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'Bioexit': navigating the policy and regulatory pathways for the biotechnology industry in a post-Brexit landscape

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The withdrawal of the UK from the European Union (EU) is a complicated event. Although implications vary by industry, the biotechnology sector is especially vulnerable to the consequences of Brexit. Accordingly, here we evaluate potential repercussions under four post-Brexit political pathways: European Economic Area (EEA) affiliation (Norwegian Model); negotiated bilateral access (Swiss Model); limited participation in EU Customs Union (Turkish Model); or independence under the World Trade Organization (WTO) designation. We conclude that all four pathways fail to protect the mutually beneficial UK–EU biotechnology relationship and that alternative pathways need to be explored. Accordingly, we outline a suite of policy mechanisms aimed at ensuring continued EU–UK regulatory synergy, with the central aim of ensuring access to biomedical innovations and ensuring patient safety.

Introduction

On June 23, 2016, the UK voted to leave the EU. The EU Membership Referendum of the UK, popularly dubbed 'Brexit,' was an unprecedented political event, and, in December 2017, it progressed to its second phase of negotiations. Although long-term implications of Brexit remain unknown, upcoming 'divorce' negotiations and a transition period leading to a 'hard' or 'soft' EU exit, will substantively transform UK commerce. Once finalized, the unraveling of harmonized policies and loss of vital trade channels will have a lasting impact on technology-driven and highly regulated sectors, such as the biotechnology industry.

Supporting nearly 500 000 jobs and generating more than £30 billion in 2015, the biotechnology and life sciences industry is a significant source of economic strength for the UK [1]. Supported as a key sector in the master plan of the EU, initiatives such as the Horizon 2020 program of the European Commission also aim to accelerate life sciences discovery by investing billions in EU research activities [2]. The UK was originally projected to capture a quarter of the €75 billion investment made by Horizon 2020 and also currently accesses funds from the European Investment Bank and European Investment Fund, but these capital flows are now in jeopardy [1,3].

The relationship of the UK with the EU is also mutually beneficial from a regulatory standpoint, because the Medicines & Healthcare products Regulatory Agency (MHRA) of the UK supports several European Medicines Agency (EMA) initiatives. MHRA–EMA regulatory collaboration includes vital biomedical functions, such as joint drug manufacturing, clinical trial/manufacturing site inspections, and facilitating drug approvals [4,5]. By harmonizing regulatory standards, the MHRA alleviates bottlenecks in the drug approval pipeline of the EU, also by administering clinical trials on behalf of EMA. This synergistic relationship helped shape EU enactment of patient-centric legislation and

expedite access to new medicines throughout Europe. However, this relationship will undergo major changes post Brexit, highlighted by the announcement by the EMA that it is moving its London-based headquarters to Amsterdam (at an estimated cost of €400 million) [6].

Accordingly, it is imperative to assess how post-Brexit policy pathways could impact the biotechnology industry in the UK. In response, here we examine four post-Brexit political options and highlight the need to explore alternative approaches, with a focus on ensuring continued investment in biomedical research and development, while also safeguarding patients' access to medicines.

Four pathways, few solutions

With more than a 72% voter turnout, the 2016 Brexit referendum received more than 30 million votes across the four constituent nations of the UK. Of those voters, 52% voted in favor of leaving the EU, triggering the first phase of a process that will force the UK to redefine its national and economic identity, while also disentangling four decades of EU integration [7]. In March 2017, Prime Minister Theresa May formally initiated the 2-year process of lawfully withdrawing from the EU by triggering Article 50 of the Lisbon Treaty. In December, the UK and EU reached an agreement on advancing to a second phase of negotiations that will lead to a transition period set to begin after exit of the UK in March 2019 and tentatively ending in December 2020. Over the course of subsequent dissolution negotiations, the UK will continue to have access to the single market, but must concomitantly negotiate the terms of its exit and explore a future trade framework with the EU.

The four most likely post-Brexit policy pathways based on current trade and legal arrangements are: (1) EEA affiliation (modeled after Norway); (2) negotiated access (modeled after Switzerland); (3) participation in the Customs Union (Turkish Model); or (4) complete severance from the EU under the WTO model.

Norwegian model

The Norwegian model is the least disruptive or 'softest' form of Brexit, because it would offer continued access to the EU single market, while exempting British exports from costly tariffs imposed on non-members. Additionally, Norway maintains its own medicines agency and controls how it reimburses and sets prices for pharmaceuticals, a model potentially compatible with the MHRA and National Health Service (NHS) [1].

Yet, under this system, Britain would not evade contentious EU governance policies or

mitigate the obligatory financial commitment accompanying access to the single market [7]. For UK policymakers, the biggest objection might be the continuing responsibility to abide by the 'four freedoms' of the EU, given that the inability to secure national borders was originally a strong political motivation behind Brexit.

Home to an array of European regulatory entities, the UK was especially persuasive in shaping EU governance. However, under the Norwegian arrangement, Britain would lose its ability to influence EU policy, because European countries party to the European Free Trade Association (EFTA) that have 'purchased' EEA access are not permitted to participate or vote on EU parliamentary matters. Without the capacity to ensure EU rules are applied favorably, the UK could face increasing EU regulatory and trade-related barriers expressed as an attempt to dissuade other nations from executing similar 'leave' referendums. Moreover, the Norwegian model will not prevent regulatory exodus, because EU policy mandates agencies reside within member nations, evidenced by the upcoming relocation of EMA [6].

In addition to the financial costs associated with 'purchasing' access to the single market, the Norwegian model requires added administrative safeguards. To sustain the integrity of the Customs Union and prevent backdoor entries, the EU requires EFTA nations to implement strict control mechanisms to verify the origin of goods and levy necessary tariffs on items entering the union. The added controls will introduce new cost burdens, while possibly delaying the movement of goods, services, and medicines across UK borders.

Overall, when factoring costs, the continuing obligation to uphold EU policies, exclusion from third-party trade agreements and loss of regulatory and political influence, the Norwegian model is inferior to the current arrangement of the UK and fails to provide advantageous economic, regulatory, or trade options.

Swiss model

Alternatively, the UK could attempt to emulate the arrangement of Switzerland with the EU. Fundamentally, the 'Swiss model' is a variation of the Norwegian model and subject to the same inherent disadvantages [7]. However, unlike the Norwegian model, this relationship with the EU (Switzerland is not an EEA member) is limited to a series of bilateral trade agreements, thus limiting EU governing authority to only certain negotiated sectors [8].

Nevertheless, the contractual responsibility of Switzerland to accept the 'four freedoms' of the

EU has resulted in frustration. In 2014, Swiss voters approved a referendum to curb immigration that directly conflicts with EU obligations [2]. In response, the EU retaliated by restricting the access of Switzerland to Horizon 2020 funding and threatened to terminate all bilateral agreements [1,2]. Revoking access to European investment capital represents a significant economic disincentive and should be viewed as a cautionary tale by UK negotiators tasked with navigating Brexit. Today, tensions between the EU and Switzerland remain, especially given the challenges of managing the benefits, consequences, and costs of a complex trading relationship that spans more than 120 bilateral agreements.

Given the inherent complexities of the Swiss relationship, the EU might not afford Britain the same opportunity; especially given that this process will likely require independent negotiations with separate industrial sectors, leading to potential policy divergence that could impact the overall integrity of the EU single market. Regardless, because the Swiss option is similar to the Norwegian model, electing to negotiate hundreds of bilateral agreements in lieu of a more comprehensive and integrative approach is likely disadvantageous, given that this pathway fails to provide any material benefits over the Norwegian option.

Turkish model

Turkey negotiated a trade relationship with the EU that exempts Turkey from implementing mandatory controls to verify the origin of goods. As a non-EU member state, Turkey aimed to reduce the cost of traditional EU commerce, without securing tariff-free trade. Thus, Turkey elected a relationship that gives it access to the Customs Union only.

Turkey is the only nation with this particular arrangement and it would be unlikely that the UK would consider this pathway. To alleviate EU concerns that Turkey could become a backdoor into the market, Turkey agreed to limit its freedom to negotiate third-party trade agreements outside the EU. Given the importance and international position of the economy of the UK, implementing restrictive national trade policies while simultaneously losing all benefits accompanying EU membership, would subject the UK to a multitude of restrictive measures and few, if any, distinct trade advantages.

WTO model

The UK might also opt to terminate all existing relationships with the EU, by defaulting to the multilateral trade framework currently operated

under the WTO, also known as the ‘hard’ or ‘no agreement’ exit. This would allow evasion of EU policy mandates, financial obligations, and third-party trade restrictions. With political independence, the UK could establish advantageous research and development (R&D) tax policies and freely negotiate other bilateral trade agreements. By contrast, independence excludes the UK from any and all EU intra-member benefits. Hence, re-establishing important trade relationships with the EU post Brexit, could become an expensive and time-consuming proposition.

The price of rebuilding EU trade channels should not be understated. Although tariffs vary depending on product, an estimated 90% of UK exports would be subject to added duties [9]. Furthermore, because the EU is the largest trading partner of the UK, the added transactional and administrative costs could tally in the billions [9]. Accordingly, industries such as biotechnology that elect to remain in Britain and import goods from the EU post Brexit, will likely not be part of the EU VAT area, leading to higher compliance costs (e.g., pending Brexit-related bills would require certain UK firms to pay VAT upfront, although the implications are unclear for the biotechnology industry) [10]. For UK patients, this could lead to increased prices for medicines, impacting affordability and access.

In addition to Brexit barring British patients from participating in EMA clinical trials, the WTO pathway is potentially damaging to patients throughout the EU, because the union could refuse to accept the efficacy, quality, or safety standards of MHRA post Brexit [1,5]. The possibility of regulatory discrepancies could introduce new customs and trade barriers, leading to delays and requiring secondary validations, further obstructing access to medicines and possibly introducing the potential for increased costs and drug shortages across Europe [4,6].

Lastly, under the WTO option, UK-based industries currently benefiting from EU investment capital will directly experience financial repercussions, because third-party nations are excluded from EU initiatives. For Britain, the termination of Horizon 2020 funding represents a projected loss of £8 billion over the next 4 years [7]. For capital-intensive UK biomedical companies, these economic implications are cause for serious concern.

Alternative pathways

Today, UK policymakers find themselves in a difficult position, because retaining an EU affiliation under a ‘soft’ Brexit will expose the UK to new disadvantages, whereas electing for complete

independence via a ‘hard’ Brexit ends vital trade, legal, and regulatory relationships. In fact, these disadvantages are already beginning to surface, because the EU recently adopted new draft Brexit negotiating guidelines that will apply during the transition period requiring the UK to adhere to any current and new EU law while also being excluded from EU institutions and decision-making. Complicating the Brexit process further, a recent amendment to the Brexit bill allows British MPs to have a ‘meaningful vote’, effectively requiring parliamentary approval before the Brexit deal is finalized.

Regardless of the pathway chosen, the biotechnology industry is bracing itself for both short-term (e.g., transferring an estimated 2400 medicine market authorizations held by UK-based firms and retaining EMA staff during relocation) and long-term challenges (e.g., decoupling of cross-EU drug supply chains and pharmacovigilance activities, and implementation of the EU Falsified Medicines Directive [6].) In fact, many firms are preparing for the possibility of a ‘no agreement’ Brexit by duplicating processes to secure medicines approval under European standards [6]. Subject to this uncertainty, it is possible that Brexit could instigate an exodus of UK-based life science firms (what we term a ‘bioexit’) to other EU member states [2].

In an attempt to alleviate anxieties and dissuade attrition, in November 2016, May promised to invest an additional £2 billion in R&D by 2020 [11]. In her speech, May emphasized the commitment of the UK Government to ensuring that post-Brexit Britain remains at the forefront of science and technology. In July 2017, Jeremy Hunt and Greg Clark (Secretaries of State for Health and Business, respectively) penned a letter in *The Financial Times* stating their desire for continued cooperation with the EU on public health and safety, including ensuring access to medicines, and signaling priorities for a new UK regulatory system closely partnering with EMA [5].

Further signaling Government commitment, the August 2017 Life Sciences Industrial Strategy of the UK outlined an ambitious plan to increase UK science funding and/or investment and clinical trial capacity, accelerate access to medicines, establish greater cooperation between industry and the NHS, and incentivize the creation of four UK biotech companies with a market capitalization of £20 billion over the next decade [12]. Importantly, the report also calls for continued MHRA–EMA cooperation and stops short of advocating for a ‘wholly free-standing [regulatory] system’ clearly emphasizing the need for continued EU partnership [12]. Recent announcements of a ‘sector deal’ involving UK

biotechnology investments further bolsters the approach of the UK of providing domestic incentives to offset projected post-Brexit losses, but are largely dependent on the health of the UK economy post Brexit. This includes the impact of Brexit on the global financial sector in the UK, which provides crucial capital and investment for biotechnology firms.

Despite these efforts, clear policy solutions to mitigate the negative impact of Brexit on the biotechnology sector for both the UK and EU have not adequately materialized in current negotiations. For example, the Joint Report of negotiators for phase 1 of Brexit focuses on protecting the rights of UK and Union citizens (including healthcare access), addressing Northern Ireland, and establishing the financial settlement of the exit. Although these are critical macro issues, there is also a need for negotiators to proactively identify vulnerable sectors in need of prioritization in phase 2 negotiations. Hence, there is a clear opportunity for providing ‘clarity’ on what the future framework of a UK–EU biotechnology relationship should look like to inform targeted negotiations moving forward.

Ideally, a ‘fifth pathway’ that would best avoid a biotechnology decoupling would need to prioritize the following areas: (i) allowing mutual recognition of UK–EU regulatory approvals; (ii) establishing free movement options and visa pathways for retaining access to biotech talent of non-UK nationals; and (iii) enacting temporary, industry-specific exemptions to the Brexit process that are focused on ensuring patient safety and access to biomedical innovations. The policy instruments to maintain these linkages will also have to be comprehensive and diverse, including: (a) establishing Mutual Recognition Agreements between the UK and EU countries; (b) establishing transitional agreements or possible temporary exemption of biotechnology and/or life sciences industries from the Brexit Withdrawal Agreement; (c) exploring UK ‘associated country’ status with EU research funding programs; (d) further extending the Brexit transition and implementation period for the biotechnology sector; (e) enacting national legislation that is compatible with EU law that also implements policy solutions for key related biotechnology concerns (e.g., mobility and/or immigration of life science professionals); and (f) renegotiation of UK membership in existing EU Free Trade Agreements and ultimate negotiation of a UK–EU bilateral trade or economic partnership agreement specific to biotechnology to ensure elimination of tariffs, nontariff barriers, and customs controls (versus a bespoke deal that covers all economic sectors) [1,4].

Crucially, this collection of policy interventions would need to be in place before the exit in March 2019 to ensure regulatory continuity and avoid disruptions that could impact patients.

Designing a fifth pathway that introduces sector-specific exemptions is possible, because both Switzerland and Norway negotiated exclusions in their respective trade relationships with the EU. Switzerland maintains its own regulatory body for science and medicine (Swissmedic), and EMA acknowledges the safety standards of the country, thus allowing the importation of medications into the EU without requiring burdensome secondary validations. Likewise, when Norway joined the EEA, it negotiated specific exclusions exempting certain industries from EU amalgamation [1].

Considering this past precedence, the start of phase 2 negotiations marks a critical opportunity for policymakers and negotiators to specifically prioritize the biotechnology sector in a post-Brexit framework. As the time to renegotiate this robust and synergistic relationship runs

short, exploring alternative pathways will be critical to the future of biotechnology in the UK, EU, and beyond.

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