The UK's biopharma and health industries after Brexit

Paul Ranson, of global law firm Morgan Lewis' London Life Sciences Practice, examines how the UK Biopharma sector must now adapt to a changing landscape following the UK's vote to leave the EU. It may come as no surprise that a pre-referendum 'Brexit' poll conducted by the UK Pharmaceutical Directors Club of senior management within the UK pharmaceutical industry resulted in a vast majority in favour of 'Remain' with local management and head offices concerned about the possibility of the UK exiting the EU and negative implications for their businesses. This article is an attempt to determine what implementing the referendum result means for the UK and EU pharmaceutical and medical device sectors and to consider practical responses.

Some regulatory consequences

Medicinal products

For a medicinal product to be placed on the EU market it must have a marketing authorisation ('MA'). An MA may be granted on a 'centralised' basis whereby the European Medicines Agency ('EMA') reviews an application and makes recommendations to the European Commission. The product may then be sold throughout the EU. This route is compulsory for most biotechnology products and orphan medicines and generally followed with other high technology products. Alternatives are the decentralised or mutual recognition procedures whereby an application is considered by a 'reference Member State' residing in the EU and once assessed or approved by that country, the other EU 'reference Member States' should in principle grant consistent national approvals. Issues arise as to whether the UK could continue to be the reference Member State for authorised products after it leaves the EU. Additionally, an MA applicant or holder must be 'established' in the EU.

Further, the sponsor of a clinical trial in the EU, who is not established in the EU, is required to appoint a 'legal representative' with responsibilities for managing the trial locally. Similarly, a sponsor of a medicine with orphan drug designation will need to be established in the EU.

In addition, the import of medicines into the EU requires an import authorisation and manufacture within the EU requires a manufacturing authorisation and these allow the holder to release the product for supply throughout the EU. Similarly, those distributing or brokering the supply of medicinal products are required to obtain authorisations to do so.

Finally, pharmacovigilance ('PV') requirements mean that the Qualified Person for PV must be established in the EU and that the PV database and master file must be accessible from within the EU.

Medical devices

The placing on the market of a medical device requires the manufacturer (who again needs to be established in the EU or who must appoint an authorised representative residing in the EU) to obtain a CE-mark with respect to the product evidencing its compliance with certain 'essential requirements' set out in one of the three medical device directives. In the case of low-risk (class I devices) the manufacture may affix the CE-mark following a self-certification procedure. However, for higher risk, class II and III products the CE-mark must be obtained from a 'notified body,' a private organisation certified as competent to accredit a product as meeting the essential requirements. Once a CE-mark is granted it allows the product to be sold freely throughout the EU.

Planning for regulation post-referendum

The EMA and other EU medicinal product organisational and licensing arrangements are restricted to EU and EEA members, so the UK, if outside the EEA, will be excluded. Indeed, the EMA will, in these circumstances, be expected to move its headquarters out of the UK and relocate in one of the remaining EU countries. Nor will rapporteurs from the UK be accepted. However, as part of the forthcoming negotiations, it would seem sensible for the UK to agree a Mutual Recognition Agreement - such agreements already exist between the EU and Switzerland, Canada and Australia.

The EMA will certainly regret the loss of the UK competent authority, the Medicines and Healthcare Products Regulatory Agency ('MHRA') in so far as it is one of the most respected Member State competent authorities and the most used rapporteur under the centralised system and reference Member State under the mutual recognition and decentralised systems.

A particular irony is that the new Clinical Trials Regulation which introduces the possibility of a single approval for a pan-EU clinical trial which has been sought after for many years, may now come too late for the UK to benefit. The Regulation will probably come into force in October 2018.

For medical devices, a question arises whether they should

retain an authorised representative or manufacturer in the UK? Similarly, should manufacturers continue to use a UK notified body? However, joining the EEA or entering into a mutual recognition agreement under the EFTA, could mean that UK-originating devices would still benefit from access to the EU market.

The likelihood of an extended negotiation period means there may be little material change for at least two years and probably substantially longer. However, before any action is considered, it would be appropriate to identify all applied for or granted marketing authorisations, clinical trial approvals or legal representative status, orphan designations and supply chain licences held by UK affiliates as well as any key regulatory functions performed by them including qualified or responsible persons and siting of databases. For medical devices, one would similarly identify those products for which a UK company is either the manufacturer (CE-marking holder) or the authorised representative and where the selected notified body is based in the UK.

If the UK goes the EEA route, little will need to change, even after Brexit, as all EU rules will apply within the UK wholesale with UK companies able to apply for and hold the requisite approvals and licences. An exception is that MA approvals under the centralised route would need to be nationally implemented as they would not apply automatically in the UK.

Were the UK to go the Swiss route or the WTO route, much of UK life sciences law is derived from EU law either through directives implemented nationally in the UK or through EU regulations which have direct effect. Accordingly, transitional measures could well be brought in to ensure that both the UK implementing laws and the EU regulations would remain in force until amended or revoked. However, the MHRA would have to transfer marketing authorisation applications for which they are either rapporteur or the reference Member State to other Member State regulatory authorities.

With goodwill on both sides, an easy solution might be a series of mutual recognition agreements in relation to both medicinal products and medical devices - as UK governance in both sectors is widely respected throughout Europe there is little reason (other than possibly political mischief making) why this would not be achievable. This would be particularly important for the supply chain to ensure importers and manufacturers would be able to release product for EU supply - and vice versa. By way of precedent, Switzerland has an agreement with the EU mutually recognising GMP licences to facilitate this. It also has a similar agreement leading to mutual recognition of CE-marking for medical devices. Similarly, UK notified bodies can point to existing mechanisms in place for non-EU countries including mutual recognition agreements involving the US, Canada, Australia, Switzerland and Japan.

Whatever way negotiations go, there is an argument for the industry not taking precipitous action as, at worst, any regulatory approvals, licences or functions could be transferred to an affiliate within the EU prior to the effective date of the UK actually leaving the EU. Ian Hudson, Chief Executive of the MHRA, stresses that the Agency is "open for business as usual in terms of its routine regulatory work whilst the Agency works with the UK Government, industry and other EU and international regulators to consider and take forward the results of the UK referendum. This continuity is also recognised and endorsed by its EU partners and EMA leadership."

Other ramifications

UK market attractiveness

The UK represents some 3% of the world market for all medicines but considerably more for more innovative, costly treatments. However, the UK's marketshare underestimates its global importance in several respects:

- its percentage of use of innovative medicines is considerably higher and between 2010 and 2014 there have been more NCE launches in the UK than any other country other than the US and Germany and more speciality NCE launches than in any other EU country other than Germany and France;
- it is joint third (with Germany) in the number of global HQs after the US and Japan; and
- it is in the top five worldwide in terms of life sciences industry and R&D headcount.

Moreover, the National Institute for Health and Care Excellence ('NICE') is a highly respected and influential health technology assessment body and the UK is widely used as a reference price by many EU countries. It has also developed its own early access scheme and 'promising innovative medicine' status for unlicensed medicines and is due to publish its (albeit delayed) review on accelerated access in response to the EU adaptive pathways initiative for early licensing, now due in September of this year.

As with most EU states however, it continues to search for financial savings so it has rationed and sought cost reductions on most of these more expensive medicines and devices. It is already known as a slow adopter of these new medicines.

So a mixed picture means that the UK's place in new product launch sequences is already under a degree of scrutiny and EU membership alone is not necessarily the most important factor in launch and investment decisions.

The industry should be prevailing upon the Government to counter EU departure risks to the sector by becoming quicker to introduce and appropriately fund new treatments through the speedy introduction of the accelerated access review and a more holistic approach. In this regard it would need to seek to demonstrate how the added investment and revenue could comfortably outweigh any increase in the healthcare products bill. The recent announcement by the now ex-Life Sciences Minister, George Freeman, that he had convened a joint government-industry steering group to "set out key priorities for the UK life sciences sector" in the negotiations with the European Union was therefore timely. The group was to be co-

chaired by the Minister, GlaxoSmithKline CEO Andrew Witty and Pascal Soriot, CEO of AstraZeneca. With the departure of George Freeman, to another role and without a direct replacement, it remains to be seen however how the group will be constituted going forward. Life Sciences will now form part of the responsibility of Nicola Blackwood, the Secretary of State for Health Services.

Pricing and reimbursement

Pricing and reimbursement of pharmaceuticals and devices within the EU is a national competence with virtually no EU harmonisation so there is likely to be little impact from the UK leaving the EU. Moreover, without the EUnetHTA (the European lead body for supporting the collaboration between European health technology assessment ('HTA') organisations at the European, national and regional levels) it may continue to go its own way in how it assesses and rewards added value and innovation in new treatments. However, key to demonstrating and assessing value in treatments is real world evidence ('RWE'). RWE collection and harnessing needs joined up health informatics systems and data science, a field in which the UK (as stated above) arguably currently has a lead over the rest of the world. This is an advantage which, given the current situation, the UK may seek to exploit more aggressively internationally.

Patents and other protection

The European Patent Convention will remain in force, as its membership goes wider and is not dependent on EU membership. However, the Supplementary Protection Certificate, extending patent life by up to five years, is purely an EU matter. This issue could be part of the negotiations, but if agreement were not reached, the UK would need to decide whether to introduce its own legislation.

However, EU membership is a requirement for the new unitary patent system. As the leading forum for pharmaceutical patent litigation, London would have been a logical choice for the pharmaceuticals branch of the Unified Patent Court ('UPC'), established to enable more consistent decision-making in EU patent litigation, but this is not now going to happen.

As to supplementary protection certificates and regulatory data protection, it remains to be seen whether the UK will keep to the existing EU regimes or go its own way.

Data protection

The UK has long since implemented the existing EU Data Protection Directive into its own national law. In May 2018 EU data protection laws will be amended by way of the General Product Data Regulation ('GDPR'). As a regulation, and hence directly enforceable in all Member States, the GDPR may well be in force before any EU departure. If the UK joins the EEA there will be no change but otherwise it would seem logical for the UK effectively to continue with the same regime especially as businesses are likely to want consistent data protection law across both the EU and the UK.

Commercial agreements and competition law

Existing agreements should be checked to see whether they contain specific references to EU territories, laws or regulators which may need amending in due course. A key question may be whether particular agreements could be terminated as a result of the UK leaving the EU. Any right of termination would depend on the terms of the relevant contract, including any force majeure or material adverse change clause, and any right to terminate on notice.

Another issue is how pre-existing contracts should be interpreted. For example, how would an obligation to comply with a specific piece of EU legislation be interpreted after the UK leaves the EU?

With specific reference to licensing and collaboration transactions, many deals have split territory or other geographic distinctions around the EU, and define 'EU' in varying ways, ranging from 'as it is constituted on the effective date' of the particular deal to 'as it is constituted from time to time' during the term of the particular agreement. These differences may impact not only the territory included in the deal, but also milestone payment triggers and royalty payment terms. Also, we often define the EU 'Major Markets' to include the UK, Germany, France, Italy and Spain. In addition, references to pharmaceutical product approvals by the EMA centralised and Member State procedures, and Member State pricing and reimbursement approvals, may need to be examined.

When entering into new contracts it should also be considered whether to include a specific provision dealing with the consequences of UK departure.

As far as competition laws are concerned, as most UK competition law derives from EU law it will be business as usual for competition law and enforcement in the UK in the immediate future. Life sciences businesses currently benefit from safe harbours such as the technology licensing and vertical agreement block exemptions against infringing EU laws which govern licensing and supply and distribution in the EU market. How Brexit would affect these provisions will depend on the nature of the UK/EU relationship. For example, should the UK go the EEA option then, while there would not be significant changes to the law itself (as the competition rules in the EEA Agreement are modeled on their EU equivalents), disputes as to its interpretation in the EEA would ultimately be resolved by the EFTA Court rather than the EU Court of Justice.

Research funding

Between 2007 and 2013 the UK received EU science grants worth €7 billion, including 18% of university research. Concern is already being expressed that new projects involving EU support are not going ahead and some collaborative activities are being cancelled. This was to be one of the areas to be

covered by the new steering group set up by the Life Sciences Minister (see above).

Employment and immigration

The EU is a major source of UK employment law. The laws relating to unlawful discrimination, working time, maternity and paternity leave, and the protection of employment upon the transfer of a business are either largely or completely due to EU directives. It is likely that the UK Government would seek to maintain the *status quo* until the political and legal implications of any exit from the EU have been resolved. On a long term basis, the impact on UK employment law will depend upon the nature of the relationship between the EU and the UK. However, the new Secretary of State for Exiting the EU, David Davis, has stated that he does not view employment law as imposing unnecessary regulatory burdens on business, which suggests that there may be limited long term change in any event.

Immigration was a key area in the Brexit campaign with many 'leave' campaigners hoping Brexit would limit immigration. Any restriction of EU free movement could potentially prejudice the attractiveness of the UK for existing and future EU workers as a research base and a centre of excellence for medicine. Non-UK EU talent at executive levels and in R&D is also critical to the UK life sciences industry. The industry and the NHS will need to ensure that any immigration restrictions respect healthcare and life sciences expertise as key workers. Employers should consider auditing their workforce to understand which employees may be affected by any future changes. It would be prudent for employers to prepare a contingency plan to deal with any gaps created by departing EU workers, who may choose to leave now due to uncertainty over their future immigration status.

Conclusions

As an acknowledged 'jewel in the crown' of the UK economy, the new Government will be anxious to mitigate the impact on the UK life sciences sector and will be open to ideas as how to exploit UK industry and research base strengths in a post-EU world. The life sciences industry therefore has a real opportunity to gain a greater share of voice through a concerted lobbying campaign to achieve its aims. These could include:

- ensuring that the negotiation of any mutual recognition agreements affecting the life sciences sector are prioritised;
- stressing the global influence of NICE determinations and the UK in international reference pricing - so everyone understands just how valuable these are for the UK on a world stage;
- working with NICE, the MHRA and Government to leverage internationally the acknowledged expertise of the MHRA and real world evidence from early access schemes;
- encouraging positive treatment of the movement of EU life sciences workers and generally protecting the UK science base;
- asking the Government to further enhance the Patent Box to the extent possible under the UK's G20 obligations;
- reinforcing the Government's appreciation of the power of effective intellectual property protection and regulatory exclusivities to attract investment; and
- seeking the adoption of regulatory and reimbursement regimes designed to encourage rather than deter the use and adoption of new treatments.

An important factor will be how well the industry can cooperate with the MHRA and NICE in a common cause.

Leslie Galloway, Chairman of the Ethical Medicines Industry Group representing smaller and medium sized UK pharmaceutical companies, stated that "The new Prime Minister and her Government will need to paint a very clear picture of how they will attract Biopharma to the UK to invest in order to deliver a healthier global future for us all. One key aspect of this will be for the new government to explain promptly how the UK will remain fully welcoming to the overseas scientific and business talent that contributes so significantly to our life sciences ecosystem."

Prime Minister May herself commented in 2013, that "We're already a world leader in pharmaceuticals, but, recognising that we can't rest on our laurels, at the end of 2011 the Government launched a strategy that will put Britain at the forefront of the new model of personalised medicine that is transforming biomedicine. We should learn from these success stories." Christian Hill of MAP BioPharma, a market access and government affairs consultancy, in reminding us of Mrs May's 2013 statement, expressed the hope that she "will demonstrate just how important these industries are to Britain's success by implementing the planned accelerated access review and by preventing any further price cuts to medicines, with the UK already paying less than almost all other first world nations."

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