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ARTICLE

Challenges to sovereign ambitions: forces of convergence and divergence within the global pharmaceutical sector and the UK's withdrawal from the European Union

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Abstract
This paper maps key regulatory, governance and legal challenges associated with the UK's withdrawal from the European Union (EU) in terms of convergent and divergent pressures within the global pharmaceutical sector. These include (i) convergent *regulatory* pressures associated with the European framework for pre-market licensing; (ii) convergent and divergent *industry* pressures with regard to drug discovery and manufacturing; and (iii) divergent and convergent *market* pressures associated with the supply, pricing and assessment of medicines. The UK's sovereign ambitions risk a loss of influence over the licensing and surveillance of pharmaceuticals under convergent regulatory and industry pressures to engage in unilateral participation in the European regime. Further, they also risk a loss of influence over processes for pricing and assessing the effectiveness of new treatment regimens under divergent market pressures from larger pharmaceutical markets outside the EU, notably the United States.

Keywords: Brexit; governance; pharmaceuticals; regulation; sovereignty

1. Introduction

On 31 January 2020, the UK exited the European Union (EU) under the UK-EU Withdrawal Agreement, signalling its intention to leave the Single Market (SM) and the Customs Union (CU); end the free movement of persons across UK borders, and the jurisdiction of the European Court of Justice (ECJ); and reclaim national sovereignty. The Political Declaration regarding the framework for the UK's future relationship with the EU is vague regarding goods in general, and medicines in particular. Instead, it sets an aspirational goal of negotiating a comprehensive free trade agreement (FTA), which shall: take account of the UK's and the EU's 'separate markets and distinct legal orders'; preserve 'regulatory autonomy'; make regulatory arrangements with a view to avoiding unnecessary barriers to trade; and explore the possibility of co-operation with EU agencies such as the European Medicines Agency (EMA) (Part II, II.A at [19]–[21], II.B at [22] and II.C at [23]). Currently, the UK government envisages a post-Brexit policy of continued participation in the pharmaceutical sector via associate membership of the EMA. Under the plan, the UK would accept the EMA's rules for marketing authorisation (MA) and post-market surveillance of medicines, carry-on conducting EMA assessments and inspections, and also contribute to the EMA's costs; but under new arrangements recognising that the UK is not an EU Member State (MS) (HMG, 2018). In the event that such status is denied, the UK government intends to participate in the European regime unilaterally, accepting

all medicinal products batch tested and released in accordance with EU rules without any additional requirements for manufacturer-led batch testing and release in the UK (Hancock, 2018).

Formally, sovereignty implies political and legal self-determination. It involves the notion of internal supremacy – i.e. the absence of other equivalent or independent jurisdictions and powers within a State; and the idea of external autonomy – i.e. the absence of hierarchical subordination to external legal or political orders. However, the increased integration of the international community raises challenges for sovereign territorial States (Cohen, 2012). In the context of the pharmaceutical sector, global integration generates powerful pressures for both regulatory convergence and divergence, which may threaten or boost the UK's aspirations to national sovereignty outside the EU [EU (Withdrawal Agreement) Act 2020, s.38]. Sovereign ambitions exist within a global context, transcending the States' traditional right to determine their own destiny independently, in which nations, corporate actors and characteristics of markets such as those of pharmaceuticals shape and inform the policy choices open to governments. Revisiting the evolving concept of sovereignty is essential to reconciling the supremacy of the rational self-interest of States with global governance, a cosmopolitan idea of community and constitutional pluralism – i.e. a plurality of actors, sources and norms, which lack hierarchy but are mutually open to each other's authority (Halberstam, in De Búrca and Weiler, 2012, 150–157 and 160–161). In particular, governance of different areas of the global pharmaceutical market, which correspond to key phases of the lifecycle of medicines, is affected by both 'centripetal' and 'centrifugal' regulatory or market forces. The former operate in areas of equivalent or convergent regulations or policies and might direct the UK towards models of regulatory alignment. The latter operate in areas of multifarious regulations or policies and might direct the UK towards models of regulatory divergence or autonomy (Wright *et al.*, 2017). Depending on the extent to which 'centripetal' or 'centrifugal' forces prevail or interact in a particular area, the UK's power to regulate the domestic and cross-border pharmaceutical market(s) may become vulnerable to downside risks or profit from upside opportunities.

This paper explores key regulatory, governance and legal challenges confronting the UK's sovereign ambitions against the backdrop of 'centripetal' and 'centrifugal' pressures within the global pharmaceutical sector, specifically: (i) convergent *regulatory* pressures associated with the European framework for pre-market licensing; (ii) convergent and divergent *industry* pressures with regard to drug discovery and manufacturing; and (iii) divergent and convergent *market* pressures associated with the supply, pricing and assessment of clinical effectiveness of new medicines. We conclude that the risks threatening the UK's aspirations to regulatory sovereignty might far outweigh the opportunities opened up by its withdrawal from the EU, with national regulatory bodies potentially losing influence over the licensing and surveillance of pharmaceuticals under convergent regulatory and industry pressures to engage in unilateral participation in the European regime; this might be exacerbated by a wider decline of the UK's influence over processes for pricing and assessing the clinical effectiveness of new treatment regimens under divergent pressures from larger pharmaceutical markets outside the EU, most notably the United States.

2. Pharmaceutical regulation: convergence and the pre-market licensing of medicines

2.1 The UK's membership of the European Medicines Agency pre-Brexit

In the UK, the key regulator for the licensing of pharmaceuticals is the Medicines and Healthcare Products Regulatory Agency (MHRA). This is part of a network of regulatory authorities, one of 33 other National Competent Authorities (NCAs), across the European Economic Area (EEA), at the centre of which is the EMA. Established in 1995, the EMA is an EU decentralised agency that coordinates the conduct of scientific evaluations regarding quality, safety and efficacy of pharmaceuticals, on the basis of which new medicines gain authorisation for use across the Union. The EMA is the repository for the methods and procedures relevant to these evaluations. It also coordinates the

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supervision of batch releases and the inspections of manufacturer facilities. Post-authorisation, it collects and holds data regarding the efficacy and safety of drugs (Scholtz, 2015).

2.2 The European regulatory framework

With the EMA at its centre, the European regulatory network is a 'pool of expertise' that facilitates the use of common evaluative frameworks and standards, and ensures the exchange of information (Gehring and Krapohl, 2007). EU law sets out four procedures through which a company might seek MA for new medicines, differentiating them by the type of product and the level of access to the European market that the company requires: (i) a compulsory centralised procedure, conducted via the EMA, which delivers EU-wide authorisation for biotechnology products, HIV, oncology, diabetes medicines, drugs for neurodegenerative and auto-immune diseases, antivirals and orphan drugs (Regulation 726/2004); (ii) a decentralised procedure, conducted via two or more NCAs, which restricts access to the nominated MSs (Directive 2001/83, Arts.27–28); (iii) a mutual recognition procedure, which is built into the decentralised procedure but expands the scope of access beyond the original MSs carrying out the assessment [Directive 2001/83, Art.28 (2)]; and (iv) a national procedure limited to specific MSs (Directive 2001/83, Art.8; Human Medicines Regulations 2012, ss.17–18). With respect to all four procedures, the analytical and inspection work is carried out at the level of NCAs, to which the EMA also outsources much of the work on the centralised procedure.

Operating within a network over which they enjoy collective control, neither the NCAs nor the EMA are gatekeepers of market access. Over time, regulatory interactions across the framework have generated a collaborative regulatory culture that emphasises cooperation with both the industry and the EMA and between NCAs. The EMA provides guidance to both individual NCAs and large transnational companies regarding standards and procedures for the drug development process, the conduct of clinical trials for new drugs and procedures for post-market surveillance. The EMA also facilitates network collaboration with other regulators around the world, forging mutual recognition agreements (MRAs) with third-country agencies relating to commonly accepted aspects of manufacturing and distribution processes (Barber, 2019). The EMA is a strategic institutional node, the point at which the network makes decisions. With the network behind it, the EMA is protected from industry and political interventions either by rogue pharmaceutical companies or self-interested third-countries (Gehring and Krapohl, 2007). In this sense, the UK's strategy for associate membership of the European framework kicks against a convergent and legally grounded regulatory pattern, which not only precludes possibilities of associate membership, but also complicates alternative policies of unilateral participation, mutual recognition or regulatory realignment.

3. Negotiating regulatory convergence outside the EU

3.1 Associate membership

Under the current state of EU law, there is no provision for third-countries to participate in the EMA as members. Only representatives of international organisations 'with an interest in the harmonisation of regulations applicable to medicinal products' may be invited by the European Commission to participate as observers in the EMA (Regulation 726/2004, Art.77). The UK's only option is to rely on its post-Brexit status as a 'neighbouring country', with which the EU could make specific arrangements, as part of a future relationship agreement, including reciprocal rights and obligations and joint activities between the EMA and the MHRA. Arguably, historical interpretation arising from the travaux préparatoires of the EU Treaties would support such a relationship. The provision on the Union and its neighbours (Art.8 TEU) removed the need to provide special associate status for withdrawing MSs (European Convention, 2003). Any special arrangement with the UK would also entail recognition of the jurisdiction and case-law of the ECJ

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(Miller, 2017). Even as a third-country regulator outside the EU, however, the MHRA would still have to negotiate the convergent pattern of European regulation either by unilaterally submitting to EU standards and procedures without having a voice in their formalisation, or by replicating them to equivalent standards under an MRA.

3.2 Unilateral participation

Outside this network, the MHRA also faces the challenge of reducing or preventing barriers to trade arising from the regulatory and financial burdens associated with its choice of a new regulatory model (DHSC, 2018 at 3, 32). For example, the option of regulatory alignment without any agreement with the EU/EEA might consist in unilateral retention/replication of EU rules and standards in UK law (EU Withdrawal Act 2018, ss.2–3, 6–7; DHSC, 2019). However, the lack of a bilateral contractual basis would preclude any automatic or induced reciprocity, creating symmetric constraints for both the UK and the EU/EEA MSs (Paris and Ghei, 2003). Under unilateral participation, the principle of mutual recognition, which would render inapplicable any national rules liable to prevent, without any valid reason, medicinal products lawfully manufactured and/or marketed in any EU/EEA MS from accessing the market in any other MS, would not apply (*DocMorris* (2003) at [67]–[75], [127]–[131]; *Synthon* (2008) at [25]–[29]; *Ker-Optika* (2010) at [47]–[51], [57]–[60]; Directive 2001/83, Arts.28–29 and Preamble [12]). While the MHRA would be bound to recognise MAs of pharmaceuticals awarded by the EMA or EU/EEA MSs' national regulators as being equivalent to those prescribed by UK law, pharmaceuticals lawfully manufactured and/or placed on the market in the UK would have to apply for a new MA in the MS(s) of importation.

The recognition of equivalence of UK licences would be left to the discretion of the EMA and the NCAs. Compliance with EU law would only make it more difficult and less likely to refuse or delay an MA. Such a model would benefit imports from the EU/EEA to the UK more than exports from the UK to the EU/EEA, adversely affecting both direct imports and parallel imports. Proprietary medicinal products covered by an MA in one MS, which are being imported into another MS as a parallel import of an identical, or essentially similar reference product, already covered by an MA in that other MS, with which they share origin, formulation, active ingredient and therapeutic effect, are presumed not to have been placed on the market for the first time in the MS of importation; and are exempted from the obligation to apply for MA unless this is precluded by considerations concerning the protection of health, and, in particular, quality, efficacy or safety (*Smith* (1996) at [21], [25]–[26], [29]–[32]; *Rhône-Poulenc* (1999) at [26]–[28], [43]–[45]; *Kohlpharma* (2004) at [18]–[20]). But this presumption does not apply to imports of products from third-countries regardless of common origin, or similarity with products already covered by an MA in the MS of importation (*BAA* (1999) at [40]–[48]). Therefore, this would not, in principle, affect parallel imports of proprietary medicines already covered by an MA in an EU/EEA MS into the UK market unless the MHRA accepted any countervailing considerations relating to the protection of health (*Novartis* (2005) at [33]). On the contrary, parallel imports of UK-licensed medicines into other EU/EEA MSs would be more burdensome as they would always require duplicate MAs and controls in the MS(s) of importation.

There would also be an adverse impact on the licensing and marketing of generic medicines. Generics can only be made available when the period of market exclusivity on the reference product has expired (*Generics* (1997) at [17], [23], [29]). UK manufacturers of generics already authorised in the EU/EEA would not benefit from the so-called abridged application procedure for MA in the EU/EEA, which would relieve them of the obligation to provide the results of preclinical tests and clinical trials. Hence, they would no longer save time and costs necessary to assemble such data, and avoid the repetition of tests on humans or animals where these were not absolutely necessary (Directive 2001/83, Art.10(1), repealing Directive 65/65, Art.4(3), point 8(a)(iii); *Rhône-Poulenc* (1999) at [25]; *Generics UK* (1998) at [2]–[4], [40]). The adverse

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impact would also extend to hybrid medicines, which are based on reference medicines but differ from them in strength, administration route or indication (Directive 2001/83, Art. 10(3); *Novartis* (2004) at [67], [72]; *Novartis* (2017) at [63]–[66]; *Napp* (2016) at [48]). Their authorisation depends partly on the results of tests on the reference products and partly on new data from clinical trials. The abridged procedure reflects the EU legislature's choice to balance the interests of the innovative undertakings with those of the manufacturers of essentially similar products for the purpose of safeguarding public health (*AstraZeneca* (2012) at [115]–[116]). This would only continue to benefit UK or EU/EEA-based manufacturers of medicinal products essentially similar to reference products already authorised in the UK. As such, a unilateral replication of EU rules and standards in UK law would not eliminate non-fiscal barriers to trade. While the MHRA recently made provisions for an abridged application procedure post-Brexit, this does not apply in the EU/EEA (MHRA, 2019). The flexibility to reduce the long periods of data and market exclusivity currently in place in the EU might instead, at least in theory, benefit the UK's bargaining position in negotiating an FTA with third-countries such as the US.

3.3 Mutual recognition agreement

Alternatively, the UK could pursue a model of regulatory equivalence or mutual recognition based on an EU/UK agreement, drafted either on bespoke terms or relying on the model(s) of MRAs that the EU has already concluded with other third-countries; namely Switzerland, Australia, New Zealand, Canada, USA, Japan and Israel. These bilateral agreements facilitate market access and reduce barriers to trade between the EU/EEA and third-countries by providing for mutual recognition of conformity in the assessment of regulated medicines. Mutual recognition includes Good Manufacturing Practice (GMP) inspections and batch certifications. Recognition of regulatory equivalence might also include Good Distribution Practice (GDP) standards for maintaining the quality of medicines throughout the supply chain (Barber, 2019).

MRAs also allow the EU/EEA regulatory authorities and their third-country counterparts to rely on each other's inspection systems, share information on inspections and quality defects, and waive batch (re-)testing of medicines upon importation. Specific controls to guarantee the quality of medicines imported from, or exported to third-countries can be waived to the extent that appropriate arrangements have been made by the EU with third-countries to ensure that the necessary controls are carried out in the exporting country (Directive 2001/83, Preamble [16]). GMP compliance certification demonstrates that the EU/EEA MSs and the third-country have equivalent GMP compliance programmes; hence the issuance of a certificate of manufacturing authorisation by an authority of one party would satisfy the other party to accept a facility as compliant with the standards of manufacturing and control of medicinal products, or to issue a similar certificate of manufacturing licence. But this would also depend on successful completion of a confidence-building exercise and evaluation of its results [EU-Canada MRA – Sectoral Annex on GMP (1998), s.2; and CETA (2017), Protocol on the Mutual Recognition of the Compliance and Enforcement Programme Regarding GMPs for Pharmaceutical Products, Arts.5 and 7].

For medicinal products covered by the MRAs, each party recognises the results of inspections of manufacturers and the manufacturing authorisations granted by the competent authorities of the other party. In addition, the manufacturer's certification of the conformity of each batch to its specifications is recognised by the other party without repeated control at import [EU-Australia MRA – Sectoral Annex on GMP (2012), s.1; EU-Switzerland MRA (2002), Annex 1, Ch.15]. The Qualified Persons (QPs) in the importing EU/EEA MS are relieved of their responsibility for carrying out GMP compliance controls of medicinal products imported from MRA third-countries, but have to certify the release of each production batch for sale instead of re-testing [Directive 2001/83, Art.51(2)–(3)].

This model does not remove all barriers to trade because it does not necessarily entail mutual acceptance of the standards or technical regulations of either party [EU-Japan MRA (2001),

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Art.11(1)]. Its scope is limited to ensuring that respective regulatory systems are sufficiently comparable to guarantee that the process of inspection, and the official GMP documents provide adequate information to determine compliance with respective statutory and regulatory requirements [EU-US MRA – Sectoral Annex for GMPs (2017), Art.1(5)]. An MA for the EU/EEA and the third-country [CETA (2017), Ch.20, sub-s.E, Arts.20.27(2), 20.28] and/or a manufacturer's licence authorising import is still required (Directive 2001/83, Arts.6 and 8(1),(2),(3)(l); MHRA, 2014, s.7; *Novartis* (2005) at [29], [32]). If combined with regulatory equivalence, an MRA would only make it easier for new medicinal products from the UK to obtain an EU-wide MA from the EMA and thus streamline access to the EU/EEA market. In this way, the MHRA could indirectly support and participate in EMA assessments.

As MRAs do not involve mutual recognition of MAs, an EU-UK MRA notwithstanding, neither UK-based pharmaceutical companies nor those based in EU/EEA MSs would enjoy the benefits of parallel trade; i.e. the promotion of intra-brand competition by way of reducing prices in the importing country to the benefit of patients or other purchasers, such as public bodies/health insurance funds, hospitals or pharmacies (AG Jacobs in *Syfait* (2004) at [74], [78], [96]-[99]; Commission 1998 at 4–5). They would not be allowed to engage in parallel imports of proprietary medicinal products for which an MA has already been granted in the country of destination. Therefore, they could no longer benefit from price divergences of pharmaceuticals across the various national markets, which would be fragmented (Commission 2003; Roth, 2007, 25, 35–42; Grigoriadis, 2014, 142–144). The competitive advantage that the UK has enjoyed pre-Brexit, given its free pricing and its status as a reference country for many EU MS, might be cancelled out by the lack of mutual recognition of MAs outside the SM; and the dual burden imposed on pharmaceutical companies to apply for an additional MA and face cross-border checks associated with third-country status. This might increase the cost of medicines and even the risk of shortages. Further, pharmaceutical companies might prioritise the launch of new products in the EU/EEA, delaying access to new medicines in the UK. Indeed, despite their bilateral MRAs with the EU, new medicines access the Swiss, Canadian, Australian or Japanese markets on average by 5–24 months later than the EU/EEA or the US markets (HC, 2018; Barber, 2019).

3.4 Regulatory divergence and realignment

Both inside and outside the EU, licensing generates strong forces of regulatory convergence. As such, the UK faces the challenge of asserting the MHRA's sovereignty, but also reconciling its autonomy with the wider layer of global governance (Cohen, 2012). In this context, a final alternative would involve a model of regulatory divergence from the EU/EEA standards that introduces an accelerated UK licensing system, which also accepts EMA assessment data on the basis of a relevant bilateral UK/EU agreement (Smith, 2019). For example, the UK could pursue regulatory alignment with the standards in one or more third-countries that have established their own alternative regulatory market(s) and play a significant role in the global pharmaceutical industry (e.g. USA, Canada, Switzerland or Australia). Under this model, UK-licensed medicines could apply for MA(s) faster and more easily in the third-countries, and *vice versa*. The UK could also conclude MRAs with other third-countries, allowing the MHRA and their counterparts to rely on each other's GMP inspections of pharmaceutical manufacturing facilities, thereby reducing duplicate controls and unnecessary costs [see e.g. UK-US MRA (2019) – Sectoral Annex for Pharmaceutical GMPs].

However, these other third-countries may already have an MRA with the EU/EEA. As such, any separate MRA concluded between the third-country and the UK could not directly benefit UK manufacturers. The EMA and the domestic regulators of the EU/EEA MSs would not be obliged to accept test reports, certificates, authorisations or results of conformity assessments issued by the MHRA unless there was an explicit arrangement/amendment in the MRA concluded between the third-country and the EU/EEA [see e.g. EU-NZL MRA (1998), Art.11]. At best, the UK's

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regulatory alignment with such a third-country could allow UK manufacturers to benefit indirectly from an MRA concluded between the third-country and the EU/EEA, making them more likely to pass an inspection by the third-country regulator with regard to their compliance with GMP; and, for UK products, to undergo duplicate control successfully in the third-country upon importation. In this way, regulatory realignment could facilitate the export of UK products from the third-country to the EU/EEA, and the award of an import licence, without the need for further controls [see e.g. EU-Switzerland MRA (2002), and (2017) Amendment of Ch.15].

4. The pharmaceutical industry: convergence and divergence in the discovery and manufacture of medicines

Transnational pharmaceutical companies develop, manufacture and distribute global product lines across broad geographic domains, selling medicines into national markets characterised by a diverse range of health and safety regulations, together with varied pricing regimes and different incidences of disease. The industry produces three types of medicines: in-patent drugs, out-of-patent generic drugs and over-the-counter drugs, with in-patent drugs being the most important to company profitability, but also involving higher initial investment in research and development. In producing these medicines, conducting the associated activities, companies are subject to both convergent and divergent pressures. Typically, large pharmaceutical firms are centralised in OECD countries, which provide their key markets for research, development, manufacture and sales. While they centralise the conduct of research and development within OECD countries, they decentralise manufacturing operations to the markets in which their products are sold. Consequently, the industry is globally convergent in terms of the research and development of product lines; but it also involves divergent multi-country dimensions given the different national safety, regulatory and pricing regimes within which companies bring products to market (Bauschke, 2010).

4.1 Support for research and development

Pharmaceutical companies rely on the governments in their home countries to support research and development and invest in the national scientific infrastructure. National industrial and research policies promote generalised bio-medical research and, by extension, generate research culture, encouraging new research consortiums and incentivising firms to expand their operations. For example, the European Horizon 2020 and Framework Programmes grants are key government initiatives that build links between universities, research institutes and companies. In MSs, national funding bodies work to supplement and synergise with these larger pools of funding, with bodies like the National Institute for Healthcare Research (NIHR) providing extensive funding for developing clinical trials, which are also important to regulators and companies. Combined with large regional investments through the European grant system, national funding enhances the attractiveness of countries like the UK as sites for major pharmaceutical companies to base their activities, and carry out research and development. With risks and costs of drug discovery extremely high, large companies often collaborate with, or buy out, smaller companies engaged in generating potentially profitable medicines (Busfield, 2003).

4.2 Common standards for manufacturing and marketing authorisation

Pharmaceutical companies also rely on governments to facilitate their capacity to realise profits on the drugs they discover. Drug discovery is extremely difficult. Few products pass through the four stages of the development process to receive MA. For those that do, the average time spent on development is about 10 years (Bauschke, 2010). At this point, the companies' potential to redeem profits on their investment depends on the proper and safe consumption of medicines.

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In other words, the industry has a strong interest in supporting and achieving stringent regulatory standards for ensuring the quality and efficacy of their products. In this way, regimes for the licensing and post-market surveillance of the safety and efficacy of new medicines (pharmacovigilance) are linked to the discovery and manufacture of pharmaceuticals and also to the ability of companies to realise profits on their investments.

Given these links, firms typically decentralise the manufacture of products to local markets in order to ensure that they satisfy national regulations for market entry, creating intermediate products in their home countries for completion and licensing in their final markets. The transportation of intermediate products, or active ingredients, involves low substance volumes, low capital investment and low costs. With the industry having strong interests in delivering safe and effective products, and with technical processes generally raising no real obstacles, companies welcome, and even prefer, strong regulation for market entry in order to guarantee safety, efficacy and profit realisation (Schweitzer, 2007).

However, pharmaceutical companies also prefer larger markets under common regulatory standards for the testing, packaging and distribution of medicines. Rather than individualising certification across a number of smaller markets, firms realise greater profits, and more quickly, through the release and monitoring of products under common standards that provide certainty for their production (Permanand, 2006). Today, trends in the sector are convergent towards regional and global harmonisation of regulatory standards; with the EU at the forefront of efforts to shape transnational acceptance of shared responsibility for good manufacturing guidelines and practices for site inspections and surveillance activity (Juillet, 2007).

4.3 Protection of market access

After a product receives MA, companies rely on the protection afforded by intellectual property (IP) or patent rights against the market entry of generic products. Highly profitable in-patent drugs are sold on the basis of their novel and/or innovative qualities, with larger firms hoping to recoup their significant investment in research and development via widespread sale to institutions and doctors during patent windows. Conversely, generic producers may rely on legislatures to enhance their profitability. In the US, the 1984 Hatch-Waxman Act was introduced to hasten the approval process for bringing out-of-patent generics to the market. Generic companies are usually much smaller than research companies; but their ability to deliver savings to consumers depends on their ability to eke out profits on expired patents. In other words, they rely on the legislature and/or regulatory authorities to prevent a patent term extension, or refuse the award of a supplementary protection certificate (SPC); and hence enable the entry of generics into existing markets at reasonable costs.

Given the importance of patent windows for the maximisation of profits, large pharmaceutical companies lobby governments and legislatures for patent extensions, citing the need to reward research and development activity and promote innovation. Alternatively, generic competitors argue that granting patent extension is a barrier to entry, and that many patents on New Molecular Entities (NMEs) do not deliver significant innovation to warrant protection. Competition between the different types of pharmaceutical firms is intense. Big research companies open disputes, engage in litigation and even file for additional patents on existing products simply to extend original patents (Busfield, 2003, 2010). Alternatively, generic manufacturers respond with claims that generics exert pressure on existing product lines, and that granting patent protections in these areas actually disincentivises larger companies to pursue genuinely innovative products.

5. Negotiating industry convergence and divergence outside the EU

The UK's withdrawal from the EU complicates its ability to accommodate and support the characteristics of the pharmaceutical sector. Aspirations to sovereignty risk compromising industry

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access to large pools of European public funding; they disturb synergies with national-level funders; and they also threaten to reduce the size of the national market via divergent standards for licensing and surveillance. However, in a more direct sense, the European regulatory framework for MA protects both direct and parallel trade in medicines, including generics. Outside the EU, parallel trade and the generics industry face stiff competition from larger research companies intent on the removal of protections for direct or parallel trade in medicines. Indeed, perhaps the greatest challenge facing a sovereign UK is to limit or counteract the effect of the marketing and lobbying powers of the global pharmaceutical industry.

5.1 Adjudicating market access

Insofar as a withdrawal from the EU reduces the ability of pharmaceutical companies to redeem profits on their investment in research and development, the UK government is likely to become the target of company lobbying initiatives, which may threaten its ability to adjudicate issues of market access on the basis of achieving optimum public health outcomes. In short, the UK government may need to develop a policy regarding the marketing of pharmaceuticals, which is currently subject to industry self-regulation.

At present, patents are usually awarded before the product receives MA and so companies need to act quickly in order to realise profits. Typically, pharmaceutical companies build large sales teams to exploit the consumption of innovative products during patent lives, marketing them to institutions, doctors and patients, and targeting each with different strategies for different types of medicines. Doctors are gatekeepers of market access. With growing product lines of broadly similar prescription drugs, they are key agents within company revenue chains, who hold the power to weigh significantly on the profitability of the industry. Doctors have the power to prescribe either in-patent drugs or out-of-patent generics, or even over-the-counter medicines (Abraham, 2005; Busfield, 2010). For this reason, companies approach doctors with promotional material and study results, aiming to position newly authorised drugs within the market.

In addition, companies are also reliant on government decision-making and consumer choices to deliver the greater part of their income. Health funds and organisations like NICE, in the UK, have powers to make medicines more readily available to doctors for prescription by delivering reimbursement approval, or to endorse and thereby mandate what medicines are available within national health systems like the NHS (HMG, 2017; *Servier* (2015) at [25]). Companies target these institutions and organisations with claims about the superiority of new, patented medicines in comparison with off-patent medicines. Even patients themselves exercise power over the industry, generating demands for specific prescriptions, or buying medicines over the counter. Thus, companies target patients with media briefings, or publicity via chemists and doctors' surgeries, which are designed to stimulate patient interest and enhance their expectations for achieving optimum health. Exiting the SM and the CU, the UK becomes a smaller market, potentially more vulnerable to industry pressure regarding licensing and reimbursement decisions. The UK government may need to devise its own efficient and more resilient strategies to avoid capture by the marketing and lobbying powers of the large multi-national companies in the global pharmaceutical sector.

5.2 Intellectual property rights and parallel imports

Protections afforded to generics and parallel imports by the ECJ have balanced the establishment and functioning of the SM for pharmaceuticals with the accomplishment of MSs' public health goals. Where a MS's public health authorities already possess all the particulars necessary for checking the efficacy and safety of a medicinal product, as a result of its importation and MA on a previous occasion, they do not require a second trader, who imports the product, to resubmit

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those particulars for authorisation (*De Peijper* (1976) at [21], [36]). As a rule, retailers, pharmacists and hospitals in one MS may procure medicines imported from other MSs unless there is a valid reason why access to another part of the SM should be denied (Roth, 2007, 42–43). This has been facilitated, on the one hand, by the principle of exhaustion of IP rights, originally developed by the ECJ (*Centrafarm* (1974) at [9]–[10]) and codified in EU legislation [e.g. Directive 2015/2436, Art.15(1)]. Accordingly, an IP rightsholder may not oppose the marketing of IP-protected products imported from another MS if they have been lawfully placed on the market in the exporting MS by the holder or with his consent. Subject to conditions, this may cover the commercialisation of pharmaceuticals repackaged by parallel importers (*Boehringer* (2007) at [32], [39], [47], [54]; *Bristol-Myers* (1996) at [79]). This principle applies where the IP rightsholders in the importing and the exporting MSs are the same persons, or even if they are different persons, they are economically linked (*IHT* (1994) at [33]–[34]). But the principle of exhaustion does not apply outside the EU/EEA. In trade agreements concluded between the EU and third-countries, parties remain in principle free to determine whether and under what conditions this principle would apply [see e.g. CETA (2017), Ch.20, sub-s.E, Art.20.4].

6. Pharmaceutical markets: divergence and convergence in the supply, pricing and assessment of medicines

While the licensing regimes, industry manufacturing and drug discovery processes generate pressures for international convergence, markets for pharmaceuticals and other health technologies are mostly divergent, with individual States differing in terms of pricing regimes and methods for conducting assessments of clinical effectiveness. EU law provides some degree of protection for national markets through safeguards regarding competition between branded and generic manufacturers, and excessive pricing of innovative products. Exiting the SM, however, the UK government faces the additional challenge of maintaining the same or equivalent level of protection in the face of convergent pressures generated by larger markets outside the EU, especially the US.

The US government pursues a particularly aggressive trade agenda in relation to the licensing and pricing of pharmaceuticals (Lopert and Gleeson, 2013; Lexchin and Gleeson, 2016). Under the influence of powerful industry lobby groups, its negotiators have consistently pushed trading partners for strong IP protections for branded pharmaceuticals against generics. Furthermore, the US has pushed trading partners to accept its own normative standards regarding coverage and access to medicines that prioritise price-setting according to market rather than public health value (Aldonas, 2004). The determination of US trade negotiators to advance the profits of US pharmaceutical companies against collectivist public health objectives, like those of the NHS, has the potential to compromise the goals of national healthcare agencies, such as NICE, to ensure comprehensive access to high-quality affordable medicines through the provisions of international trade agreements (Gleeson *et al.*, 2019).

6.1 Linkage regulations

Exiting the SM, the UK government has ambitions to conclude a far-reaching FTA with countries like the US. However, the recent experiences of Canada, Australia and South Korea demonstrate that FTAs with the US hold a potential to regulate regulators, like the MHRA. For example, under the North-American Free Trade Agreement (NAFTA) in particular, and to a lesser extent under the Australia–US Free Trade Agreement (AUSFTA), the US government pressed for gains that would enhance the capacity of US-based pharmaceutical companies to 'ever-green' branded pharmaceuticals, thereby delaying the authorisation of cheaper generics in Australian and Canadian markets. 'Ever-greening' is a descriptive term that marks an assortment of strategies through which patent owners use legal and regulatory processes to extend monopoly privileges over profitable branded medicines. As part of the NAFTA, US negotiators demanded the

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inclusion of provisions requiring generic manufacturers to notify branded competitors of their intention to enter the Canadian market. Under Australia's system of patent linkage, notification of originators by generic companies is not mandatory; instead, they can choose to certify that they are not infringing a valid patent. In Canada, however, these provisions required regulators to link approval for generics to the absence of patents. Upon receiving notification of a generic company's intention to enter the market, branded companies tend to hamper competition via the assertion of additional patents, which smaller generic companies lack the resources to challenge. In Canada, these linkage regulations have been 'extremely harmful' to the generic industry, with the public suffering delayed access to affordable medicines and increased co-payments (Faunce and Lexchin, 2007, 2).

To some extent, the Canadian government mitigated the worst impacts of these provisions through the establishment of a dedicated Office of Patented Medicines and Liaison (OPML); this audits the Canadian Patent Register providing statistics on the number of patents accepted and rejected for products, assessing whether applications for inclusion on the register are warranted. But, by way of a response, the US has been threatening trade sanctions (Faunce and Lexchin, 2007; Lexchin, 2011). Similarly, when Australian legislators challenged the wording of linkage regulations in the AUSFTA, attempting to prevent the clause having related impacts on the Australian market, Faunce and Lexchin note that the US Ambassador was reported to suggest that either the two parties would resolve their disagreements bilaterally, or the US would litigate the issue before the World Trade Organisation ('US still watchful on FTA' cited in Faunce and Lexchin, 2007). Building on their experiences with Australia and Canada, the US significantly broadened linkage provisions within the Korean–United States Free Trade Agreement (KORUSFTA): the Korean patent linkage system also required the regulator's involvement in the notification system and in administering stays on marketing (Son *et al.*, 2018).

6.2 Price controls

In addition to market entry and availability of generics, the US also targets pharmaceutical pricing regimes within national markets, which have special relevance to the role of NICE. Approaching the negotiation of the AUSFTA, the US considered the practice of reference pricing under the Australian Pharmaceutical Benefits Scheme (PBS), parallel to the conduct of technology assessments carried out via agencies like NICE, to raise 'non-tariff' barriers, 'trade distorting' and 'discriminatory', illegitimate price controls, against US companies, denying them full market access for their products (Lopert and Gleeson, 2013; Faunce, 2015). Concluding the agreement, the US failed to secure the programmatic gain of circumscribing national policies for the provision of subsidised medicines; however, via the inclusion of Annex 2C within the agreement, it made the procedural and political gains of, in the first place, addressing 'the conduct of another nation's domestic drug coverage program within a bilateral trade agreement', and, in the second place, creating the perception that the inclusion had been 'accepted', allowing 'it to appear normative', and legitimizing its 'inclusion in future trade agreements' (Marsh and McConnell, 2010; Lopert and Gleeson, 2013, 205).

In Australia, concerns regarding the potential of the AUSFTA to compromise the PBS focused on references to 'valuing innovative pharmaceuticals' in the 'Agreed Principles' clause of Annex 2C. In addition, the US pharmaceutical industry was also seeking influence over decision-making processes for the national formulary, in particular the inclusion of 'contestability mechanisms' that would shift the final decisions regarding listings from the technical expert committee 'to a non-technical appeal body' (Lopert and Gleeson, 2013, 204). As a result, public concerns grew that the agreement would allow the US to influence national policy regarding the pricing and subsidisation of medicines (Faunce et al., 2010). However, subsequent inclusions and clauses within the AUSFTA are considered to have offset US intentions; and, to date, there is no evidence that the AUSFTA has had an effect on 'PBS decision-making, pricing mechanisms, or the actual prices of medicines' (Lopert and Gleeson, 2013, 204). Programmatically, the US was certainly

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unsuccessful in its attempt to curtail reference pricing and decision-making under the Australian PBS (Marsh and McConnell, 2010).

In other trade forums, however, the US has continued to press the procedural and political gains made in relation to the AUSFTA. For example, the US also included a 'sufficiently similar' Annex in the Trans-Pacific Partnership Agreement (TPP), which held sufficient potential to expose national policy-makers to ongoing industry pressure over pharmaceutical decision-making (Lexchin and Gleeson, 2016, 609). Indeed, following the USA's withdrawal from the TPP, other countries suspended the Annex from the Agreement suggesting that they no longer saw the provision as being in their interests. With the UK exiting the SM and the CU, the point is that the US, in negotiating a UK-US FTA, will likely attempt to consolidate the procedural and political gains made in other trade negotiations with programmatic gains of the kind that it failed to make in relation to the AUSFTA (Marsh and McConnell, 2010). Obviously, each trade negotiation is independent of the other, but that independence could work both in favour and also against the UK's interests in maintaining its own provisions for the subsidisation of medicines. In such case, agencies like MHRA and NICE may need to develop capacities to advise other government bodies, such as the Department for International Trade, about means for achieving policy coherence between trade agreements and programmatic national public health goals; so that any potential UK-US FTA does not adversely affect core pharmaceutical policy objectives such as access to, and affordability of medicines through the inclusion of similar provisions (Gleeson *et al*., 2019).

7. Negotiating market divergence and convergence outside the EU

Ironically, divergent pressures within global pharmaceutical markets are a threat to the UK's ability to control its national competition and pricing regimes. Overall, while the fields of supply, pricing and assessment of the efficacy of new medicines are generally dominated by divergent market forces both within and outside the EU, EU law offers some degree of protection against abuse of patent rights and excessive pricing. Facing-off against aggressive trade partners, the UK government is likely to face the challenge of upholding current levels of protection for the national pharmaceutical market afforded under EU competition law against the convergent pressures generated by larger markets, particularly the US.

7.1 Protecting competition

Pre-Brexit, the UK has been afforded protection against linkage practices through EU competition law, and in particular through enforcement by the European Commission and the ECJ. UK authorities have used EU provisions to counteract attempts made by originator pharmaceutical companies to impede or delay the introduction of generics, or new innovative drugs, which might compete with their branded reference products that are already on the market (Dworschak, 2016, 97ff., 138ff.). Practices by pharmaceutical companies which aim to prolong market exclusivity, such as patent clusters or thickets, and patent settlements, or any other anti-competitive strategy that results in high prices may amount to a breach of Art.101 or 102 TFEU (*Lundbeck* (2016) at [118]; cf. CMA, *Paroxetine* (2016) 9ff.). Such practices may also act as a strong disincentive to innovation. Competition from generics encourages pharmaceutical companies to make the best possible medicines available (Commission 2009). For instance, in the *AstraZeneca* case, the pharmaceutical group was fined for abusing its dominant market position by exploiting the systems of patent protection and MA in order to prevent or delay competition to its blockbuster drug from generics and parallel imports. The breach was upheld by both the General Court and the ECJ [*AstraZeneca* (2012)]. The first abuse consisted in making misleading representations to national patent offices and courts in EU/EEA MSs in order to obtain or maintain SPCs (Regulation 469/2009, Art.13), to which the group was not entitled or entitled for a

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shorter period. This was considered a method that fell outside the scope of 'competition on the merits', serving only and wrongfully to keep generic manufacturers away from the market (*AstraZeneca* (2012) at [68], [75], [98], [106]–[108]). The second abuse consisted in misusing rules and procedures applied by national regulators, by selectively deregistering the MAs in a number of MSs, combined with the withdrawal of capsules and the launch of diversified, multiple-unit tablets. This was ruled liable to make it impossible, or more difficult, for generic manufacturers to benefit from the abridged procedure of MA for essentially similar medicinal products; and also to remove licences from parallel importers. The measure was regarded as capable of delaying, impeding or preventing market access of generics and parallel imports, without any objective justification or grounds relating to the protection of legitimate interests (e.g. investment) of an undertaking engaged in 'competition on merit' (*AstraZeneca* (2012) at [116]–[118], [123]–[124], [131], [134], [149], [153]–[155]; cf. OFT, *Reckitt* (2011) 131ff.).

Outside the EU/EEA, the UK can only rely on protection against such abuses if similar provisions are provided for in domestic law or in international/bilateral trade agreements (Dworschak, 2016, 82). At the very least, the UK government needs to include the more limited (two to five-year-long) *sui generis* patent protection afforded to patent-protected (active ingredients of) pharmaceuticals, which have been granted their first MA in each of the parties to CETA (Ch.20, sub-s.E, Arts.20.27 and 20.28). Beyond including these provisions, the UK government must also prevent their subversion via the content of FTAs that its negotiators might settle with larger market players (Walls et. al., 2015).

7.2 Protecting pricing and parallel imports

Divergences in national pricing regulations, or the lack of harmonisation at EU level, have been a major driver of parallel trade in pharmaceuticals within the SM (*Roussel* (1983) at [24]; Schwarze 1998). Parallel imports of medicinal products from low-price to high-price MSs are, in principle, protected as an integral part of free movement of goods (Art. 34 TFEU; *Grund* at [62]–[67]; Roth, 2007; Grigoriadis, 2014, 151–153; Dworschak, 2016). Limits to parallel trade arise, *inter alia*, from EU legislation; and especially from the duty incumbent on manufacturers and wholesalers to ensure appropriate and continued supplies of medicinal products to a MS's domestic market (Directive 2001/83, Art.81). Manufacturers are, in principle, free to adopt their own supply and pricing policy; but its implementation across the MSs must comply with EU law (including Arts.101–102 TFEU). Not all dual-supply or dual-pricing schemes operated by the same manufacturers in different MSs are automatically caught within the net of EU competition law (*GlaxoSmithKline* (2006) at [107], [117], [177]–[179], [271]–[272]; *GlaxoSmithKline* (2009) at [102]–[104]). However, agreements between manufacturers and wholesalers in one MS, which set higher prices for wholesalers exporting medicines to other MSs than the prices for reimbursable drugs already charged within those markets, may unlawfully restrict competition inasmuch as such practice has the effect of partitioning markets on the basis of national borders (*GlaxoSmithKline* (2009) at [59]–[61], [66]–[67]; *EAEPC* (2018)). Likewise, unilateral stock allocation schemes operated by manufacturers for the purpose of controlling the supply of medicines to wholesalers in one MS, who might engage in exports to another MS, may also amount to abuse of dominant market position unless the orders placed by wholesalers are out-of-the-ordinary and go beyond the necessary levels of supply for the former MS's domestic market [*Lélos* (2008)].

Furthermore, excessive pricing of medicines may also constitute abuse of dominant market position, which 'may, in particular, consist in directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions' [Art.102(a) TFEU]. Under EU law, a price is excessive and unfair when it has 'no reasonable relation to the economic value of the product', which would have prevailed 'if there had been normal and sufficiently effective competition'; the economic value is based on the production costs, including a necessary profit margin (*United*

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Brands (1978) at [249]–[251], [254], [256]). In order to determine whether a price is unfair and abusive, the ECJ has set out a twofold test, which involves assessing whether the profit margin (i.e. difference between the costs actually incurred and the price actually charged) is excessive; and if so, whether the price is unfair either in itself or when compared to competing products (*United Brands* (1978) at [252]; cf. CMA, *Pfizer* (2016) 342ff.). Alternative methods have not been ruled out (*United Brands* (1978) at [253]). These may include a comparison with prices charged for similar products in one or several other MSs, which reveals that the prices charged by the dominant undertaking are appreciably higher. Such comparison must be based on comparators selected in accordance with objective, appropriate and verifiable criteria and carried out on a consistent basis. There can, therefore, be no minimum reference MSs to compare, but the choice of appropriate comparator markets may depend on the specific circumstances of each case (*AKKA* (2017) at [38], [41], [44], [53], [55]).

However, when assessing the pricing practices of pharmaceutical companies, the particularities of the pharmaceutical market relating to the nature and lifecycle of pharmaceuticals, together with the role of regulation, must be taken into account. Some products, especially medicines that are essential to life and health, are characterised by high inelasticity of demand: patients depend on them, but often do not directly pay for them. Equally, doctors prescribe them, but also neither consume nor pay for them; and national health services and/or insurance providers may have limited influence on prescription, consumption or price; but also have to pay for them (*Duphar* (1984) at [17], [20]–[22]). This may render the sector more prone than others to unfair pricing practices. With regard to the three main phases of a medicine's lifecycle, the first phase, i.e. discovery and development, is generally lengthy and costly; the second phase, i.e. launch and sale on the market, while benefitting from product exclusivity owing to IP protection, may allow originators to enjoy very high profits as a reward for innovation and investment; while the third phase, which follows the loss of exclusivity, may (or depending on the circumstances of particular markets, may not) allow effective competition by generics to take place and thus may (or may not) result in competitive price levels. Thus, within the SM, some protection is afforded because high prices or price increases in relation to off-patent medicines are less likely to be justified, and hence more likely to be caught by Art.102 TFEU, because the inventor/originator has already benefitted from legal exclusivity as a reward for innovation (EUOECD, 2018 at [14]–[23]).

8. Conclusion

The global pharmaceutical sector generates powerful 'centripetal' and 'centrifugal' pressures for convergence and divergence, which may threaten the UK government's aspirations to regulatory sovereignty outside the EU. To sum up, firstly, the models of regulatory convergence that dominate the licensing of medicines, both within and outside the EU, impact so heavily on divergent models, especially in smaller or medium national markets, that the latter risk being marginalised or ostracised. This may render the UK's sovereign ambitions Sisyphean, even antediluvian. Secondly, notwithstanding the interaction between regulatory convergence and divergence, which generally characterises the fields of discovery and manufacturing of medicines, both within and outside the EU, the lack of a centralised regulatory model outside the SM is likely to render the pursuit of 'frictionless' cross-border (direct or parallel) trade in medicines (including generics) extremely difficult, costly or impossible to achieve. Last but not least, notwithstanding the regulatory divergence, which largely dominates the fields of supply, pricing and assessment of new medicines, both within and outside the EU, there is a discrepancy between the minimum effective protection afforded by EU law against abuse of patent rights and excessive pricing and the experience of negotiations of international FTAs between third-countries. This adds to the challenge facing the UK in ensuring comparable protections to those afforded under EU law within any FTAs post-Brexit. All these considered, the challenges raised by 'centripetal' regulatory and market forces to the UK's power to regulate the domestic and cross-border

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pharmaceutical market(s) may far outweigh any opportunities opened up by 'centrifugal' forces in the global pharmaceutical sector. Thus, the UK's pursuit of national sovereignty via withdrawal from the EU may well result in a significant loss of regulatory control over the UK's pharmaceutical sector with serious consequences for national public health objectives such as access to affordable medicines and, in time, even the sustainability of the UK's single-payer health system.

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