based on the certification of medicinal batches by Qualified Persons (QPs); and a regional pharmacovigilance system involving constant data-sharing. This is the legal geography that Brexit has come to disturb.

We have analysed this change by highlighting three main issues. First, our analysis focused on the additional burdens that Brexit has brought about to the flows of reagents and final medicines, with companies and researchers facing delays and additional bureaucratic work. This can potentially provoke a relocation of research activities and manufacturing units. Second, we focused on the UK's separation from the EU's system of QP certification aimed to manage clinical risks. On the EU side, this introduced new costs for organisations importing medicines from the UK into the EU, while the UK has been postponing the decision as to whether recertification of medicines from the EU will also become mandatory. Thirdly, we demonstrated how the new situation creates legal voids which can be filled by new regulatory services and products, making the ATMP landscape become increasingly marked by a commercial management of legal functions.

Currently, Brexit has created many uncertainties or, as Heusler[71] put it: '[…] there are still many open questions for the industry as well as for the regulators.' In this regard, the phenomena reviewed here have some similarities with issues detected in studies on other technology-intensive domains. In the software field, it has been noted that Brexit has been particularly challenging for companies with intense networks in Europe,[72] which reflects the difficulties of ATMP-related companies in maintaining their strategic access to the EU market. In the car industry, there is a major reliance on the operations of international players that comply with international

[70]Samuel Roscoe and others, 'Managing supply chain uncertainty arising from geopolitical disruptions: evidence from the pharmaceutical industry and Brexit' (2020) 40 *International Journal of Operations & Production Management* 1499 at 1500.

[71]Heusler, 'Brexit and its impact on pharmaceutical law: implications for global pharma companies' (n 48).

[72]Lon L. Fuller, *The morality of law* (Yale University Press, 1964).

standards, making the Brexit-related discourse about regulatory freedom sound as an illusion.[73] Equally, it has been claimed here that the ATMP domain is to a great extent dominated by multinational players and fostered by international collaborations, hence the current need for much help from international consulting firms able to quickly understand and navigate the new regulatory situation. The ATMP domain also reproduces the dilemmas of the biotechnology domain, in which, according to Mackey and Annaloro,[74] different regulatory solutions have been considered since the Brexit referendum but none of them seem as favourable for technology advancement as the situation that prevailed before the UK's exit from the EU. Therefore, possible disinvestments and missed opportunities for scientific collaboration are not an appanage of ATMPs at this moment. Other questions, such as the possible reduction of research funding for UK players, have also to be considered but go beyond the scope of this paper.

These hardships are compounded by the new situation faced by regulatory agencies. The European regulator (EMA) now lacks the close and fruitful collaboration with the UK regulator (MHRA) it used to enjoy. In its turn, the UK has been postponing key decisions, a stance that marked the country's participation in the Brexit negotiation after the referendum. The country has also failed to participate in important regulatory advances made on the EU side, such as the 2021 publication of a new directive for clinical trials.[75]

In this way, the new ATMP legal geography is beginning to display some of its features – some of which have been analysed here – but is taking time to acquire a clear configuration. Its emerging delineation reveals how technology- and science-intensive domains react in the face of a massive legal and political change. Political, technical, and institutional redefinitions necessarily ensue, redefining the legal geography and remodelling the possibilities of technology development, technology deployment, and business strategies.

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[73]Humphreys and Munro, *Brexit and the car industry* (n 2).
[74]Mackey and Annaloro, '"Bioexit": navigating the policy and regulatory pathways for the biotechnology industry in a post-Brexit landscape' (n 1).
[75]https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-directive-200120ec_en

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